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1 **Twenty years of amino acid determination using capillary electrophoresis: A review**

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17 **Abstract:** In this review, we have attempted to highlight the advancements in the the field of
18 amino acid determination using capillary electrophoresis. The technique has been developed
19 through the years, and the assessment of publications from the past twenty years reveals the
20 different developmental processes. Although there are relatively fewer publications on capillary
21 electrophoresis (CE) every year, the advancements in both fluorescence and UV detection
22 techniques make it a simple and powerful tool. We showed that recent developments in the
23 coupling of CE with mass spectrometry or conductimetry pave the way for high throughput
24 solutions for applications in metabolomics or in clinical biology analysis. This review describes
25 the use of these different detection methods, and reports the most advanced applications:
26 medical studies, amino acid determination in neurosciences, metabolomics, and foodomics.
27 Through this review, we intended to show that as a tool for amino acid detection, CE has reached
28 an advanced stage of development.

29
30 **Abbreviations:** AA, amino acid; BGE, background electrolyte; C⁴D, capacitively coupled
31 contactless conductivity detection; CBQCA, 3-(4-carboxy- benzoyl)-2-

32 quinolinecarboxaldehyde; CS, chiral selector; CSF, cerebrospinal fluid; CTAB,
33 cetyltrimethylammonium bromide; GABA, γ -aminobutyric acid; FA, formic acid; FITC,
34 fluorescein isothiocyanate; Hcy, homocysteine; IAF, iodoacetomido-fluorescein; LEDIF, LED
35 induced fluorescence; NBD-F, 4-fluoro-7-nitro-2,1,3-benzoxadiazole-labeled; Orn, ornithine;
36 TCAC, tricarboxylic acid cycle, 18C6H4, (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid
37
38

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87 **1. Introduction**

88 Amino acid (AAs) separation using capillary electrophoresis (CE) is a subject of
89 particular relevance that has been discussed extensively in the past 20 years in almost 3000
90 articles. In particular, the topic has been reviewed by various authors. Some of the notable
91 researchers in this field of study are Poinot *et al*, who have published detailed review articles
92 every 2 years [1–8]; Denoroy and Parrot, who have studied these topics for a longer period [9];
93 and Song *et al*, who have studied biological samples from patients with specific diseases
94 between 2012 and 2016 [10]. This is the first review to discuss studies conducted and reported
95 over such an extensive time period, given that 20 years is sufficient to measure technical
96 evolutions and apprehend novelties in a field. We will describe the key works that were
97 published during this period, and occasionally, we will refer to the basics published earlier. Fig.
98 1 shows the variation in the number of publications, where the phrase “capillary
99 electrophoresis” is present in the title and “amino acid” in the abstract (source: the Web of
100 Knowledge). We observed that there two parallel curves are formed, which indicates that CE is
101 less frequently used in analytical studies that result in publications, and as a consequence, AA
102 studies are also less frequently reported. When comparing these curves with those on
103 CE/fluorescence studies on AAs, we also observed a parallel decrease. The application of
104 CE/mass spectrometry (MS) in AA determination does not show this tendency of reduction,
105 with MS being a considerably popular technique used in analytical experiments as well as by
106 major organizations (*i.e*, Agilent, Sciex) manufacturing CE/MS instruments. Capacitively
107 coupled contactless conductivity detection (C⁴D) with CE is the only detection mode whose
108 applications have increased. This is an expected observation, owing to the universality of the
109 method; currently, it is considered a useful AA determination method.

110 Several studies have described the use of simple background electrolytes (BGEs) for
111 capillary zone electrophoresis (CZE), where AAs or their derivatives migrate in proportion to
112 their charge and in inverse proportion to the size of the solvated ion. Micellar kinetic
113 chromatography (MEKC) involves the migration of surfactants and their associated micelles in
114 an electrolyte. At pH values above 7, the micelles play the role of a pseudo-stationary phase

115 with which AAs can be associated. Therefore, a complementary criterion for separation comes
116 into play: the partition of AAs between the pseudo-stationary phase (in which limited migration
117 occurs) and the buffer (in which they migrate as in CZE). Cyclodextrin (CD) can also be added
118 to the MEKC electrolyte to establish a supplementary equilibrium (AAs inside CD or outside
119 CD), which modifies the migration dynamics of the AAs. The AA/CD complex, being
120 considerably larger than free AAs, migrates at a different electrophoretic velocity. CD also
121 helps separate enantiomers.

122 Since it is neither feasible nor desirable to peruse all 3000 research articles published
123 over the 20-year period, we have discussed various developments in the analysis of AAs using
124 CE coupled to UV absorbance detection, C⁴D, fluorescence detection, or MS. Following this,
125 we have discussed the various common fields of applications: metabolomics, medical science,
126 neuroscience, and foodomics. We have presented the key findings of these articles with
127 precision, and expect that it will assist readers in the selection of an appropriate CE method for
128 implementation in experimental settings. We have also added a critical synthesis at the end of
129 each section.

130

131 **2. CE/UV**

132 Most AAs do not contain a chromophore moiety, and resultantly, do not absorb UV
133 radiation sufficiently. Only aromatic AAs (Phe, Tyr, Trp, and His) and Cys can be easily
134 detected using UV radiation. Therefore, the labeling of an AA with a chromophore is necessary
135 for the use of CE/UV in AA studies. A handbook on derivatization was edited 20 years ago; it
136 describes a variety of dyes, their related bibliography, and the reaction and separation conditions
137 in high-performance liquid chromatography (HPLC) or CE [11]. A more concise publication,
138 which may be considered old but not outdated, was published by Toyo'oka [12]. Generally,
139 labeling is performed off-line prior to conducting CE/UV measurements; however, specific
140 attempts have been made to achieve on-column derivatization. Other attempts have been aimed
141 at studying AAs without derivatization with indirect UV detection or detection of changes in
142 the refractive indices of zones containing the AAs after CZE separation. Table 1 outlines the
143 basic analytical conditions adopted in the studies that have been reviewed in this chapter.

144 **2.1. CE/UV with AA derivatization**

145 Fluorescamine is particularly suitable for AA derivatization in relevant CE separation
146 procedures. For example, in an experiment using a robust method of taurine determination, at

147 pH 3, labeled taurine was observed to be negatively charged and lag behind other AAs during
148 migration [13].

149 Phenylisothiocyanate (PITC) derivatization was popularly used for AA determination
150 approximately 50 years ago (in Edman degradation reaction). In a particular study, it was used
151 to analyze 18 L-AAs (except Trp or Asn) with a buffer containing β -cyclodextrin (β -CD). A
152 long separation step (53 min) was required. PITC-derivatized Arg migrated close to the
153 electroosmotic flow (EOF). The majority of AAs were separated, and only Leu and Ile
154 comigrated. The limit of detection (LOD) ranged from 1 μ M (Gly) to 4 μ M (Phe) [14].

155 Dansyl chloride has mostly been used for the identification of AAs using CE/UV and to
156 a lesser extent using CE/fluorescence. Jorgenson and DeArman Lukacs were the first to publish
157 a report on CE that dealt with the separation of dansylated AAs detected using fluorescence
158 [15]. In the last 20 years, CE/UV has undergone advancements primarily related to enantiomer
159 separation procedures. Chen *et al* [16,17] proposed the use of Cu(II)-L-phenylalaninamide and
160 Cu(II)-L-alaninamide followed by Cu(II)-L-prolinamides as chiral selector (CS) molecules for
161 separating DL-AAs by ligand exchange CE. Zn(II)-L-phenylalaninamide [18] and a mixture
162 of Zn(II)-L-4-hydroxyproline and γ -CD [19] have also been used. Similarly, L-Ala-derivatized
163 amino acid ionic liquids have been synthesized, which led to [1-butyl-3-methylimidazolium][L-
164 Ala] formation. When associated with Mn(II) and β -CD, it facilitated the effective separation
165 of proteinogenic AAs (except Gly). However, the fact that the enantioseparation of DL-Cys and
166 DL-Lys has not been reported is a pertinent issue, whereas DL-ornithine (Orn) has been
167 resolved using this method [20]. The detection of biogenic amines and AAs using CE/UV with
168 dansylation has been compared to that using CE/laser-induced fluorescence (LIF) after labeling
169 with fluorescein isothiocyanate (FITC). The selectivity and sensitivity of fluorescence detection
170 was observed to be suitable for the quantitation of these compounds [21].

171 Terguride-based CS molecules were developed and used with polyacrylamide-coated
172 capillaries, wherein the aim was to separate D-Ser (after dansylation) in samples derived from
173 the mammalian body. 1-Allyl-5S,8R,10S-terguride was shown to be the best CS for separating
174 0.01% D-Ser from 99.99% L-Ser [22]. Usually, the enantioselectivity of dansylated AAs has
175 been studied using a combination of β -CD and tetraalkylammonium Arg ionic liquids in
176 nonaqueous CE using N-methylformamide. The results have shown that the resolution between
177 enantiomers is above 2 (Trp, Phe, His, Cys, and Ala were tested) [23].

178 The Folin's reagent, 1,2-naphthoquinone-4-sulfonate, is a common reagent used for measuring
179 the levels of primary amines [24], has also been used for resolution. Under the selected

180 separation conditions, Leu, Ile, and Phe peaks were partially resolved, and His and Leu were
181 observed to comigrate. The lack of selectivity was overcome using the spectral and
182 electrophoretic differences of analytes to recover their pure electrophoretic and spectral profiles.
183 Each compound could be effectively quantitated [25,26]. Additionally, this dye has been used
184 for in-capillary labeling via the sandwich configuration, in which reactive/sample/reactive
185 zones are used for derivatization. Trp, Phe, Met Thr, Pro, and Ala could be effectively separated
186 using stacking with large-volume samples (of low conductivity), with an LOD of 0.4 μM (Trp)
187 to 1.4 μM (Phe) achieved for standard AAs [27].

188 Zhang and Gomez [28] demonstrated in-column derivatization using phthalic anhydride
189 (in acetonitrile) injection after the application of the AA sample (composed of standard His,
190 Trp, Leu, Met, Thr, Ser, and Gly (also diluted in acetonitrile)), followed by electrophoresis. The
191 differential migration velocities allowed the two zones to penetrate each other in the electric
192 field. In a review on on-capillary derivatization, it was shown that the technique enhances
193 sensitivity; in particular, the author focused on the methodologies that are used for reactant
194 mixing in the capillary [29]. Ptolemy and Britz-McKibbin [30] reviewed the application of on-
195 line sample preconcentration with chemical derivatization and reported its on-line use for
196 derivatization. Following this, the authors described the in-capillary derivatization of phospho-
197 AAs with 9-fluorenylmethyloxycarbonyl chloride (FMOC) using CE/UV analysis. In this
198 method, the analytes were focused using a dynamic pH junction, and FMOC labeling was
199 influenced by buffer pH, ionic strength, sample injection length, and dye concentration. The
200 LODs achieved were $\sim 0.1 \mu\text{M}$ [31].

201 Terabe's lab [32] suggested the use of a capillary with an internal diameter (ID) of 100
202 μm packed with 5- μm C18-coated particles (basic-pH compatible). The capillary was filled
203 with a running buffer containing a derivatization reagent, *o*-phthalaldehyde (OPA)/ β -
204 mercaptoethanol (BME), and borate buffer (pH 10). After the electrokinetic injection of a
205 mixture of biogenic amines (histamine, serotonin, tyramine, putrescine, and cadaverine) or
206 AAs, only free biogenic amines entered the anodic site of the capillary and travel along the
207 column, where the analytes reacted with OPA/BME and were separated, and were then detected
208 by measuring absorbance at 340 nm. In a mixture consisting of these biogenic amines and 17
209 AAs, the biogenic amines were selectively separated and detected based on their absorbance at
210 340 nm. Similar, Koval *et al* [33] proposed the use of in-capillary derivatization with OPA/BME
211 separated in an alkaline BGE using 2-hydroxypropyl- γ -CD as a CS. First, two hydrodynamic
212 injections of an AA sample (negatively charged) were administered, followed by the injection
213 of an OPA/BME mixture (neutral). Next, an electric field was applied to facilitate merging of

214 the two zones, derivatization, and separation of the derivatives. UV absorption detection at 230
215 nm yielded an LOD of 3 μM . Baseline resolution of D- and L-serine derivatives could be
216 achieved in less than 10 min. The tertiary amino function of ofloxacin acyl chloride is charged
217 in acidic and neutral media and can be used to label AAs. Amantadine (amino drug), tranexamic
218 acid (nonproteinogenic AA), Gly, and Met have been analyzed by this method using CE/UV at
219 300 nm. The LODs ranged from 1.0–2.5 μM . An application of tranexamic acid analysis to
220 plasma samples has been demonstrated earlier [34].

221

222 **2.2. CE/UV without AA derivatization**

223 Procedures for CE without derivatization have also been designed. Direct UV detection
224 can be used for the determination of proteinogenic and non-proteinogenic AAs [35], which is a
225 process that only works on standards. Indirect UV detection was performed for the identification
226 of 3 phospho-AAs in phosvitin hydrolysate using AMP (with 2.5% Brij 35, pH 7.5), as UV-
227 absorbing constituents of the BGE [36]. Zunic *et al* [37] reported the separation and
228 quantification of 30 underivatized physiological AAs and peptides using *p*-aminosalicylic acid
229 buffered with sodium carbonate at pH 10.2 (Fig. 2). The LODs ranged from 2 μM (Glu) to 20
230 μM (Gly). This analytical procedure was successfully performed for studying plasma and a
231 macrophage culture supernatant, for which the sample preparation procedures only involved
232 protein precipitation and dilution steps. The use of indirect UV detection (215 nm) of
233 gabapentin (using Glu as an internal standard) in a bulk drug and capsules over a concentration
234 range of 20–200 $\mu\text{g}\cdot\text{mL}^{-1}$ was developed as a pharmaceutical application. The analytes were
235 separated using 5 mM 5-sulfosalicylic acid and 0.5 mM cetyltrimethylammonium bromide
236 (CTAB) at pH 11 [38]. The CE conditions were improved for the separation of AAs in blood
237 and/or plasma samples [39]. The method involved direct detection using a BGE containing
238 disodium monophosphate for detection of compounds with absorbance in the UV region.
239 Conversely, detection by indirect absorbance using *p*-amino salicylic acid facilitated the
240 quantification of 30 underivatized physiological AAs and peptides. A preconcentration method
241 combining large-sample injection based on a dynamic pH junction with a sweeping process was
242 designed by Xu *et al* [40]. The sweeping process involved indirect UV detection (with 20 mM
243 benzoic acid used as the chromophore) using 10 mM β -CD and 6% (v/v) methanol within the
244 sample matrix (3 mM H_3PO_4). The LOD ranged from 0.85 μM (Glu) to 0.4 μM (Asp). AAs in
245 human serum samples have been analyzed by adding a mixture of acetonitrile and methanol to
246 precipitate proteins. Transient isotachopheresis (NaCl in the sample and HEPES in the BGE)

247 for the on-line preconcentration of high-salinity samples was used for 3-nitrotyrosine
248 quantitation in atherosclerosis and other inflammatory diseases. The analyte was quantitated by
249 UV detection using MEKC [41].

250 A simple 30 mM phosphate buffer (pH 9.25) for Arg, choline, and allantoin detection was
251 described by Zhang *et al* [42], and UV absorbance was measured at 200 nm. Derivatization or
252 indirect UV detection were not necessary. The LODs ranged from 2.0 μM (Arg) to 0.4 μM
253 (choline). Lys, Met, Thr, and cystine were detected in fish flour using borate buffer. The LOD
254 ranged from 20 μM (Cys-Cys) to 140 μM (Lys). The on-line sweeping preconcentration
255 technique was combined with the coordination interactions between AAs and Cu^{2+} ions to
256 improve CE/UV detection sensitivity and to analyze AAs in human saliva and green tea
257 samples. The LOD for the seven separated AAs ranged from 0.1 μM (Leu) to 0.5 μM (Phe)
258 [43]. Phe and Tyr in urine have been analyzed using pH junction preconcentration [44]. Before
259 sample injection, a plug containing NH_4OH solution was injected, following which the urine
260 sample was mixed in a 1:1 (v/v) ratio with a BGE (1 M formic acid (FA)). For analysis, 1.7 nL
261 of 12.5% NH_4OH solution was injected first, followed by 196 nL of urine. The LODs were in
262 the 0.01 μM range.

263 N-acyl derivatives of 2,6-diaminopimelic acid are considered possible inhibitors of N-succinyl-
264 L,L-diaminopimelic acid desuccinylase. The amide function shows absorbance at 206 nm.
265 Besides, these compounds can be easily detected using CZE or MEKC (with SDS or cetyl
266 trimethyl amine bromide). Eight separation conditions were tested at acidic or basic pH to
267 determine the degrees of purity of 13 mono-N-acyl derivatives of 2,6-diaminopimelic acid [45].

268 An interesting study was performed for comparing the efficacy of CE/UV (195 nm) and
269 C^4D in determining the dissociation constants (pK_a) of 20 proteogenic AAs using 22 buffers
270 with pH ranging between 1.5 and 12.0. A short-end injection method was developed to reduce
271 the effective length (8 cm) of the capillary. Consequently, the analysis time per AA was less
272 than 2 h when the 22 buffers were used [46]. This study reported the pK_a values of 11 AAs as
273 well as the corresponding electrophoretic mobility rates deduced using eight buffers at different
274 pH levels [47].

275 CE/UV with derivatization is easy to perform because the labeling reactions are identical
276 to the ones used in liquid chromatography (LC). Although fluorescamine, FMOC, and dansyl
277 chloride can be used, the sensitivity is observed to be limited to micromolar concentrations
278 when these are used, and selectivity could be limited owing to the matrix effect. A study,
279 possibly the most notable one on this topic, showed the effective separation of phospho-AAs

280 labeled with Fmoc with an LOD of 0.1 μM [31]. Owing to their negative charge, phospho-
281 AAs were effectively separated from non-phosphorylated AAs, and an LOD of 0.1 μM was
282 achieved using capillary labeling along with a dynamic pH junction. The non-labeling methods
283 are limited to the identification of aromatic AAs.

284

285 3. CE/C⁴D

286 The use of C⁴D for CE-based detection was proposed more than 20 years ago by Zeman
287 *et al* [48] and Fracassi da Silva [49]. They suggested using two cylindrical electrodes placed at
288 a distance of several millimeters around the capillary, forming a cylindrical capacitor. Electric
289 conductivity of the electrolyte in the gap is measured by a function generator, which applies a
290 sinusoidal signal to the first cylinder. The second cylinder is connected to a current-to-voltage
291 converter. The rectified signal is proportional to the conductivity of the inner solution in the
292 gap.

293 Kuban and Hauser [50] recently published a review article outlining the developments
294 in C⁴D for CE in 20 years. They mentioned that the effectiveness of this method is indicated by
295 the fact that there were 1200 articles published on the topic, and that C⁴D is a commercialized
296 detection method; furthermore, they also mentioned that this equipment could be connected to
297 all CE instruments owing to its compactness. An advantage of C⁴D is that it can be used for the
298 detection of all small inorganic ions and organic compounds. The LOD usually lies in the
299 micromolar range. Table 2 summarizes the basic analytical conditions in the studies discussed
300 in this chapter.

301 Coufal *et al* [51] were the first to propose the separation of 20 underivatized
302 proteinogenic AAs using a simple BGE composed of 2.3 M acetic acid and 0.1% w/w
303 hydroxyethylcellulose. The LOD of these AAs ranged between 9 μM (Lys) and 29 μM (Asp).
304 The separation was realized in 32 min. The results could be improved using 6 mM lactic acid
305 as the BGE. This modification helped achieve LODs of 0.2 μM for Arg and 0.4 μM for His,
306 while the LODs ranged from 0.5 to 50 μM for the other nine AAs tested. The basic reaction
307 environment at pH 10–11 established using a mixture of 2-amino-2-methyl-1-propanol and
308 CAPS facilitated the separation of the 20 AAs in less than 9 min, where only Trp, Leu, Met,
309 and Gln were observed to comigrate [52]. Three AAs and four monosaccharides were also
310 separated using a basic buffer (10 mM NaOH, 4.5 mM Na₂HPO₄, 1 mM CTAB, pH > 12) [53].

311 Samcova and Tuma [54] reported the separation of 18 proteinogenic AAs, creatinine, 1-
312 Me-His, 3-Me-His, Orn, and citrulline. Only the two Me-His comigrated with the BGE

313 containing 1.7 M acetic acid and 0.1% hydroxyethylcellulose (HEC); however, the separation
314 time was 48 min, which was considerably high. This separation protocol was applied on plasma
315 samples (deproteinized using acetone/water at 1:1 ratio). The LODs reported ranged from 4.3
316 μM (Arg) to 42.9 μM (Cys). 3-Me-His, 1-Me-His, and His were resolved using a BGE
317 containing ammonia (0.5 M acetic acid, 0.1 % HEC, 20 mM NH_4OH); however, in this case,
318 apart from the 19 proteinogenic AAs, no other components were separated [55].

319 Twenty-eight AAs were analyzed using a capillary with an effective length of 18 cm,
320 and 14 of them were completely resolved. The short separation pathway decreased the
321 separation time of AAs (below 6.5 min), and the LODs also reduced to a submicromolar range
322 (Lys: 0.1 μM , Asp: 1.7 μM) [56]. Pormsila *et al* [57] reported the quantitation of carnitine and
323 six acylcarnitines in plasma and urine samples using CE/ C^4D with 0.5 M acetic acid and 0.05%
324 Tween 20. In a notable study, choline, creatinine, Orn, Lys, Arg, His, Gly, Ala, Val, Ile, Leu,
325 Ser, Thr, Gln, Glu, Phe, Tyr, and Pro were separated in a dried blood spot (DBS) after elution
326 using 20 μL of methanol/water (1:1, v/v) in a BGE containing 1.6 M acetic acid, 1 mM (+)-(18-
327 crown-6)-2,3,11,12-tetracarboxylic acid (18C6H4), and 0.1 % (v/v) Tween 20. Phe
328 concentration was detected to be 61.3 μM [58]. Fig. 3 shows the electropherograms obtained
329 for DBS from five patients.

330 AAs from ocean water samples have also been quantitated, taking into account the
331 challenges posed by the high salinity of water. In the absence of sample dilution, 5 M acetic
332 acid with 10 mM 18C6H4 and 10% acetonitrile were shown to be necessary to separate β -Ala,
333 His, γ -aminobutyric acid (GABA), Gly, Ala, 2-aminoisobutyric acid, Val, Ser, isovaline (with
334 the isomers of Val not separated), Leu, Glu, and Asp [59].

335 Chiral separation was also performed using 18C6H4 in a BGE containing 10 mM citric
336 acid/Tris at pH 2.2. An LOD of 2.5 to 20 μM was achieved for DL-Arg, DL-Val, DL-Ser, DL-
337 Phe, DL-Tyr, and DL-Asp, and migration durations less than 28 min were obtained [60]. Of
338 note, *cis/trans*-amines were also effectively separated using a cyclic ether [61]. Elsewhere, DL-
339 Asp and DL-Glu were enantioseparated using 5 mM vancomycin at pH 7.35 in a BGE
340 containing 10 mM Tris, 4.4 mM maleic acid, and 0.03 mM CTAB. Experiments in which Tween
341 20 was used have also been reported [62].

342 Samples used in neuroscience studies, such as microdialysates, have also been analyzed
343 using C^4D ; however, it is necessary to preconcentrate them owing to the lack of sensitivity in
344 this detection method. Microdialysates of periaqueductal gray matter were preconcentrated by
345 filling 25% of the capillary with the microdialysate sample diluted in acetonitrile (1:3, v/v) [63],
346 followed by focusing of the ions in the sample using an electric field while simultaneously

347 forcing the acetonitrile zone out of the capillary by increasing the pressure in the cathodic vial.
348 The researchers could easily identify GABA, Glu, and Gly among several other components.
349 When a microdialysate was used, several ions from Ringer's perfusate were visible in the
350 electropherograms. The concentrations of these AAs in the periaqueductal gray matter of rats
351 were monitored after treatment with 1% m/v carrageenan for induction of hyperalgesia,
352 followed by administration of 300 mg·kg⁻¹ paracetamol after 60 min of dialysis. The LODs
353 improved to 29 nM (GABA and Gly) and 37 nM (Glu) using this stacking method. Asp was not
354 quantitated [64]. Val, Ile, and Leu were also quantitated in a microdialysate using 2.1 M acetic
355 acid in 20% (v/v) MeOH + 1% (v/v) INST (a coating solution used for the elimination of EOF
356 in CE [Biotaq, Gaithersburg, USA]). The microdialysates were diluted four-fold with
357 acetonitrile acidified using 0.01 M HCl to attain the best sensitivity and resolution. The LOD
358 for these AAs was 0.1 μM [65]. This coating method has been compared to a covalent one
359 implemented after a reaction with poly(acrylamide-co-(3-
360 acrylamidopropyl)trimethylammonium chloride) containing 1% m/m of (3-acrylamidopropyl)
361 trimethylammonium chloride. This coating reversed the flow (direct polarity is maintained) and
362 yielded the best results at 14.4 cm effective length during the high-performance separation of
363 Ala, Val, Ile, Leu, Ser, Gln, and Glu from rat plasma in less than 5 min with a buffer containing
364 3.2 M acetic acid and 20% methanol [66]. Food chemical analyses were also performed using
365 this method. Lys, Ala, Pro Glu, and Asp in royal jelly supplements were quantitated using 2 M
366 lactic acid as the BGE [67]. Taurine, choline, and niacin were separated in two capillaries, each
367 containing a buffer selective for taurine (150 mM Tris/lactic acid, pH 8.96) and another
368 selective for choline and niacin (150 mM Tris/acetic acid, pH 9.5). The contents of these
369 compounds in energy drinks were quantitated [68].

370 Theoretical studies have also been performed using such detection methods. The
371 effective mobility rates of free AA⁺ and AA²⁺ have been determined using CZE with a
372 laboratory-made contactless conductivity detector and a double detection cell (1 cm and 1.442
373 cm distance between the two detection cells). The acidic BGE (chloroacetic acid lithium
374 hydroxide mixtures at pH ranging between 2.0 and 3.2) at constant equal ionic strength (10
375 mM) allowed the measurement of the effective mobility of the cations. The data were fitted to
376 the regression functions depending on the pH of the electrolytes. pKa values were obtained
377 using the Onsager theory and McInnes approximation [69]. A similar study was conducted at a
378 lower acidic pH (1.6–2.6, to ensure a higher degree of AA protonation), with poly(vinyl alcohol)
379 added to the BGE to prevent adsorption on the capillary wall [70].

380 Table 2 shows that 0.5–4.0 M acetic acid is a common buffer that can be supplemented
381 with 18C6H4 (as a CS) or hydroxycellulose for better stacking. For most applications to AAs,
382 this is the simplest and most efficient detection method for AA quantitation at a submicromolar
383 concentration. C⁴D is considered a universal detection method for AA quantitation using CE,
384 either in an acidic or basic BGE. This method may soon be used by companies employing CE
385 for routine clinical applications. This is primarily because in contrast to CE/UV, this method
386 does not require derivatization, and sensitivity is sufficient for the clinical analyses of AAs.

387

388 4. Developments in CE/fluorescence

389 The use of fluorescence detection of AAs in conjunction with chromatographic and
390 electrophoretic separation procedures was first reported in the 1980s [15], and has since been
391 reported in multiple original articles [71,72]. Marina and Castro-Puyana provided an overview
392 of the derivatization methods used for CE applications by reviewing previous reports [73].
393 Unfortunately, most AAs do not emit fluorescence intrinsically. Similar to the issue experience
394 with UV absorption, researchers have attempted to develop efficient methods for labeling these
395 molecules for fluorescence detection. The reports on derivatization relevant for UV detection
396 can be consulted herein [11,12]; these extensive studies have also been reviewed recently [74].
397 LIF- or light-emitting diode (LED)-induced fluorescence (LEDIF) detection is limited by the
398 wavelengths of lasers or LEDs available and the restricted number of fluorophores that allow
399 the excitation of an AA at different available wavelengths after derivatization. Table 3 outlines
400 the basic analytical conditions in the articles that are reviewed in this chapter.

401 4.1. Native fluorescence

402 Two notable reviews have been published that have showcased the developments in
403 native UV fluorescence detectors and discussed multiple articles on aromatic-AA separation
404 procedures [75,76]. The use of native fluorescence to detect aromatic AAs is no longer restricted
405 to owners of expensive UV lasers. Chang *et al* [77] reported the application of a low-cost diode
406 frequency quadrupled pulsed laser with emission at 266 nm. Bayle *et al* [78] detailed the
407 determination of Tyr and Trp in cerebrospinal fluid (CSF) after 1:20 dilution in water using a
408 pulsed laser (Fig. 4). Trp was detected at a concentration of 0.15 nM, indicating that the process
409 was 105-fold more sensitive than UV absorbance. Zhang and Sweedler described an improved
410 inexpensive "turnkey" NeCu laser operating at 248.6 nm and interfaced with a sheath flow-
411 based CE system; this setup performed similarly to an expensive large-frame frequency-

412 doubled Ar ion laser at 257 nm. The LODs for serotonin, dopamine, and Trp (27 nM, and 8
413 μ M, and 63 nM, respectively) were within the range of those achieved using a frequency-
414 doubled Ar ion laser at 257 nm (21 nM, 8 μ M, and 2 nM, respectively) [79].

415 A 266-nm diode-pumped laser with a 10 ps duration pulse and a repetition rate of 40
416 MHz was used with a time-correlated single-photon counting device to detect DL-Trp. The
417 chiral separation of DL-Trp was performed using CD, sulfated CD, and highly sulfated γ -CD at
418 different pH values. Highly sulfated γ -CD (0.35 %, pH 2.5) was found to be the most effective
419 CS. The LOD for Trp was 65 pM [80]. Beyreiss *et al* [81] have described a similar UV-LIF
420 detector based on lifetime detection. The abovementioned 266-nm laser was used for excitation,
421 and the process was also coupled with time-correlated single-photon counting detection. The
422 average fluorescence lifetimes were independently determined for Trp, Ser, propranolol, and 3-
423 phenoxy-1,2-propanediol. Using lifetime measurements, a better discrimination of background
424 fluorescence and a better signal-to-noise (S/N) ratio were obtained. These methods can be
425 applied to protein analysis.

426 In an interesting attempt first made by Park *et al* [82], they suggested the use of a
427 wavelength-resolved electropherogram of AAs with single-cell injection of an individual
428 cerebral ganglion neuron. The natively fluorescent AAs and biogenic amines were detected
429 after excitation with a 257-nm Ar laser, and fluorescence detection was implemented using a
430 charge-coupled device (CCD) spectrometer. The resulting fluorescence spectrum ranged
431 between 260 and 710 nm. This UV-LIF detector could detect Trp, Tyr, Phe, and dopamine in
432 an individually injected neuron. Conversely, in a standard solution of tryptamine, serotonin,
433 norepinephrine, octopamine, N-acetylserotonin, dopamine, epinephrine, Trp, Tyr, Phe, and 3,4-
434 dihydroxyphenylalanine administered by electrokinetic injection, the LOD varied from 3.9 μ M
435 for norepinephrine to 4.8 nM for tryptamine.

436 Nanomolar LODs were achieved using a capillary containing a bubble cell for detection
437 and a pulsed 266-nm LIF detector, which increased the sensitivity by a factor of 3 for Trp and
438 5 for atenolol. The increase was limited by photodegradation, which could be attenuated by
439 adjusting the laser power in the bubble cell [83]. The values last reported were well below those
440 mentioned in a previous report on UV-LIF detection [78] or Hg-lamp fluorescence detection
441 [84].

442 When a 224-nm pulsed He-Ag metal vapor laser (low-cost but low-lifetime laser) or a
443 264-nm expensive Ar ion laser was used, detection at variable emission wavelengths allowed
444 the quantification of Trp, Tyr, and their related metabolites. The optimal detection wavelength

445 for these analytes was determined by scanning the fluorescence emission using an automated
446 CCD device. The LOD obtained using the wavelength-resolved system was 1 nM for serotonin
447 and 88 nM for Tyr [85]. The LODs of these aromatic AAs and amines could be improved using
448 a deep UV laser and two-photon excitation to quantitate Phe, Tyr, and Trp. The LODs of these
449 AAs added as residues in a polypeptide chain reached 15 amol [86].

450 As the optical gating of fluorophore-labeled analytes facilitates the use of shorter injection
451 lengths and rapid separation procedures and offers the highest separation efficiency, a UV-LED
452 array (900 mW, 365 nm) was designed [87]. On-line photolytic injection of caged 5-
453 carboxyfluorescein-bis-(5-carboxymethoxy-2-nitrobenzyl)-ether-alanine-carboxamide-
454 succinimidyl ester derivatives was performed. Photolytic optical gating involves the use of a
455 caged fluorophore with a low fluorescence quantum yield prior to photolysis by UV radiation.
456 In this method, the samples were injected upon transient exposure to UV radiation via photolytic
457 uncaging of the fluorophore to generate highly fluorescent sample plugs. Photolytic optical
458 gating offered good sensitivity by providing a low-background signal and reduced noise. The
459 uncaged derivatives were detected at 496 nm (using an Ar laser). Studies on the applications of
460 this technique with labeled citrulline and Arg have been published, wherein a nanomolar LOD
461 was achieved [87].

462 Several studies published prior to the time period considered in this review for UV-LIF
463 experiments used considerably expensive UV lasers. These developments may be considered
464 “dated” at present; however, they reflect interesting approaches that facilitated the quantitation
465 of aromatic AAs and amines in neurochemical applications. Presently, some researchers use a
466 266-nm pulsed laser to detect these AAs. The LOD can be considerably improved using an
467 efficient stacking process, as proposed by Hsieh and Chang [88]. The authors in this study
468 described a pH and viscosity stacking process between a sample zone at acidic pH and a viscous
469 separation buffer at higher or lower pH, using which they achieved an LOD of 0.3 nM for
470 tryptamine and epinephrine.

471 Photodegradation serves as a limitation in this type of pulsed diode laser for aromatic-
472 AA detection, which limits sensitivity [89] and prevents the construction of linear quantitative
473 curves [90].

474 266-nm pulsed lasers are readily available and are useful for the determination of AAs
475 with native fluorescence using UV-LIF detection, with LODs achieved in the nanomolar range
476 (for Trp, Tyr, and their metabolites). Serotonin can be detected in microdialysates using a highly
477 efficient stacking process in CE. While UV-LIF detection has shown considerable promise, it

478 remains a relatively expensive process (€10000 for a laser), and the use of pulsed lasers limits
479 sensitivity owing to photodegradation. The attempts to use a time-correlated single-photon
480 counting device have also been promising; however, since only laboratory-made detectors were
481 used, the process faced certain limitations. Therefore, CE UV-LIF is a simple technique for the
482 quantitation of highly fluorescent AAs and their derivatives present at nanomolar
483 concentrations.

484

485 **4.2. Visible LIF or LEDIF detection**

486 Using visible-range lasers or LEDs, AAs can be detected after a derivatization step.
487 Different applications have been described using 2,3-naphthalene dialdehyde (NDA). This
488 fluorogenic dye has largely been employed in neurochemical applications, where several
489 technical advances have been made that are relevant to the topic at hand.

490

491 **4.2.1. NDA**

492 The use of NDA, a fluorogenic dye specific for primary amines, was extensively
493 described by Rammouz *et al* [91]. It has been used in multiple studies on the quantitation of
494 AAs in microdialysates for neurochemical applications, as NDA reacts rapidly with the primary
495 amine in AAs in the presence of KCN. A 457-nm Ar laser was first used to excite NDA
496 derivatives of AAs in hydrolysates of peptides and proteins [92]. Ar lasers are more stable than
497 HeCd lasers (442 nm), even though 457 nm is not the optimal wavelength for detection of the
498 obtained 1-cyano-2-benz[f]isoindole derivatives (440, 420, and 405 nm are the optimal
499 excitation wavelengths). Robert *et al* demonstrated the detection of dopamine and
500 norepinephrine present at nanomolar concentrations in microdialysates, and monitored their
501 concentrations in rat brain [93]. Conversely, Glu, Asp, and phosphoethanolamine [94] were
502 quantitated by adding NDA to a well-adapted reactor for on-line labeling of AAs in
503 microdialysates. Six neuroactive compounds (Gly, Glu, Asp, GABA, dopamine, and
504 noradrenaline) were labeled with NDA, separated, and quantitated using MEKC and lithium
505 dodecyl sulfate, with an LOD lower than that achieved with SDS [95]. In the mentioned study,
506 the method used was compared to HPLC fluorescence analysis of NDA derivatives. Better
507 results were obtained with MEKC/LIF (HeCd laser, 442 nm). Moreover, the authors reported
508 differences in derivatization rates (dopamine is labeled five-fold more rapidly than Gly), and
509 molar UV absorption coefficients (Gly has an absorbance 2.5-fold greater than that of Asp) of

510 the NDA derivatives. They highlighted the fact that all NDA derivatives do not have the same
511 absorption maximum (λ_{\max}); for example, the λ_{\max} value for Lys is 460 nm, while it is 442 nm
512 for the other AAs studied.

513 At present, it is difficult to purchase HeCd lasers as they are manufactured by a limited
514 number of suppliers. Therefore, it is necessary to use other light sources. In this respect, LED
515 or mercury lamps are suitable as excitation sources. Melanson and Lucy [96] demonstrated the
516 analysis of NDA derivatives using an LED (405 nm) source expected to have a lifetime of
517 50,000 h, which was 10-fold greater than that of Ar or HeCd lasers. Moreover, their costs are
518 considerably lower. With excitation at 457 nm, the LODs achieved were reported to be 40-fold
519 higher than those achieved using the 442-nm HeCd laser. Using a similar LED source (405 nm)
520 and an electrolyte containing poly(ethylene oxide) (PEO) and CTAB, Chen *et al* [97] achieved
521 an LOD ranging from 9.5 nM (GABA) to 50.5 nM (Thr) for a mixture of 14 AAs or primary
522 amines. In the presence of CTAB and acetonitrile, the adsorption of PEO on the capillary wall
523 was suppressed, which led to the formation of a rapid and more reproducible EOF and enabled
524 separation in less than 4 min. Branched-chain AA determination in ascites was performed using
525 PEO-containing buffers (1.5% m/v PEO) with 5-s gravimetric injection (height difference: 30
526 cm), and an LOD of 10 nM was achieved [98]. The reaction with NDA and CE of NDA
527 derivatives (excited using 405-nm LED) using PEO 8,000,000 improved the separation, as
528 stated by Hsieh and Chang [99]. The use of PEO 8,000,000 for increasing the resolution and
529 speed could be optimized by varying capillary length, separation voltage, buffer composition,
530 pH, and ionic strength, and a low matrix effect was observed when this polymer was used.
531 Moreover, intensive sample stacking could be employed. NDA has also been utilized for Arg,
532 monomethylarginine, asymmetric dimethylarginine (ADMA), and symmetric dimethylarginine
533 (SDMA) determination by CE as well as glass microchip CE with a 14-cm separation channel
534 [99]. In both cases, 5 mM sulfobutylether- β -CD was added.

535 In addition, NDA was used with a fluorescence detector equipped with a 100-W high-
536 pressure mercury lamp for excitation radiation, an excitation filter of 400–490 nm, and a
537 dichroic mirror at 510 nm to detect histamine and His. The derivatization conditions and
538 separation parameters, including pH and concentration, were optimized. The optimal
539 derivatization reaction was performed using 1.0 mM NDA and 20 mM NaCN (pH 9.1) for 15
540 min, while the separation of NDA-labeled histamine and His could be achieved in less than 200
541 s using 40 mM phosphate buffer (pH 5.8). The LODs for histamine and His were 5.5 and 3.8
542 nM, respectively. The method was successfully applied to the analysis of these molecules in

543 P815 mastocytoma cells and in beer samples [100]. The same method was also applied
544 successfully for the baseline separation of phosphothreonine, phosphotyrosine, and
545 phosphoserine (LOD = 7.0, 5.6, and 7.2 nM, respectively) within 180 s and for validation using
546 a β -casein hydrolysate [101].

547 In-capillary derivatization electrophoresis using electrophoretically mediated
548 microanalysis (EMMA) is a useful technique for derivatization with NDA/NaCN. In EMMA,
549 reactants are injected in an ascending order corresponding to their electrophoretic mobility
550 rates. The reactants migrating most rapidly merge with the slowly migrating reactants [102].
551 Fig. 5A shows the injection/derivatization scheme. The separation of standard AAs is illustrated
552 in Fig. 5B. Plasma and culture medium samples are subjected to protein precipitation by the
553 addition of a mixture of MeOH and propanoic acid (4:1) at 100-fold dilution. EMMA has been
554 applied to metabolomic studies on human embryos to find a correlation between the
555 developmental potential of an embryo and AA turnover. Optimized EMMA was compared to
556 the transverse diffusion of laminar flow profiles [103].

557 NDA and BME were used in a post-column reactor in coaxial-gap mode, where a thin
558 polyimide sleeve with a length of 10 mm was used to align the separation and reaction
559 capillaries with a 20- μ m gap. Owing to gravitational pull, NDA and BME were transferred into
560 the reaction capillary through a 20- μ m annulus between the separation and reaction capillaries,
561 with a 5-mm reaction distance from the annulus to the LIF detector (473 nm). The liquid level
562 difference between the NDA/BME solution and outlet buffer as well as the annulus dimensions
563 and reaction distance were adjusted, which helped achieve an LOD ranging from 80 to 1000
564 nM with a separation efficiency $\sim 1.4 \times 10^5$ theoretical plates. This post-column reactor was
565 optimized and yielded better results (1000-fold more sensitive) when the flow rate of the
566 derivatization solution and the reaction distance were increased [104]. The primary issue with
567 NDA derivatization using BME is the instability of the obtained fluorescent compounds, which
568 become non-fluorescent [105].

569 An in-column fiber-optic LIF detector was evaluated using a 457-nm diode-laser. An
570 optical fiber was inserted into the capillary and positioned in the detection window.
571 Fluorescence emission was recorded using a 40 \times microscope objective (focused on a spatial
572 filter) and passed through a band pass filter; the photomultiplier tube (PMT) measured the
573 obtained signal. NDA-derivatized D-penicillamine was quantified with an LOD of 0.8 nM
574 [106]. One of the most important limitations of this optical detection scheme is the
575 photodegradation of the compounds of interest owing to irradiation for a longer period than that

576 required in a conventional detector. A similar optical arrangement was used for AAs labeled
577 off-line with NDA or FITC, using violet (425 nm) and blue (480 nm) LEDs (a single LED has
578 the ability to emit at these two wavelengths). AAs labeled with NDA or FITC were monitored,
579 and the LODs achieved ranged from 17 to 23 nM for NDA derivatives and from 8 to 12 nM for
580 FITC derivatives [107].

581 A 25-mW diode laser (well adapted for such applications) was used at 445 nm with a 25
582 μm ID capillary (effective length: 20 cm) to achieve the rapid separation of Glu and Asp labeled
583 with NDA. The separation was performed in a highly diluted buffer (10 mM sodium phosphate
584 pH 7.5) to ensure migration times between 51 and 56 s with resolution above 2 and an LOD of
585 ~ 300 nM (100 picomole/planarian). This approach has been tested for quantitation of these AAs
586 in *Planaria*, which are free-living flatworms serving as a model organism for studies on
587 primitive central nervous systems [108].

588 The rapid kinetics of the reaction with NDA/CN⁻ makes CE/LIF suitable for the
589 detection of AAs (except Pro) in the nanomolar range. The dye is fluorogenic, and because
590 excitation can be achieved using an LED with emission at 405 nm, LEDIF detection is selective.
591 EMMA can help achieve efficient separation, and even with an unadapted 488-nm laser
592 (available with the majority of LIF detectors), nanomolar concentrations can be detected.

593

594 **4.2.2. Other aromatic dialdehydes (3-(4-carboxy-benzoyl)-2-quinolinecarboxaldehyde** 595 **[CBQCA], 3-(2-furoyl)quinoline-2-carboxaldehyde [FQ], and OPA)**

596 There are other compounds that act as fluorogenic dyes specific for primary amines. A
597 pioneering study on AAs was performed by Liu *et al* [109] using CE/LIF at 488 nm (with an
598 Ar laser), in which they synthesized CBQCA. In presence of KCN, the reagent reacted with
599 primary amines to generate highly fluorescent isoindole derivatives, which could be excited
600 using the classic 488-nm Ar laser (as well as a 480-nm LED). Additionally, the isoindole
601 nucleus contained a negatively charged carboxylic function. Bergquist *et al* [72] reported the
602 use of CBQCA for the analysis of ten AAs (Arg, Gln, Thr, Val, GABA, Ser, Ala, Gly, Glu, and
603 Asp) in CSF. The separation procedures were performed at pH > 9. The CBQCA derivatives
604 should have a single negative charge for Lys and Arg, double negative charge for neutral AAs,
605 and triple negative charge for acidic AAs (Asp and Glu). We recently demonstrated that, when
606 derivatives (synthesized in D₂O) are analyzed using negative-ion electrospray ionization (ESI)
607 high-resolution MS (HRMS), the carboxylate function of the AA is eliminated, and Trp is

608 considerably difficult to identify owing to the decrease in fluorescence sensitivity (100-fold less
609 fluorescence than that emitted by Leu). Possibly, intramolecular quenching occurs due to the
610 proximity of the indole and isoindole nucleus of the Trp to quinolone moieties [109]. Lastly,
611 we compared the feasibility of quantifying Trp in mouse plasma using CE/LEDIF (480 nm)
612 with CBQCA derivatization and using CE/C⁴D without derivatization. Quantitation was only
613 feasible using C⁴D detection [110]. Boulat *et al* used CBQCA with a greater number of AAs
614 and amines (29 compounds) [111] and achieved remarkable separation in less than 55 min using
615 MEKC in the presence of SDS and γ -cyclodextrin (γ -CD). The S-S dimer of homocysteine
616 (Hcy) could be detected; however, neither free Cys nor free Hcy could be detected (owing to
617 the intramolecular reaction of the thiol group with the CBQCA nucleus instead of CN⁻), and
618 neither could Trp be detected. Arriaga *et al* showed that the Arg derivative shows a good
619 fluorescence yield allowing detection even at zeptomolar levels; however, the authors were
620 unable to label this AA when it was present at levels less than 0.1 μ M [112]. In addition,
621 CBQCA was used to detect considerably low levels of AAs in a study where the analytical
622 parameters, including sodium borate concentration, buffer pH, operating voltage, and operating
623 temperature, were extensively monitored. The rate of derivatization, stability of the labeled
624 AAs, and AA quantitation varied for each amine. The authors claimed to have detected these
625 derivatives at 17 pM (Met) to 383 pM (Glu). Interestingly, they could detect Pro, the only
626 secondary-amine-containing AA, which would not have been labeled. A bacterial AA in a
627 chemically defined medium was successfully detected using this method [113]. Recently, it was
628 shown that CBQCA could be used for AA detection in mouse tear fluid (70 ± 25 nL, collected
629 via phenol red thread). The levels of Arg, Ala, Asp, Glu, His, and taurine were in the micromolar
630 range [114].

631 FQ is another fluorogenic dye that reacts with primary amines (in the presence of CN⁻
632 ions) and can be excited at 488 nm. It has been used for the detection of AAs. Although it is
633 considerably similar to CBQCA, it is uncharged. Ehlen *et al* [115] used factorial analysis as an
634 efficient technique to correlate the variables of the separation conditions (pH and concentration
635 of borate buffer, β -CD, and SDS) and to optimize the analysis, since these conditions depend
636 on analytes, sample composition, and the sample matrix. Nine buffering conditions were
637 studied, and microdialysates collected from near the suprachiasmatic nucleus of male hamsters
638 were analyzed. An LOD of 8 nM was achieved for GABA, 110 nM for Glu, and 25 nM for Asp.
639 FQ was also utilized for the in-capillary derivatization of AAs present in pharmaceutical
640 formulations [116]. The development of other quinolone carboxaldehydes has been performed.

641 For example, 3-(4-bromobenzoyl)-2-quinolinecarboxaldehyde was synthesized, and its
642 derivatization was optimized (pH 8, 55 °C, 50 min, 30:1 reagent/amine, 15:1 KCN/amine) using
643 an optimal running buffer containing 120 mM boric acid (pH 9.1), 38.5 mM SDS, and 19%
644 acetonitrile (v/v) with a 75 μ m ID 60.5/50 cm capillary and a 22.5-kV 488-nm laser. Samples
645 containing Asn, His, Met, Gln (unseparated), Ser, Thr, Tyr, Gly, Glu, Asp, Ala, taurine, GABA,
646 norepinephrine, Val, dopamine, Ile, Leu, Phe, and Arg were analyzed. The LODs for AAs
647 ranged from 0.65–5.00 nM, while for catecholamines, the LODs ranged from 58–73 nM.
648 Human plasma and vitreous perfusate samples treated or untreated with medication after
649 intraocular hypertension were studied [116]. Another quinolone carboxaldehyde, 3-(4-
650 chlorobenzoyl)-2-quinolinecarboxaldehyde, was reported to react in the same manner. It has
651 been used in CE/LIF (488 nm) experiments to detect AAs and catecholamines in HEK293 and
652 PC12 cell samples under optimized MEKC conditions. LODs ranging from 1.4 to 100 nM were
653 achieved, which was twice higher than that achieved using the brominated compound, and had
654 a nanomolar range (barring the LODs for norepinephrine and dopamine: 60 nM with 3-(4-
655 bromobenzoyl)-2-quinolinecarboxaldehyde) [117].

656 OPA/BME derivatives are commonly used in HPLC fluorescence assays for amine
657 detection [118]. If the derivatives are not adequately stable, the reaction is rapid and can be
658 performed to label primary amines on-line at the output of a chromatographic column.
659 Nonetheless, OPA has rarely been used in CE owing to the lack of an available laser
660 wavelength. HeCd (325 nm) could be used, but it is expensive and has a short lifetime.
661 However, a 100-mW 365-nm UV LED (expensive, with short lifetime) was used effectively to
662 excite Glu and Asp OPA derivatives (which are formed off-line), and an LOD of 47 nM was
663 attained for each [119]. The authors described an on-line labeling method that involved the
664 introduction of both the sample and derivatization reagents (OPA/BME) into a mixing tee at a
665 rate of 1.2 μ L/min using a syringe pump. The outlet of the reaction tee was connected to a 100
666 μ m ID capillary. The reaction time (dependent on the length, flow rate, and capillary ID) was
667 70 s. The reaction capillary was interfaced with the separation capillary (25 μ m ID, 8 cm
668 effective length) through a flow-gating interface, where a crossflow (1 mL/min) of separation
669 buffer was continuously applied across the gap to prevent analyte transfer between the two
670 capillaries. The sample was injected into the separation capillary via temporary disruption of
671 the crossflow; meanwhile the separation capillary was maintained at constant high voltage. The
672 reported LOD was approximately 7 nM for these two AAs (Fig. 6). The use of a laser-drilled
673 capillary has been described as well, where an aperture created using laser ablation was used

674 for mixing OPA/BME with free Lys Arg, Glu, and Asp separated by CE; micromolar LODs
675 were achieved [120]. 3-mercaptopropionic acid, N-acetyl-L-cysteine (NAC), and N-isobutyryl-
676 L-cysteine were used instead of BME for OPA in-column derivatization, as these form more
677 stable derivatives. In addition, NAC and N-isobutyryl-L-cysteine have an asymmetric carbon,
678 which forms diastereoisomers after derivatization of a mixture of enantiomers, which can be
679 separated using CE. The use of NAC and γ -CD enabled the most effective indirect
680 enantioseparation of 16 AAs with resolution above 2.6. In this case, the derivatization occurred
681 within the capillary through “sandwich injection”: the derivatization solution was injected
682 sequentially before and after the sample [121]. The selective enrichment of aminothiols labeled
683 with OPA and BME using Tween 20-capped gold nanoparticles prior to CE-LIF analysis (with
684 the instrument equipped with a 355-nm diode-pumped solid-state laser) yielded an LOD of 4
685 nM for Hcy, which was equivalent to an eleven-fold improvement in sensitivity [122].

686 2-((5-fluoresceinyl)aminocarbonyl)ethyl mercaptan, which emits fluorescence at 488
687 nm, is also used along with OPA for AA detection; 2-((5-fluoresceinyl)aminocarbonyl)ethyl
688 mercaptan replaces the conventional thiol used for OPA derivatization. The presence of Tris(2-
689 carboxyethyl)phosphine prevents thiol loss resulting from S-S bridge formation. Owing to the
690 reactivity of OPA, the reaction is considerably rapid (<30 s). The LODs achieved for dopamine,
691 norepinephrine, Glu, and Asp were shown to be below 0.5 nM [123].

692 OPA is highly suitable for LIF detection when on-line labeling can be performed. However, the
693 requirement of a UV light source limits its use. CBQCA is suitable for the detection of most
694 AAs and their metabolites (except Pro and Trp); the sensitivity achieved is in the nanomolar
695 range, and the separation procedures are effective at resolving most AAs. Although it is more
696 expensive than NDA, it can be excited at 488 nm, which is useful because most instruments
697 available exhibit emission at this wavelength.

698

699 **4.2.3. Fluorescein-based dyes**

700 Fluorescein-based dyes are widely used in studies with CE/LIF experiments. For
701 example, FITC has been used for almost 50 years to label the amino functions of AAs and
702 proteins [124]. These dyes are used because they have a high fluorescence yield (significantly
703 higher than that of previously described reagents). Cheng and Dovichi were the first to use these
704 in CE/LIF studies [125]. These have been used in several technical advances in fluorescence
705 detectors.

706

707 **4.2.3.1. Fluorescence detector optimization using an FITC-labeled AA**

708 Jong and Lucy [126] were pioneers in the designing of LEDIF experiments using FITC
709 derivatives. A 470-nm LED was focused on a capillary with a lens obtained from a discarded
710 DVD-ROM. The fluorescence was recorded at 45° through an ocular obtained from a pen
711 microscope and was passed through a band-pass filter to a photodiode. Using this simple device,
712 the LOD obtained (which was above the micromolar range) for FITC-labeled AAs was higher
713 than that obtained using an LIF detector [127]. Understandably, the device in question was less
714 sensitive than a commercial instrument; however, the estimated cost of the detector was claimed
715 to be approximately \$50. To enhance light transmission in a LEDIF detector, glycerol was used
716 to optimize i) irradiation using a 470-nm LED in the optic fiber illuminating the capillary and
717 ii) measurement of fluorescence between the capillary and the collecting optical fiber. Glycerol
718 was employed to reduce the refractive index discontinuities in the silica/air interfaces. This led
719 to a 2.8-fold improvement in the S/N ratio. The LOD for FITC-labeled AAs (Lys, Trp, and Phe)
720 was between 10.9 and 4.8 nM [128]. Of note, glycerol is relatively volatile, which may have
721 affected the stability of detection.

722 The construction of a miniaturized liquid core waveguide-CE system and a LEDIF
723 system (470 nm) was reported [129]. The system consisted of a Teflon AF-coated silica
724 capillary, which served both as the separation channel and as a transversely illuminated liquid
725 core waveguide. This device took advantage of flow injection-based split-flow sample
726 introduction through a falling-drop interface. The Teflon AF separation capillary was fixed on
727 a glass slide. The inlet reservoir also served as the falling-drop interface for coupling with the
728 flow injection system. A 478-nm LED served as an excitation source near the outlet of the
729 capillary. At this outlet, a buffer reservoir containing a large-core optical fiber aligned with the
730 capillary channelized the emitted fluorescence (trapped in the Teflon AF capillary) into a PMT.
731 No focusing arrangement was employed. AAs labeled using FITC have also been studied. A
732 total of 144 samples/h could be analyzed with precision using the continuous flow injection of
733 a series of samples (30 µL each). Baseline separation was achieved for FITC-labeled Arg, Phe,
734 and Gly. The LOD ranged from 1.3 µM (Arg) to 1.9 µM (Phe, Gly). Kostal *et al* [130] described
735 a similar miniaturized fluorimetric detection cell, where the excitation wavelength was 488 nm
736 and a compact CCD spectrometer was connected to the detection optical fiber for detecting the
737 fluorescence signal. This detection cell was used with off-line labeling (with FITC and
738 iodoacetamidofluorescein [IAF]) to detect fluorescein-labeled AAs in plasma. The levels
739 measured in healthy volunteers were compared to those measured in patients with inherited

740 metabolic disorders. The LODs were better than those achieved using a conventional LIF
741 detector.

742 Using a confocal microscope, Zhu *et al* [131] attempted to determine why the best LIF
743 sensitivity is obtained in CE when the laser does not illuminate the capillary along the axis used
744 in fluorescence collection. A shift of 20 μm from the axis of the capillary helped reduce the
745 noise and increase the S/N ratio ($\times 8.3$). Separation of FITC-labeled Arg, Phe, Gly, and Glu at
746 100 pM was presented. Additionally, a compact handheld quasi-confocal LIF detector ($9.1 \times$
747 6.2×4.1 cm, weighing 350 g) with a 450-nm laser diode was also constructed. Arg, Phe, Ala,
748 Gly, Glu, and Asp labeled with FITC were separated with an LOD of approximately 0.4 nM
749 [132], which indicated good sensitivity.

750 4.2.3.2. The use of FITC in CE/fluorescence

751 Even though FITC is largely used for testing new detectors and instrument
752 arrangements, its reaction with an amine aqueous medium generates a high number of
753 impurities that are responsible for numerous parasitic peaks in electropherograms. FITC is not
754 fluorogenic, and its peaks are considerably high compared to those of AAs owing to its high
755 abundance in the reaction mixture, along with that of its degradation products. However, as its
756 derivatives are highly fluorescent, the sample obtained after derivatization can be diluted, and
757 adequate separation can be achieved with considerably high sensitivity. The fluorescein nucleus
758 can be excited using a 488-nm Ar laser, with its fluorescence yield depending strongly on the
759 pH of the separation buffer [133], which must be above 9.0–9.6 (pKa of the phenolic function)
760 to generate the dianion form [134]. Lalljie and Sandra [135] stated that it is difficult to label
761 AAs at a concentration below 0.1 μM if quantitative results are to be obtained. Therefore, FITC
762 finds application in several biochemical studies. For example, it has been applied to AA
763 determination in cerebrospinal fluid [136] and wine [137], where AAs are present at
764 concentrations above the micromolar range, but the samples are diluted 1000- or 2000-fold prior
765 to injection to obtain the best resolution and the lowest influence of the sample matrix on the
766 separation process. Compared to UV absorption, the detection process is significantly more
767 selective [137]. FITC has been used widely for AA quantitation (at concentrations above 0.1
768 μM) [138]; however, its reaction time is high at ambient temperature. Zinellu *et al* [139] devised
769 a 20-min derivatization procedure at 100 $^{\circ}\text{C}$ using a 200 mM Na_2HPO_4 (pH 9.5) buffer; 12-min
770 AA separation procedures were performed using an 18 mM phosphate running buffer (pH 11.6),
771 and several biological samples (cultured cells, CSF, saliva, and vitreous humor) were studied

772 to determine the limits of quantitation (approximately 0.2 μM) (S/N ratio = 10). In addition to
773 these developments with FITC, the migration time reproducibility rates of PITC-, FITC-, and
774 tetramethyl rhodamine isothiocyanate-labeled AAs have been investigated. Several methods to
775 improve the procedures have also been suggested [140].

776 Tan *et al* [98] described a combined detection system based on C^4D and fluorescent
777 detection for CE in a common cell. A blue LED (470 nm) served as the excitation source, and
778 an optical fiber was employed to measure fluorescence. Inorganic ions (K^+ , Li^+ , Mg^{2+} , Ca^{2+} ,
779 and Ba^{2+}), FITC-labeled AAs (Trp, Phe, Lys, and Gly), and a small peptide were separated and
780 detected using the combined system, with LODs ranging from 0.8 to 2.5 μM for AAs.
781 Electropherograms with good resolution were presented by superimposing the signals of the
782 conductometer for inorganics and the fluorometer for AAs, both in the same run.

783 A capillary array electrophoresis system with a rotary confocal fluorescence scanner has
784 been described [141], in which a high-speed direct-current rotary motor, combined with a rotary
785 encoder and a reflection mirror, directed the excitation laser beam precisely onto an array of
786 capillaries, which were symmetrically distributed around the motor. The separation and LIF
787 detection (488 nm) of enantiomers of Glu, Met, and Trp labeled with FITC were also described.

788 Three different LEDs (430, 450, and 480 nm) were collimated into a single-mode optical
789 fiber for fluorescence detection using the same in-column fiberoptic LIF detector. This
790 excitation source allowed the simultaneous determination of FITC-labeled L-Asn (480 nm), 4-
791 fluoro-7-nitro-2,1,3-benzoxadiazole-labeled (NBD-F) epinephrine (450 nm), and CBQCA-
792 labeled L-Leu (430 nm). The LODs attained were 0.8, 120, and 40 nM, respectively.
793 Fluorescence was detected using a PMT, which measured the emission wavelength of the three
794 dyes. Migration was implemented using a 75 μm ID capillary. After single-LED excitation
795 (corresponding to one of the three dyes) for analyzing the mixture of the three labeled
796 molecules, the electropherograms showed two main peaks (for the dye and the corresponding
797 labeled AA accurately excited at the given wavelength) and a small peak corresponding to other
798 weakly excited dyes. Therefore, at 430 nm, CBQCA-Leu was primarily detected, whereas a
799 short peak of FITC was observed. At 450 nm, NBD-F- and NBD-labeled epinephrines were
800 primarily detected along with FITC. At 480 nm, FITC and FITC-Asp were detected while a
801 short peak of NBD-F was recorded. The authors claimed that the performance of the newly
802 developed multi-wavelength LED excitation source was superior to that of the single-
803 wavelength LED [142].

804 A coated capillary with a buffer containing hexadimethrine bromide and 20% isopropyl
805 alcohol was used for the analysis of FITC-labeled AAs in beer using a 470-nm LED or a 488-
806 nm Ar laser [143]. The resolution achieved with the laboratory-made instrument was
807 significantly poorer than that achieved using the commercial device, because the light beam of
808 the LED was ~3-fold wider than the laser beam. In addition, the LODs of the FITC-labeled
809 compounds were approximately 1.8-fold poorer than those obtained with the conventional
810 fluorescence system when the LED was used.

811 Multiphotonic excitation fluorescence (MPEF) using a diode laser (808 nm, 1 W) was
812 described by Chen *et al* [144]. The separation of off-line FITC-labeled AAs was demonstrated
813 using CZE and MEKC. Although the LODs of AAs were not specified by the authors, the one
814 for Rhodamine B was reported to be 1.2 μM , which is considerably high. The effectiveness of
815 MPEF detection and classic fluorescence detection (at 488 nm) were compared using six FITC-
816 labeled biogenic amines (histamine, spermidine, cadaverine, putrescine, phenylethylamine, and
817 spermine). MPEF was reported to show superior electrophoretic resolution with detection
818 volume in the attoliter range. The quantitative analysis of varying concentrations of biogenic-
819 amine species seemed to indicate that this approach may help obtain a yoctomolar LOD. MPEF
820 coupled with MEKC has been used to determine the biogenic-amine profile of decayed oriental
821 crucian, wherein LIF detection was found to be considerably more sensitive than MPEF [145].

822 In conclusion, FITC offers the key advantages of high fluorescence yield; good
823 reactivity with an amine group facilitating derivatization at submicromolar concentrations;
824 ability to derivatize primary and secondary amines; and ability to be doubly charged, which
825 results in compounds bearing three negative charges. However, it is not fluorogenic, and its
826 purity is ~90 %, which makes the identification of unknown compounds difficult, because
827 numerous FITC peaks are formed.

828 FITC is the most sensitive dye for LIF detection, as the LODs obtained are in the
829 picomolar range. Moreover, its reaction rate is considerably lower (than that of the above
830 mentioned dye), and can extend to several hours at ambient temperature. It is difficult to identify
831 some AAs when they are present at low concentrations, because they migrate at the same
832 migration rate as FITC and its degradation byproducts. Furthermore, FITC is reported to
833 ineffective as a labeling agent at concentrations lower than the micromolar range. It can only
834 be used to label AAs present at micromolar concentrations, that too, primarily acidic and basic
835 ones, which migrate behind or ahead of FITC and its byproducts.

836

837 4.2.4. Other fluorescein-based reagents

838 Dichlorotriazinylaminofluorescein (DTAF) has also been used for LIF detection
839 coupled with CE. It appears to be more reactive at lower concentrations than FITC, which leads
840 to the quantitation of AAs even at lower levels (10 nM) [135]. DTAF has been used in the
841 quantitation of phospho-AAs using MEKC. Different variables affecting the derivatization
842 (DTAF concentration, pH, temperature, and time) and separation (surfactant type, pH, and
843 buffer concentration) have been studied. In one study, baseline separation of three phospho-
844 AAs was achieved in less than 11 min with good reproducibility. The LODs ranged from 0.5–
845 1.0 nM. The method was used to detect phospho-AAs in hydrolyzed phosphorylated-protein
846 samples [146]. Molina and Silva [147] proposed the use of in-capillary derivatization with
847 DTAF; they emphasized that the success of the in-capillary reaction of analytes by LIF detection
848 hinges on the “excellent” labeling chemistry of the reagent. The optimization of the
849 electrophoretic conditions and mixing step in this protocol allowed the determination of AAs,
850 biogenic amines, and phospho-AA herbicides with LODs in the $\mu\text{g}\cdot\text{L}^{-1}$ range and relative
851 standard deviations ranging from 3.5% to 5.8%. Phospho-AAs have also been derivatized using
852 N-hydroxysuccinimidyl fluorescein-O-acetate at 40 °C for 40 min in borate buffer (pH 8.5).
853 Fluorescein-O-acetate fluoresces at 488 nm, and LODs in the nanomolar range can be achieved
854 [148]. 5-carboxyfluorescein-N-succinimidyl ester has been used with CE/LIF (488 nm) for the
855 quantitation of Asp and Glu in rat periaqueductal gray matter. The LODs were reported to be
856 0.69 and 0.81 nM, respectively [149]. 6-carboxyfluorescein-N-succinimidyl ester has been used
857 for precolumn derivatization of gabapentin in plasma. Optimal separation and detection were
858 achieved in an electrophoretic buffer containing 50 mM sodium borate (pH 9.5) using an Ar
859 laser (488 nm). The calibration curve, ranging from 0.3 to 150 μM , was linear, and the LOD in
860 plasma was 60 nM [150].

861 The analytical potential of synthetic 6-oxy-(N-succinimidyl acetate)-9-(2'-
862 methoxycarbonyl) fluorescein has been investigated using CE-LIF. Derivatization was
863 performed at 30 °C for 6 min in boric acid buffer (pH 8.0). The derivatives were baseline-
864 separated in 15 min using a 25-mM boric acid running buffer (pH 9.0) containing 24 mM SDS
865 and 12.5% (v/v) acetonitrile. The LOD attained for biogenic amines was 80 pM (S/N ratio = 3).
866 The optimal results obtained using the running buffer indicated that a weak acidic BGE offers
867 better separation than a basic one. Several fluorescein-based probes for amino compounds were

868 compared. This dye has been reported to exhibit excellent photostability and pH-independent
869 fluorescence (pH 4–9). This method was applied to the detection of biogenic amines in three
870 different beer samples [151].

871 In the chapter on medical applications, we will present the use of IAF, which has largely
872 been employed for the selective identification of thiol-containing AAs and glutathione (GSH)-
873 derived peptides [152]. Maleinimide fluorescein has been used as well. Diastereoisomers can
874 be obtained with the latter, as the reaction between the thiol group and maleinimide leads to the
875 formation of an asymmetric carbon [153]. Though less popular, 5-(bromomethyl)fluorescein
876 can also be utilized to selectively detect thiol AAs and GSH. Of note, this molecule can react
877 with the carboxylic function as well. The separation of Hcy, Cys, GSH, Cys-Gly, Glu-Cys,
878 cysteamine, penicillamine, mercaptopropionylglycine, and mercaptoacetic acid (internal
879 standard) was successfully performed using this reagent, with LODs achieved between 61 nM
880 (Hcy) and 183 nM (penicillamine) [154].

881 DTAF has been described as a better nonfluorogenic dye than FITC, and its reactivity
882 allows the labeling of all AAs at low concentrations; the LODs are in the nanomolar to
883 picomolar range. The reaction rate is identical to that of FITC (several hours at ambient
884 temperature). IAF is highly suited for the detection of thiols; it has been used extensively in
885 several applications owing to its high fluorescence, selectivity for the -SH function, and
886 capacity for excitation with the 488-nm line of an Ar laser or a 480-nm LED.

887

888 **4.2.5. Other amine reagents**

889 Fluorescamine is another dye that is widely used for labeling AAs [155]. Nonetheless,
890 in CE, its use is restricted by the lack of an available laser or diode that can generate excitation
891 at 360–390 nm. However, an AA mixture, after derivatization with fluorescamine, was analyzed
892 using a 355-nm pulsed laser, with LODs obtained in the nanomolar range [77]. Fluorescamine
893 has been used to separate enantiomers using MEKC with hydroxypropyl- β -CD [156]. This has
894 led to the development of one of the most remarkable applications of CE/LIF—the Mars
895 Organic Analyzer [157]. This is a microfabricated CE instrument for sensitive AA biomarker
896 detection. It consists of a four-wafer sandwich combining glass CE separation channels,
897 microfabricated pneumatic membrane valves and pumps, and a nanoliter fluidic network. It
898 allows the analysis of AAs at concentrations ranging from 1 μ M to 0.1 nM. The Mars Organic
899 Analyzer was first used to analyze soil extracts from the Atacama Desert (Chile), and could
900 detect AAs present at 70 parts per trillion to 100 parts per billion in jarosite, which is a sulfate-

901 rich mineral associated with the liquid water that was recently detected on Mars. Kang *et al*
902 [158] developed an in-column derivatization method for a fully automated assay of Hcy and
903 other thiols. It involved the direct injection of a sample containing Hcy and 4-aminosulfonyl-7-
904 fluoro-2,1,3-benzoxadiazole, which reacted for 10 min at 50 °C. Hcy was detected within 7 min,
905 and the LOD obtained for Hcy with LIF detection was 5 nM; this decreased to 2.5 nM with
906 precolumn LIF detection.

907 Based on a report by Ruyters and de Wal [159], NBD-F has been used regularly in
908 analytical studies, similar to 4-chloro-7-nitro-2,1,3-benzoxadiazole [160]. The NBD nucleus
909 can be excited at 470–490 nm. The reactivity of these dyes was studied 40 years ago by Imai
910 and Watanabe [161]. Zhang *et al* [162] used NBD-F for in-capillary derivatization. The best
911 NBD-F/sample molar ratio was found to be 215, and the injection process, spanning 4 s for the
912 sample and 2 s for the NBD-F solution, was performed in a capillary whose temperature was
913 maintained at 45 °C. The LOD was ~100 nM for Ala and 600 nM for Asp. With off-line
914 labeling, the separation of DL-Ser was studied using 40 mM hydroxypropyl- β -CD and
915 implemented in the rat brain tissues for the detection of D-Ser, with an LOD of 300 nM [163].
916 However, the major issue with this dye is that its fluorescence yield is highly sensitive to the
917 polarity of the separation buffer, and highest fluorescence is obtained in a low-polarity solvent
918 [164]. EMMA was also used with NBD-F, and the ratio of the dye to AA was studied. The
919 LODs obtained were in the nanomolar range [165]. R(-)-4-(3-isothiocyanatopyrrolidin-1-yl)-
920 7-(N,N-dimethylamino sulfonyl)-2,1,3-benzoxadiazole was synthesized for enantiomeric
921 separation using fiberoptic LEDIF and CE, and an LOD of ~3 μ M was achieved for DL-Tyr
922 derivatives [166].

923 Maleinimide eosin has been used to study thiols. We have previously indicated that
924 diastereoisomers are obtained as the reaction of the thiol residue with maleinimide results in the
925 formation of an asymmetric carbon. In a study, an inexpensive, 515-nm diode laser was used as
926 the source [167]. The LOD obtained for GSH was 0.18 nM, and the derivatization conditions
927 were optimized.

928 NBD-F is certainly a popular dye for AA labeling. Micromolar concentrations of AAs
929 can be detected, and the labeling rate appears to be higher than that of FITC or DTAF but lower
930 than that of NDA or CBQCA. The 7-nitro-2,1,3-benzoxadiazole nucleus is highly sensitive to
931 electrolyte polarity; this poses a limitation when data are adjusted for evaluating migration.

932

933 In summary, NDA- and CBQCA-labeled AAs are largely used to quantitate AAs in the
934 presence of KCN; their reactivity levels are good, as are their fluorescence yields. Nevertheless,
935 these dyes cannot be used to label secondary amines. Trp is considerably difficult to detect in
936 most such studies. For the selective detection of thiols, IAF is also commonly used. While
937 attempts at derivatization with other derivatives are documented, only a few studies have
938 described the process, as these reagents are not commercially available or as the resultant
939 sensitivity may be insufficient. FITC has been widely used; it has several advantages (a high
940 fluorescence yield and a charge); however, it is not fluorogenic, and only low purity FITC
941 (90%) is available commercially. It can be used when AAs present at micromolar concentrations
942 are to be detected. Additionally, 1000–2000-fold dilution of the sample in water prior to
943 injection is necessary to ensure effective separation.

944

945 **5. CE/MS**

946 ESI MS allows the determination of the m/z values of $[M+H]^+$ ions of each AA and the
947 recording of electropherograms for the m/z values. Therefore, using this method, an AA can be
948 characterized based on its m/z value and migration time. In contrast, in other detection methods,
949 different AAs are only characterized based on their migration time. Moreover, in ESI/MS/MS,
950 the $[M+H]^+$ ions of the AA can be fragmented into smaller ions, and the m/z values of the
951 molecular ion(s) F^+ is characteristic for each AA. Therefore, for each AA, if we consider its
952 diagnostic fragmentation $[M+H]^+ \rightarrow F^+$, we introduce a supplementary parameter that increases
953 the selectivity of detection. Consequently, the AA will be characterized based on its migration
954 time, the m/z value of $[M+H]^+$, and the specific m/z value of F^+ . Precise determination of the
955 m/z value of $[M+H]^+$ using HRMS helps determine the chemical formula of the compounds,
956 based on which researchers can detect several hundred nonproteinogenic AAs.

957 Fanali *et al* [168] and Ferré *et al* [169] recently published review articles on CE/MS and
958 its state-of-the-art applications; among them, some applications are discussed. CE-ESI/MS is
959 now popularly used for the detection of AAs after pioneering developments by Soga and Heiger
960 [170]. Since 2000, numerous authors have described CE/MS applications where AAs are
961 detectable even when their identification is challenging owing to low molecular mass [171,172].
962 Table 4 summarizes the analytical conditions of the studies reviewed.

963

964 **5.1. General CE/MS studies**

965 Soga and Heiger [170] used simple conditions for AA separation [1 M FA and a sheath
966 flow of 10 $\mu\text{L}/\text{min}$ of 5 mM ammonium acetate in 50% (v/v) methanol–water in a 100 cm long
967 50 μm ID capillary] using Agilent CE and a quadrupole MS instrument. They selected the
968 multiple-reaction monitoring mode (MRM) to study nine free AAs and monitored protonated
969 $[\text{M}+\text{H}]^+$ ions for AA detection, with a sampling time of 44 ms for each. At an m/z value of 132,
970 isobaric ions of Leu, Ile, and hydroxy-Pro were found to be well separated. The LODs ranged
971 from 0.3–11.0 μM . Around the same time, Klampfl and Ahrer [173] reported a study in which
972 CE/MS was used to quantify free AAs in infant food samples using a sheath flow interface (4
973 $\mu\text{L}/\text{min}$). Based on the zwitterionic nature of the analytes, two different modes of separation
974 and detection were tested: a basic electrolyte (established using a 100-mM triethylamine
975 electrolyte) with negative-ion MS analysis and a highly acidic carrier electrolyte (300 mM FA)
976 with MS detection in positive-ion mode. The latter was found to be the optimal solution. Free
977 AAs in different infant food preparations were analyzed without sample pretreatment.

978 DL-2-amino-2-methyl-3-(3,4-dihydroxyphenyl) propanoic acid (MDOPA) and DL-2-
979 amino-3-(3,4-dihydroxyphenyl) propanoic acid (DOPA) enantiomers were separated and
980 identified using electrokinetic chromatography coupled with ESI^+ MS [174]. A double-junction
981 CE/MS interface was used to maintain the separation efficiency and alleviate ion suppression
982 from sulfated β -CD. The double-junction interface consisted of an inlet reservoir connected to
983 a separation capillary leading to a liquid junction reservoir and a capillary of 5 cm/50 μm (ID)
984 adjoining the separation capillary. The other end of the connecting tube was adjusted in the
985 sheath liquid reservoir of the ESI emitter. At an S- β -CD concentration of 2%, the CDs acted as
986 carriers of the positively charged molecules DOPA and MDOPA. During separation (reverse
987 polarity), the S- β -CD anions carried cationic analytes from the inlet reservoir toward the
988 junction reservoir. By controlling the polarity of the connecting column, the CD anions were
989 retained in the junction reservoir, whereas the positively charged analytes continued to migrate
990 to the ESI source for detection. S- β -CD was prevented from entering the ESI source, and ion
991 suppression was avoided. In this arrangement, all enantiomers of DOPA and MDOPA were
992 separated and detected efficiently with LODs in the range of 0.5 μM in MRM, and the
993 repeatability of migration times and peak areas ranged from 2.5%–8.0% (RSD%, $N = 3$) and
994 10.9%–19.5% (RSD%, $N = 3$), respectively. This method was used for analyzing methyl-DOPA
995 tablets [174].

996 Sheathless CE/ ESI^+ MS is highly sensitive owing to the low CE flow rates (nL/min); a
997 split-flow technique [175] for interfacing CE with MS was used for the detection of

998 underivatized AAs for separating D/L-enantiomers. The AAs were separated and detected at
999 low-femtomole levels using a fused-silica capillary with length 130 cm and ID 20 μm modified
1000 using 1 M FA and a 30 mM 18C6H4 solution as the BGE. The same was also used for the
1001 separation of L-Arg and L-canavanine (an analog of Arg) in a complex mixture containing all
1002 standard proteinogenic AAs. In a study on blood samples, two metabolic diseases
1003 (phenylketonuria and tyrosinemia) were diagnosed [176].

1004 The last study mentioned has launched a debate between researchers who favor the
1005 sheath flow and sheathless methods.

1006 A third interface was devised by Wojcik *et al* and commercialized by CMP Scientific.
1007 This interface used an electrokinetically driven sheath flow (and not mechanically pumped
1008 sheath flow) to generate a stable nanospray [177]. The generation of negative ions during
1009 electrospray requires the application of a negative potential to the emitter. To attain a stable
1010 flow and the best sensitivity, the surface chemistry of the emitter can be manipulated. An amino-
1011 coated borosilicate glass emitter with a positively charged surface and a negatively charged
1012 double layer was prepared, and the separation capillary was threaded into the emitter tip. The
1013 emitter preparation procedure had sufficient reproducibility. Detection of the metabolites
1014 extracted from stage 1 *Xenopus laevis* embryos facilitated the manual identification of over 100
1015 features [178].

1016 As described above, MS helps increase both the sensitivity and selectivity of CE.
1017 Mamani-Huanca *et al* [179] suggested the use of in-source fragmentation of 57 AAs to identify
1018 the mechanisms underlying major fragmentation reactions observed for diagnostic ions
1019 generated in ESI⁺ HRMS. The in-house library of diagnostic ions was used to establish a
1020 workflow for the targeted extraction of AAs that are not easily identifiable. Therefore, the
1021 authors showed that fragmentation mechanisms constitute an informative reference for accurate
1022 molecular identification.

1023

1024 **5.2. Developments in sheath flow CE/MS (CE/SF-ESI-MS)**

1025 Soga *et al* [180] proposed a method for AA separation using CE under acidic conditions
1026 (1 M FA as a BGE) and detection using tandem MS (MS/MS). Using a sheath flow (5 mM
1027 ammonium acetate in 50% [v/v] methanol–water) of 10 $\mu\text{L}/\text{min}$, they found that the position of
1028 the electrospray probe is a factor that affected sensitivity. Through MRM detection for
1029 increasing selectivity and sensitivity, they showed that the LODs for the 32 free AAs studied

1030 ranged between 0.1 and 14 μM , which was adequately sensitive for AA detection in urine
1031 samples. Because AAs yield characteristic MS/MS spectra, the MRM approach is selective,
1032 quantitative, and reproducible; however, it does not permit the detection of unknown
1033 compounds. The use of CE/ESI-MS and CE/ESI-MS/MS for the detection of nonproteinogenic
1034 AAs helped identify the oxidation and nitrosation products of N^g-hydroxy-L-Arg. Citrulline,
1035 cyano-Orn, and N^g-nitroso-arginine could be identified using the standard [181].

1036 To determine the exact mass and achieve high sensitivity at low m/z values, Hirayama
1037 and Soga [182] proposed the use of two lock masses (the ¹³C isotope ion of the methanol dimer
1038 with m/z = 66.0632, and a [hexakis(2,2-difluoroethoxy)phosphazene] protonated ion with m/z
1039 = 622.0290). High mass-spectrometric resolution helped obtain resolved electrophoretic peaks
1040 using single ion monitoring (SIM). Most LODs ranged from 100–300 nM.

1041 In transient-isotachopheresis using a pH junction in a stacking process with CE/MS,
1042 AAs present at nanomolar concentrations were detected in samples with AAs diluted in
1043 ammonium acetate buffer, where a 1 M FFA solution served as the BGE. The migration behavior
1044 of charged metabolites was modeled (for assessing the role of absolute mobility and pKa) to
1045 support MS characterization in a multiplexed approach for studying the selective nutrient uptake
1046 behavior of *Escherichia coli*. Computer simulations in Simul 5.0 [183] facilitated the *de novo*
1047 identification of unknown nutrients [184].

1048 CE/ESI-MS has also been used for detecting anionic metabolites in urine. Among nucleosides,
1049 carboxylic acids, and phosphorylated species, Pro and pyroglutamic acid were detected in the
1050 micromolar range using different water/methanol (1:1, v/v) solutions containing 25 mM
1051 triethylamine or ammonium acetate at pH 11.7 or 9.0, and a sheath liquid containing one of
1052 them at 5 mM concentration. A study using human urine samples led to the identification of an
1053 average of 231 molecular features [185].

1054 HRMS increases the selectivity of MS, which helps improve metabolite detection. The
1055 use of CE/HRMS has been suggested for fluxomic studies, in which AA detection using ¹³C
1056 labeling is conducted for carbon flow calculation. ¹³C labeling analyses usually involve
1057 conventional gas chromatography (GC)/electron ionization (EI)-MS after AA derivatization for
1058 isolation of N,O-*tert*-butyldimethylsilyl derivatives. Using CE-SF-ESI/HRMS, the same
1059 treatment used in GC/MS was used for flax (*Linum usitatissimum* L.) embryos. Nonetheless, no
1060 derivatization was performed to volatilize them. The water-solubilized and lyophilized AA
1061 extract was directly injected into a CE instrument. It was shown that Val, Leu, and Ala were
1062 not synthesized from the same pyruvate pool during the accumulation of reserves in flax seeds

1063 [186]. A grounded nebulizer of the CE/SF-ESI-MS source was constructed to measure the
1064 concentrations of 28 AAs using ESI⁺ and 6 organic acids using ESI⁻ HRMS; this approach
1065 helped distinguish between homoarginine (m/z 189.1346) and N⁶-trimethyl-Lys (m/z
1066 189.1598), which have the exact same migration time in CE. The significant improvement in a
1067 high-resolution setup enabled researchers to identify 270 metabolites [187] (Fig. 7).

1068 Neonatal screening for inborn defects of metabolism was realized using CE/MS
1069 detection of AAs and acylcarnitines in DBS samples. On-line sample preconcentration and
1070 desalting steps helped improve the sensitivity and limit the ionization suppression or
1071 interferences caused by the presence of isomers and isobars. During these steps, an acidic BGE
1072 was used, whereas the sample was buffered with ammonium acetate. The buffer discontinuity
1073 enabled the electrokinetic focusing of AAs and acylcarnitines; meanwhile, strong electrolyte
1074 salts (Na⁺ and NH₄⁺) present in the sample migrated ahead of the analytes. The linearity of
1075 twenty target metabolites was determined in five replicates at five different concentrations over
1076 a 90-fold concentration range for most AAs. A 200-fold concentration range was used for Arg
1077 and 4-OH-Pro. Interday precision of quantitation was reported to be below 11% [188].

1078 A multivariate strategy for *de novo* quantification of AAs and other cationic metabolites
1079 was designed using CE-ESI-MS. Multivariate calibration was implemented between the
1080 measured relative response factor of polar molecules and the physicochemical parameters
1081 associated with ion evaporation in ESI-MS: the octanol–water distribution coefficient (log D),
1082 absolute mobility, molecular volume, and effective charge. It was revealed that a limited set of
1083 properties can be analyzed to predict the relative response factor of various classes of molecules,
1084 provided that an appropriate training set is validated and ion responses are normalized to an
1085 internal standard. Micromolar levels of metabolites added into red blood cell lysates were
1086 quantified using CE-ESI-MS in this model. The authors claimed that the study demonstrated
1087 the feasibility of virtual quantification of low-abundance metabolites in real-world samples
1088 based on physicochemical properties estimated using computer modeling. This method also
1089 helped obtain a wider view of the disparities in solute responses during ESI-MS. The predicted
1090 ionization efficiency may enable the rapid and semiquantitative analysis of a newly discovered
1091 chemical when standards are unavailable [189].

1092 An assay using 1 M FA buffer was developed by Wakayama *et al* [190], who analyzed
1093 34 amines and AAs simultaneously with 12 organic acids without derivatization. The LODs
1094 ranged from 2.5 μM in the ESI⁺ mode to 5 μM in the ESI⁻ mode. In cases in which the total ion
1095 electropherogram was difficult to interpret, the electropherograms were used to identify each

1096 AA with ease. The technique was applied to the metabolomic analysis of diurnal changes in
1097 pineapple leaves, in which changes in Asp, Asn, and citrate concentrations were measured.
1098 Butylation of the carboxylic function of AAs has been reported to improve ionization efficiency
1099 rates and detection sensitivity. In addition, the esters formed have higher masses and ensure
1100 better mass selectivity. Sanchez-Hernandez *et al* [191] added butanol at 80 °C to a dry residue
1101 of AAs (Orn, β -Ala, GABA, alloisoleucine, citrulline, and pyroglutamic acid) extracted from
1102 vegetable oils in a 30-min reaction. Under acidic migration conditions and with ESI/MS/MS
1103 detection, they achieved LODs between 0.04 and 0.19 ng/g.

1104 AA fingerprints from index, middle, and ring fingers were investigated for the
1105 improvement of existing fingerprint enhancement techniques using an optimized CE/ESI⁺-MS
1106 method. Using full mass spectra and extracted ion electropherograms, nine underivatized AAs
1107 were quantitated in a fingerprint sample (Orn, Lys, His, Gly, Ala, Val, Ser, Pro, and Asp). Gly
1108 and Ser were found to be the most abundant AAs. Ile/Leu (unseparated) and Glu were only
1109 detected and not quantified, as they were present at concentrations below the quantitation limit.
1110 Overall, 17 AAs yielded calibration data with a quantitation limit ranging from 20 ng (Lys) to
1111 180 ng (Met) when deposited on a Mylar film used for AA fingerprint collection. MS/MS
1112 fragmentation experiments were conducted for additional identity confirmation (except for Gly,
1113 which does not fragment). The authors mentioned that the migration times had appropriate
1114 CV% (between 9.6% and 14.6%), with the MS technique being adequately selective for
1115 confirming the identity of the compound migrating between 12.9 min (Arg) and 29.3 min (trans-
1116 4-hydroxyproline) [192].

1117 The kynurenine pathway of Trp catabolism has been studied using CE/ESI⁻-MS. Three
1118 specific metabolites, 3-hydroxyanthranilic acid, quinolinic acid, and picolinic acid, were
1119 quantitated without any isotopic internal standard. A covalently coated sulfonated capillary was
1120 prepared, and different separation and ionization parameters (such as pH, the type of BGE, and
1121 the type of organic modifier) and the optimization of ESI^{+/-}-MS modes were tested [193]. The
1122 separation time was less than 10 min. The authors reported the migration profile of the initial
1123 substrate, 3-hydroxyanthranilic acid, as well as the formation of picolinic acid and quinolinic
1124 acid after the double-enzymatic reaction of 3-hydroxyanthranilate-3,4-dioxygenase and α -
1125 amino- β -carboxymuconate- ϵ -semialdehyde decarboxylase.

1126 Chirality has also been studied effectively using CE/MS; recently, Lee *et al* [194]
1127 proposed the use of a partial-filling technique to reduce contamination of the ESI source by the
1128 CS, *i.e.*, 18C6H4, which is nonvolatile. In this partial-filling experiment, the capillary contained
1129 two electrolytes: one on the injection side and another one on the MS side. Here, the length of

1130 the separation zone (on the injection side) was adjusted to 70% of the capillary, and the zone
1131 was filled with 30 mM 18C6H4 in water, and the other 30% (on the MS side) was filled with 1
1132 M FA. The complex AA/18C6H4 ions could not be observed, whereas the (AA+H)⁺ ions were
1133 predominant. The enantiomers of the isobaric ions (DL-alloisoleucine, DL-Ile, and DL-Leu)
1134 were successfully separated using CE. LODs ranging from 13 μM (Gly) to 0.5 μM (Phe) were
1135 achieved. A derivatization protocol was also designed to separate the D/L enantiomers of Ser,
1136 Asn, Asp, Gln, and Glu using (+)-1-(9-fluorenyl)ethyl chloroformate. The resultant separation
1137 of diastereoisomers was found to be dependent on the pH of the BGE (150 mM acetic acid
1138 adjusted to pH 3.7 using NH₄OH). Submicromolar concentrations were detected, and the
1139 method was evaluated for CSF analysis. It was concluded that the matrix effect was marginal,
1140 and the recovery rates ranged from 46% to 92% [195].

1141 FITC has been used to derivatize Orn to facilitate the separation of D/L enantiomers,
1142 and the derivative has been studied using CE-ESI⁺/MS/MS. The [M+2H]²⁺ ion was the ion
1143 detected predominantly (m/z 456, doubly labeled Orn); it fragmented at m/z 522 (singly
1144 protonated FITC-Orn) and 390 (singly protonated FITC). The m/z 456 → m/z 390 transition
1145 has been used for Orn determination in beer. The optimized CE buffer contained 0.75 mM γ-
1146 CD. The LOD obtained using CE/MS/MS was 2.5 nM, whereas resolution between the two
1147 enantiomers was ~2.5. The migration durations were ~28 min, as the authors employed a long
1148 capillary [196]. The use of 6-deoxy-6-(1-(2-amino)ethylamino)-beta-CD, 6-deoxy-6-(N-(2-
1149 methylamino)pyridine))-beta-CD, and 3-mono-deoxy-3-monoamino-beta-CD as CS molecules
1150 for CE-ESI⁺-MS and CE-LIF experiments has been investigated for the enantioseparation of
1151 FITC-labeled Asp, Glu, Ala, Asn, and Arg. The presence of electrical charges in the CD is
1152 usually advantageous because it can induce additional ionic interactions with the analyte and
1153 can be used at a low concentrations compatible with ESI⁺. CE/LIF experiments with 0.5 mM
1154 3-mono-deoxy-3-monoamino-β-CD at pH 8 yielded better resolution (up to 16 for DL-Asp)
1155 between different enantiomers, with the LODs ranging from 40 to 90 nM. In CE-MS, the
1156 resolution values ranged from 0.9 (DL-Arg) to 4 (DL-Asp), and the LODs ranged from 68 to
1157 1870 nM when these AAs were assayed in vinegar and soya [197].

1158 An original study on metal (M = Zn, Cu, Mn, and Fe) complexes with Gly, known as
1159 glycinate (M(Gly)_x(H₂O)_y(SO₄)_z)_n, was performed using CE/induced coupled plasma (ICP)-
1160 MS and CE/ESI-MS/MS. The buffers used were 20 mM ammonium acetate (pH 7.4) for
1161 CE/ICP-MS experiments and 50 mM ammonium acetate (pH 7.4) for CE/ESI-MS/MS. The
1162 compounds were identified and quantitated, and the authors showed that glycinate integrity was

1163 preserved under the conditions employed. The LODs in CE-ICP/MS for ZnGly, CuGly, and
1164 MnGly were ~0.8–4.0 μM , which allowed glycinate detection in premixes or feed samples
1165 [198].

1166 CE-SF-ICP-MS and CE-SF-ESI-MS/MS have been applied for the identification of Zn^{2+} -
1167 binding ligands in Goji berry extracts [199] using 20 mM ammonium formate (pH 9) as a BGE.
1168 Electrophoretic peaks corresponding to Zn^{2+} were identified. ESI[±]-MS/MS assays of molecules
1169 containing the two most abundant isotopes of Zn revealed fragments that did not contain the
1170 Zn^{2+} ion. Nine different complexes were identified; among them, $\text{Zn}(\text{Gly})^+$ and $\text{Zn}(\text{Met} +$
1171 $2\text{H}_2\text{O} + \text{OH}^-)^+$ were detected.

1172 In conclusion, several studies on CE/MS with a sheath flow interface have been
1173 published in which the flow rate ranged between 5 and 10 $\mu\text{L}/\text{min}$ with a composition primarily
1174 based on FA (a certain quantity of MeOH or propanol may have been added). The sheath flow
1175 helps ensure good stability and tolerance to changes in BGE composition; however, spatial
1176 dilution at the interface capillary/sheath flow and greater noise can limit its utility for the
1177 detection of AAs, which have low m/z values. Based on this, few authors have reported the
1178 need for derivatization to increase the mass of the molecules. Nonetheless, sensitivity in such
1179 studies is not considerably better than that in studies involving free-AA determination. The
1180 commercial CE/MS interfaces [mostly obtained from Agilent (Walbrun, Germany), and from
1181 Analis (Namur, Belgium) at times] are robust and easy to use with all CE instruments.
1182 Sensitivity in the micromolar range has been reported in most studies. Because the interface is
1183 robust and not as expensive (less than €5000), and requires a simple fused silica capillary, its
1184 use has facilitated the rapid growth of CE/MS applications in the field of AA determination. In
1185 the chapters on the applications of these methods, it has been shown that these methods are
1186 most commonly applied in metabolomic studies, and only a few laboratories worldwide use
1187 CE/MS in AA assays.

1188

1189 **5.3. Sheathless CE/MS (CE/SL-ESI-MS)**

1190 For a sheathless setup, a porous tip at the end of the capillary is formed by removing
1191 25–40 mm of the polyimide coating of the capillary and etching this section with a 49% HF
1192 solution. The electrical connection to the capillary outlet is implemented by simply inserting
1193 the capillary outlet containing the porous tip into the metal ESI needle and filling it with the
1194 BGE. To test the utility of this tip, an assay was performed using 17 AAs. An FA/18C6H4
1195 solution served as a complexation reagent to enhance the sensitivity of AA detection. It was

1196 noted that the complex increased the apparent masses of the AAs. The results obtained with the
1197 porous tip were similar to those obtained using a conventional interface design. It was noted
1198 that bubble formation due to redox reactions of water at the high-voltage electrode occurred
1199 outside the separation capillary and did not affect the separation or MS performance [200]. Age
1200 estimation of silk textiles on the basis of AA racemization rates was realized based on the 2500-
1201 year L-to-D conversion half-life of aspartic acid in silk. The analysis required only 100 μg of
1202 silk fiber [201]. Moini has published a detailed review article on the uses of the porous tip
1203 interface [202]. Recently, SL-ESI-MS using a commercial porous tip emitter was reported by
1204 Zhang *et al* [203], with 10% acetic acid solution used as the BGE. The authors obtained a
1205 nanomolar LOD (1–92 nM) and identified AAs and biogenic amines in a methanol/water extract
1206 from 500 HepG2 cells. Ramautar published a precise description of the CE-SF-ESI^{+/−}-MS
1207 protocol for analyzing amines and AAs (positive ions) as effectively as acidic molecules
1208 (phosphoesters) [204].

1209 Because metabolomic studies lead to the identification of molecules containing acid,
1210 alcohol, or amine functions, which can be identified using either negative or positive ESI,
1211 Huang *et al* [205] proposed an original two-step labeling method for identifying organic acids,
1212 amines, and AAs using ESI⁺. In this method, 300 mM 3-(diethylamino)propanoylchloride was
1213 added to a dried sample extract to obtain an ester with alcohol and an amide with amines. Next,
1214 N-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-
1215 methylmethanaminium hexafluorophosphate-N-oxide (1 M) was reacted with N,N-
1216 diethylethylenediamine and the abovementioned derivatized sample to convert the acid group
1217 into an amide one. Finally, all chemical functions were converted into esters or amides using
1218 an NN-dimethyl amine nucleus, which could be protonated easily. Even though Leu/Ile were
1219 not separated, LODs in the nanomolar range were obtained, and 17 AAs and 5 organic acids
1220 were identified.

1221 A sheathless interface was designed using an ionophore membrane-packed
1222 electroconduction channel to prepare a “durable” interface that functioned well with a volatile
1223 alkaline BGE and enabled short analysis duration (<15 min). The MRM mode and
1224 electrokinetic injections yielded LODs as low as 0.05–0.81 μM , whereas the RSDs of intraday
1225 and interday repeatability were less than 3%. The determination of free AAs from serum using
1226 isotope dilution mass spectrometry (IDMS) resulted in recovery rates of 96.3%–101.8%. The
1227 concentrations of Ala, Phe, Pro, Leu/Ile (not separated), Tyr, and Val in serum (after simple

1228 filtration through a filter with a molecular weight cutoff of 10,000) were measured in both
1229 HPLC-IDMS and CE/IDMS experiments. The two techniques yielded similar results [206].

1230 Metabolomics is currently being applied in an increasing number of functions and
1231 represents the most important research topic in CE/MS.

1232 At present, only a few studies have been published that have used a sheathless interface.
1233 The two primary reasons for the same are as follows: Sciex is the major supplier of the
1234 instrument, and the interface has been commercialized for less than 6 years; the capillaries with
1235 porous tips are considerably expensive, and therefore, have limited use. A study comparing
1236 sheathless and sheath flow interfaces was published a few years back (2014). Bonvin [207]
1237 demonstrated that the ionization efficiency of the sheathless interface for small molecules was
1238 20–40-fold higher (at submicromolar concentrations); the LODs reported in the latest AA
1239 studies were mostly in the nanomolar range. The efficiency rates achieved were also better when
1240 the sheathless technology was used, which is more important for lower-electrophoretic-mobility
1241 compounds. This could be attributed to the absence of the nebulizing gas and sheath liquid, as
1242 these exert a suction effect that broadens the peaks. Therefore, the sheathless technology is
1243 easier to use, and the installation step is simpler. In both cases, the buffer composition is a major
1244 limitation in CE/MS experiments; the components must be volatile, and ammonium formate or
1245 acetate are mostly used. The addition of 18C6H4 helps separate D/L AAs. For major AA
1246 applications, the determination of AAs at nanomolar concentrations is not particularly useful;
1247 at present, the (cost per analysis)/(high sensitivity usefulness) ratio for sheath flow interface in
1248 AA determination is more favorable.

1249

1250 **5.4. CE-MS as a metabolomic tool: diverse horizons**

1251 The field of metabolomics has seen considerable contributions in the last decade. In
1252 particular, CE-MS coupling for accessing metabolomics data has undergone significant
1253 advancement. Consequently, the emphasis has been placed on human and animal fluids and on
1254 plants. There has been specific interest regarding cell or tissue metabolomics, often related to
1255 cancer and other pathologies. Recently, Hirayama *et al* [208] published a detailed study about
1256 the use of this technique for tissue analysis in the MRM mode. Rodriguez *et al* [209,210] have
1257 published a simple and well-described CE/SF-ESI⁺/MS method for the quantitative
1258 determination of 27 AAs (including Leu, Ile, alloisoleucine, Orn, citrulline, GABA, carnosine,
1259 and hydroxyproline) in urine within 30 min. The BGE used was 0.80 M FA and 15% methanol,
1260 and the pH-stacking procedure involved the injection of 12.5% NH₄OH solution at 0.5 psi at 9

1261 s prior to sample injection. The LODs ranged from 0.63 to 29 μ M. Urine samples were collected
1262 from children with vesicoureteral reflux.

1263 The generation of unidentified peaks in CE-MS analysis is a major obstacle that is yet
1264 to be overcome in metabolomic studies. A novel metabolomics-based chemoinformatic
1265 approach has been designed for ranking candidate structures. The approach utilizes information
1266 about known metabolites detected in samples containing unidentified peaks and involves three
1267 discrete steps: i) identification of the “precursor/product metabolites” as potential reactants or
1268 products derived from the unidentified peaks; ii) search for candidate structures for an
1269 unidentified peak against the PubChem database using a molecular formula, which are then
1270 ranked by structural similarity against precursor/product metabolites and candidate structures;
1271 iii) prediction of the migration time for refining candidate structures. To initiate the validation
1272 of this “proof-of-concept tool” for the 20 proteinogenic AAs represented by the pseudo-
1273 unidentified peaks, the authors identified precursor/product metabolites of 18 of the 20 AAs,
1274 with Arg and Trp being the only exceptions. The authors also proposed the analysis of two
1275 unidentified peaks in a urine sample, which were shown to correspond to glycoyamidine and
1276 *N*-acetylglycine [211]. This method and its further development may help metabolomists
1277 optimize their findings.

1278

1279 **5.4.1. Application in cancer**

1280 The use of CE/MS in metabolomic applications involving small molecules has been
1281 developed and reviewed extensively [204,212], and the importance of its use is particularly well
1282 evaluated. Here, we summarize and discuss new developments reported in the most recent
1283 articles.

1284 A deeper understanding of the metabolomics of cancer cells has driven specific therapeutic
1285 advances. The tumor microenvironment has been studied in surgically resected tissues from
1286 lung and prostate tumors. CE-MS detection of AAs has revealed widely different profiles
1287 between normal tissues and tumors, with the AA content significantly higher in tumors.
1288 Squamous cell carcinoma and other types of lung cancer can be distinguished using CE-MS,
1289 and the elevated phosphorylation levels of pyruvate kinase and phosphofructokinase in tumor
1290 tissues indicate hyperactive glycolysis [213]. Investigation of the oral squamous cell carcinoma
1291 (OSCC) metabolic system has revealed glucose consumption associated with lactate production
1292 (Warburg effect), which is concomitant with a higher rate of glutaminolysis [214]. The
1293 decarboxylation of isocitrate to α -ketoglutarate has been demonstrated in gliomas and acute

1294 myeloid leukemias. In one mutant (IDH1), higher transformation of α -ketoglutarate to D-2-
1295 hydroxyglutarate was documented. Consequently, D-2-hydroxyglutarate was suggested to act
1296 as an oncometabolite. Glutaminolysis has also been shown to be activated in gliomas [215].
1297 Serum samples from patients with chronic hepatitis C receiving pegylated-interferon or
1298 ribavirin therapy showed higher Trp levels than those collected from healthy controls [216].
1299 Saliva has been found to be a useful biofluid well-suited for the diagnosis of a wide range of
1300 diseases, including cancers. A metabolite assay of saliva samples obtained from 215 individuals
1301 (including 69 patients with oral, 18 with pancreatic, and 30 with breast cancer; 11 patients with
1302 periodontal disease; and 87 healthy controls) was performed using CE/MS. The obtained results
1303 indicated that 57 principal metabolites could be used as predictors of these diseases. Higher
1304 concentrations of most metabolites were detected in all three cancer types, with salivary
1305 metabolites forming a cancer-specific signature. Most of the AAs were included in these 57
1306 metabolites, along with several biogenic amines (*e.g.*, putrescine, cadaverine, piperidine, and
1307 burimamide) and unidentified molecules (with only their chemical formulae known) [217].
1308 OSCC has also been studied using saliva samples. A study on twenty-two Japanese patients
1309 with OSCC and 21 healthy controls led to the identification and quantitation of 499 metabolites.
1310 Only 25 metabolites were shown to constitute a molecular signature of OSCC. These included
1311 amines (choline and cadaverine), acids (*p*-hydroxyphenylacetic acid, and 2-hydroxy-4-
1312 methylvaleric acid [$P < 0.001$], 3-phenyllactic acid, hexanoic acid, octanoic acid, terephthalic
1313 acid, 3-(4-hydroxyphenyl)propionic acid [$P < 0.01$], among others), proteinogenic AAs (Val,
1314 Leu, Ile, Trp, and Ala), and non-proteinogenic AAs (γ -butyrobetaine, N^6, N^6, N^6 -trimethyllysine,
1315 taurine, among others) [218].

1316 Esophageal cancer has been studied using paired tumor tissues (Ts) and nontumor
1317 esophageal tissues (NTs). In one study, the Ts and surrounding NTs were surgically excised
1318 pairwise from 35 patients with esophageal cancer. One hundred and ten compounds could be
1319 quantified using CE/MS. The concentrations of the metabolites between Ts and NTs, between
1320 stage pT1 or pT2 (pT1-2) and stage pT3 or pT4 (pT3-4), and between node-negative (pN-) and
1321 node-positive (pN+) cases were compared by principal component analysis and hierarchical
1322 clustering analysis. These statistical methods revealed specific metabolomic differences. The
1323 concentrations of most AAs (except Gln) were higher in Ts than in NTs. The authors inferred
1324 that metabolomic characteristics differ significantly between tumor and nontumor tissues,
1325 which may help implement personalized medicine [219].

1326 CE-SF-ESI⁺ MS was used for targeted (MRM mode) and untargeted (full scan mode)
1327 analyses of the sub-5 kDa urine metabolome of patients with prostate cancer [220]. The

1328 capillary was coated with trimethoxysilylpropyl polyethyleneimine-HCl (a cationic polymer),
1329 using a buffer composed of 0.5% (v/v) FA and 50% (v/v) methanol. It was possible to separate
1330 Ala from sarcosine (N-methyl-Gly), its isomer [221]. In a targeted experiment, sarcosine, Pro,
1331 Cys, Leu, Glu, and kynurenine were quantitated in four patients and in pooled urine sample
1332 collected from healthy volunteers. Untargeted analysis (full scan: m/z 50 to 850) of patient urine
1333 also led to the identification of over 400 compounds per patient. The authors stated that the
1334 introduction of urine sample collection into the surgery workflow would be a promising strategy
1335 for the construction of an abaque (or “nomogram”) for proper adjustment of cancer treatment.
1336 A small plug of ammonia/water injection before sample injection facilitates the on-line
1337 concentration of urine in CE. Urinary metabolic changes (indicated by AA and organic acid
1338 contents) in breast cancer after chemotherapy were assessed using CE-MS via a similar
1339 concentration method. Both negative and positive ionization modes were employed to analyze
1340 the two types of compounds. After chemotherapy, Gly, Cys, His, Trp, and cystine levels were
1341 found to decrease in chemotherapy-sensitive patients.

1342

1343 **5.4.2. Other human pathologies**

1344 Subsequent studies have focused on obesity, particularly on metabolically healthy
1345 patients with obesity who do not exhibit insulin deficiency or altered lipid profile that could be
1346 used to distinguish them from non-healthy patients. Serum samples were analyzed using GC-
1347 MS and CE-MS, and gene expression in adipose tissue were studied in parallel. The
1348 combination of collected data indicated that branched-AA catabolism and tricarboxylic acid
1349 cycle (TCAC) are less downregulated in healthy patients [222]. Multisegment injection CE/MS
1350 has been used to study the effect of high-intensity training (6 weeks for cardiorespiratory fitness
1351 enhancement) on glucose tolerance. Aromatic- and branched-chain-AA downregulation in
1352 plasma was monitored after oral glucose loading. Such studies assist the designing of
1353 personalized lifestyle improvement programs [223]. Ra *et al* primarily focused on fitness in
1354 their study on fatigue symptoms in soccer players [224]. CE-MS analyses were performed using
1355 saliva samples obtained from athletes after three consecutive days of intense sport activity. The
1356 levels of 3-methyl-His, taurine, and some other AAs increased significantly with fatigue. To
1357 optimize heart examination and health, it is important to understand cardiac metabolomics. As
1358 the energy content in cardiac muscles depends on fatty acid oxidation, and the two ventricles of
1359 the heart work under different pressures, it would be interesting to determine the metabolic
1360 profiles of arteries and ventricles. Using CE-MS, the levels of nucleotides and AAs (Pro, Ile,

1361 Trp, Phe, Gly, Asp, Ala, Met, Glu, Arg, Lys, His, Gln, and Asn) were measured. These were
1362 found to be present at similar concentrations in the two ventricles; however, the levels of lactate,
1363 acetyl-coenzyme A, and TCAC metabolites were higher, and the phosphate pool was more
1364 enriched in the ventricular tissues than in the atrial tissues [225].

1365 A search for biomarkers as early indicators of nephrotoxicity resulting from drug
1366 absorption was performed using plasma samples from rats. CE-MS was used successfully to
1367 select 3 metabolites (among the 169 identified) as potential biomarkers: 3-methyl-His, 3-
1368 indoxyl sulfate, and guanidoacetate [226]. CE-MS was also applied in studies on the urine
1369 metabolic profile of rats fed bisphenol A for 45 days to evaluate its toxicity. The results
1370 indicated perturbations in Val, Leu, and Ile biosynthesis and in Gln/Glu metabolism. The levels
1371 of neurotransmitters (Glu, GABA, and norleucine) and related metabolites were found to be
1372 altered, suggesting the toxic effects of bisphenol A even when administered at levels lower than
1373 $50 \text{ mg}\cdot(\text{kg}\cdot\text{day})^{-1}$ [227].

1374 *Leishmania*, the trypanosome that causes leishmaniasis, has gradually gained resistance
1375 to classic antimonial treatments. Information regarding the development of resistance is
1376 important owing to the small number of treatment options available. GC, LC, and CE-MS have
1377 been used to analyze the metabolic changes in the parasite during resistance development. An
1378 increase in the level of free AAs was observed in resistant parasites [228].

1379 Piestansky *et al* [229] reported a CE/SF-ESI+MS study where they reoptimized CE conditions
1380 to separate Leu and Ile. They proposed the use of 0.5 M FA to achieve optimal resolution of the
1381 two AAs. They obtained the highest sensitivity in MRM mode with LODs in the range of 1 μM .
1382 Urine samples from patients with Crohn's disease treated with azathioprine were diluted 10-
1383 fold using water, passed through disposable membrane filters (pore size 0.22 μm), and
1384 immediately injected into the CE/MS instrument.

1385 Balderas *et al* [230] analyzed plasma and urine samples from children with type I
1386 diabetes mellitus for evaluating the effect of insulin therapy on glycemic control. Even though
1387 no remarkable difference was noted between healthy volunteers and patients with diabetes,
1388 specific changes were detected, particularly in the levels of proteins, AAs (Ser, Asp, Lys, Val,
1389 Leu/Ile, Phe, and Cys in urine), glucose, and hemoglobin glycosylation. Cultured HK-2
1390 proximal tubular cells were used to study diabetic nephropathy. High-glucose level-induced
1391 metabolic alterations in HK-2 cells were monitored using three culture treatments: 25 mM
1392 glucose (high-glucose group), 5.5 mM glucose (normal-glucose group), and 5.5 mM glucose
1393 and 19.5 mM mannitol (osmotic control group). Extra- and intracellular media were studied,
1394 and 11 AAs were identified. In the high-glucose group, the major changes were observed in the

1395 extracellular medium, where increased levels of Ala, Pro, Glu, and Cys were detected, along
1396 with Amadori products [231].

1397 CE/MS metabolomic analysis was performed for quantifying 60 metabolites in 32
1398 plasma samples collected from male patients exhibiting lower urinary tract symptoms; a
1399 multivariate analysis revealed that an increase in the level of Glu and decrease in the levels of
1400 Arg, Asp, and inosine monophosphate were statistically significant compare to a control group
1401 [232].

1402 Changes in the metabolite levels in plasma samples collected from 33 medication-free
1403 patients (who were subsequently treated for 8 weeks) with major depressive disorder (MDD)
1404 and 33 non-psychiatric control subjects were investigated in another study. The levels of 33
1405 metabolites differed between the medication-free MDD patients and the control subjects.
1406 Several ratios, including kynurenine/Trp, Gln/Glu, and Met/methionine sulfoxide, differed
1407 significantly between the two groups. After treatment, the first two ratios normalized, which
1408 indicated the mechanism underlying the action of antidepressant agents in MDD [233].

1409 Mutations in glycine cleavage system genes may be associated with schizophrenia. To
1410 investigate this, a metabolomic study using five plasma samples from patients harboring glycine
1411 cleavage system (CGS) variants and five controls was performed using CE/MS. The PyroGlu,
1412 Asp, and Glu levels were found to change, and the Asp levels showed negative correlation with
1413 negative symptoms [234].

1414 The global metabolomic alterations associated with the onset of schizophrenia are well
1415 recognized. A CE-SF-ESI-MS study on 30 patients with first-episode schizophrenia, 38 healthy
1416 controls, and 15 individuals with autism spectrum disorders revealed increased levels of
1417 creatine and decreased levels of N,N,N-trimethyl-Gly (betaine), nonanoic acid, benzoic acid,
1418 and perillic acid. These changes indicated the abnormalities in Hcy metabolism, hyperCKemia,
1419 and oxidative stress [235].

1420 Alteration in the plasma levels of Hcy, Cys, Met, and Glu is a common symptom of
1421 amyotrophic lateral sclerosis (ALS). A CE-MS/MS method was validated and yielded RSD
1422 values below 6% and 11% for intraday and interday repeats, respectively [236]. In a study on
1423 samples from 20 healthy subjects (controls) and 39 patients with ALS, a quantitative
1424 comparison of these AAs revealed significantly elevated concentrations of Glu ($p = 0.004$) and
1425 Cys ($p = 0.0006$) in the plasma of patients with ALS; however, Met and Hcy concentrations did
1426 not differ significantly between the controls and patients.

1427 Identification of metabolites in the sweat of screen-positive infants with cystic fibrosis
1428 was performed [237]. Such studies may involve the conventional sweat chloride test [238].

1429 Nontargeted metabolite profiling was performed by multisegment injection-CE-MS [239] as a
1430 high-throughput method for the detection of polar/ionic metabolites in sweat samples available
1431 in small quantities. Asn and Gln were found to be the two endogenous sweat metabolites
1432 associated with asymptomatic affected infants [237].

1433 The metabolomic profiles of feces, urine, and plasma samples from mice with adenine-induced
1434 renal failure and control mice housed under germ-free or specific pathogen-free (SPF)
1435 conditions were studied. Using CE/MS, the authors evaluated the influence of gut microbiota
1436 on the retention of uremic toxins during chronic kidney disease in mice. A total of 183
1437 molecules were quantitated, and the plasma levels of 11 of these molecules were found to be
1438 significantly lower in germ-free mice than in SPF mice with renal failure. Microbiota-derived
1439 short-chain fatty acids and efficient AA utilization may have exerted a renoprotective effect,
1440 and the loss of these factors may have exacerbated renal damage in germ-free mice with renal
1441 failure [240].

1442 Homozygous Watanabe heritable hyperlipidemic (WHHL) rabbits have specific
1443 symptoms of familial hypercholesterolemia and are model organisms for certain human cardiac
1444 pathologies. Using CE-SF-ESI MS, 230 metabolites were analyzed in plasma and tissue
1445 samples collected from the liver, aorta, cardiac muscles, and brain of affected and control
1446 rabbits. N,N,N-trimethyl-Gly, N,N-dimethyl-Gly, and N-methyl-Gly were found to accumulate
1447 in the analyzed tissues (lipid metabolism). 3-methyl-His downregulation was observed in the
1448 liver and cardiac muscle, whereas citrulline downregulation was observed in the cardiac muscle
1449 and brain. Homoserine, O-acetyserine, and homocarnosine levels were affected as well. When
1450 the rabbits were treated with simvastatin, only negligible differences were observed in AA
1451 concentrations between the controls and the WHHL group [241].

1452

1453 **5.4.3. Metabolomics in food**

1454 Diet exerts significant effects on human health. The complete profile of metabolites
1455 present in foods, as well as the influence of food production and processing systems (which
1456 could alter the metabolome) are unknown. Certain metabolomic studies have been designed to
1457 measure the impact of agricultural practices, processing, and storage on global chemical
1458 composition of food to identify novel bioactive compounds. This approach could be also used
1459 for the authentication and region-of-origin classification [242].

1460 Rice is a common and widely studied plant model. Kusano *et al* [243] published a review
1461 summarizing current knowledge on rice metabolites, including sugars, AAs, aromatic

1462 compounds, organic acids, and phytohormones, as analyzed using CE-MS, LC, or GC. In C3
1463 plants, an increase in CO₂ partial pressure enhances photosynthesis, whereas nitrate assimilation
1464 and nitrogenated molecule synthesis are inhibited. CE-MS revealed that plants overexpressing
1465 NAD kinase 2 show a primary metabolite profile different from that in wild-type plants when
1466 CO₂ partial pressure is increased. This could be attributed to the increase in the concentrations
1467 of Asn, Gln, Arg, and Lys [244].

1468 Soybean is also a relevant crop in this respect. The metabolite profiles of aphids growing
1469 on leaves of resistant and susceptible soybean strains were analyzed using CE-MS. The levels
1470 of specific AAs, TCAC components, and glucose-6-phosphate were similar between aphids
1471 cultured on Tohoku149 (an aphid-resistant soybean strain) leaves and those cultured under
1472 starvation. Two methylated metabolites, S-methyl-Met and trigonelline, were undetectable or
1473 present at a lower level in the aphids cultured on Tohoku149 plants. These metabolites are a
1474 sulfur carrier and an osmoprotectant, respectively [245].

1475 Root exudates improve nutrient acquisition by plants. Metabolites present in a common bean
1476 root exudate were analyzed at different phosphate concentrations. The levels of organic acids
1477 and AAs (such as Orn, Arg, Asp, among others) were found to be higher in the exudates of
1478 plants grown in the absence of phosphate [246].

1479 Differences in the metabolite profile of two strains of maitake mushrooms (*Grifola*
1480 *frondosa* [Dicks.] Gray) under different conditions of culture on sawdust substrate from trees
1481 were studied by Sato *et al* [247] using CE-SF-ESI/MS. The authors conducted a metabolomic
1482 study of strains Gf433 and Mori52 by culturing them on sawdust substrate from *Betula ermanii*
1483 (birch), and then analyzed the Gf433 strain cultured on sawdust substrate from *Betula ermanii*
1484 mixed with sawdust from *Larix leptolepis* (larch). They reported that the AA and organic acid
1485 contents in Gf433 were not affected by the type of sawdust. They found that the strain Mori52
1486 contained more AAs, particularly Glu and Orn, than the strain Gf433 did.

1487 Metabolic profiling has also been applied to food quality control. Storage of porcine
1488 meat for long durations reduces its quality. CE-MS metabolic profiling has indicated that the
1489 levels of glycolytic compounds (and related AAs, *i.e.*, Phe and Tyr), ATP degradation products,
1490 and protein hydrolysis products (Met and Tyr) increase with storage time [248]. A similar CE-
1491 MS approach was applied in studies on the foot muscle and gills of brackish water clams
1492 collected from different areas. Although no metabolite could be used to distinguish between
1493 male and female specimens, the β -Ala, choline, GABA, Orn, Gly, and betaine levels were found
1494 to vary based on water salinity [249].

1495

1496 **5.4.4. Miscellaneous metabolomic studies**

1497 Ohashi *et al* [250] introduced sonication treatments during the methanol extraction of
1498 metabolites from His-auxotrophic *E. coli* cells. They mentioned that this approach improved
1499 the extraction of phosphate-containing molecules. The authors identified 375 charged
1500 hydrophilic metabolites, and provided quantitative data on 198 molecules to evaluate the
1501 changes in response to His starvation. The intracellular levels of His synthesis intermediates
1502 rapidly increased in response to the drop in His levels. TCAC, glycolysis, AA biosynthesis, and
1503 nucleotide biosynthesis may be independently activated under conditions of starvation.
1504 The metabolomic profile of *Synechocystis* (a cyanobacterium) has been studied under nitrogen
1505 starvation, as nitrogen availability is crucial for the survival of these aquatic and photosynthetic
1506 bacteria [251].

1507 The metabolomic profile of dried *Orostachys japonicus* A. Berger, a perennial medicinal
1508 herb, has been compared with that of *O. japonicus* fermented with *Lactobacillus plantarum* to
1509 elucidate the metabolomic changes induced by the fermentation process. A total of 144 cationic
1510 metabolites and 86 anionic ones were identified, and the relative peak areas were determined.
1511 Monitoring of the TCAC metabolites (Arg, Glu, Asp, and 2-oxoglutaric acid) revealed that their
1512 levels were altered by the fermentation process, which was also observed for components of the
1513 urea cycle, as indicated by the significant increase in histamine concentration [252].

1514 An original study combining the advantages of matrix-assisted laser desorption
1515 ionization (MALDI) and CE/ESI-MS was performed to study single cells from pancreatic islets.
1516 Optically-guided MALDI MS facilitates the high-throughput identification of cellular lipids and
1517 peptides; however, it is not quantitative and cannot detect several low-mass metabolites owing
1518 MALDI matrix interferences. CE/ESI-MS allows the quantitation of cellular metabolites and
1519 offers increased analyte coverage; however, it has a low throughput. A custom liquid
1520 microjunction surface sampling device mounted on an xyz translational stage offered $90.6\% \pm$
1521 0.6% analyte removal efficiency. The microjunction component was composed of two
1522 concentric capillaries. The outer one delivered an analyte solution for extraction (1:1
1523 methanol/water, 0.5% acetic acid [v/v]), while the inner one aspirated the liquid droplets at the
1524 end of the outer capillary. When the microjunction came in contact with a cell, it extracted
1525 molecules with a spatial accuracy of $42.8 \pm 2.3 \mu\text{m}$. The analyte extraction footprint was
1526 represented by an elliptical area with the longest diameter of $422 \pm 21 \mu\text{m}$. Single rat pancreatic
1527 islet cells were first analyzed using optically-guided MALDI MS to classify cells into
1528 established cell types (α_i , β_i) based on their peptide content. Following this, microjunction

1529 extraction coupled with CE/ESI-MS helped collect qualitative information on metabolites (AAs
1530 and dopamine) [253].

1531

1532 **6. Medical applications**

1533 Some of the most critical studies in the field of AA medical applications involve total
1534 Hcy measurement. Researchers have been encouraged by the significant importance of this
1535 compound in the diagnosis of cardiovascular diseases. Most published studies have used LIF
1536 detection owing to its sensitivity, since Hcy is present at micromolar concentrations in plasma.
1537 Although UV detection has also been used, it is either non-sensitive or lacks sufficient
1538 selectivity. However, it is considerably less expensive, and sample processing is not mandatory.
1539 A number of studies have characterized thiols in biological samples [254].

1540

1541 **6.1. Hcy and aminothiols**

1542 **6.1.1. Laser-induced fluorescence detection**

1543 Several strategies to analyze these molecules using CE/LIF have been implemented.
1544 Carboxylic function labeling with 5-(bromomethyl) fluorescein reduced the analysis time to
1545 less than 2 min, and the resulting sensitivity was better than 0.19 μ M for all analyzed
1546 compounds. The usefulness of carboxylate derivatization for diagnostic purposes was
1547 confirmed in a study on 91 patients (79 with cystinuria and 12 with homocystinuria) [154]. The
1548 amine group can also be modified [255] with FITC to study the plasma samples from patients.
1549 Nonetheless, these two methods detect all the AAs and lack selectivity. The thiol group was
1550 successfully derivatized using fluorescein-5-maleimide, and Cys, Hcy, and GSH could be
1551 selectively detected [153]. However, this approach gave rise to two peaks for each thiol owing
1552 to the presence of diastereoisomers after derivatization.

1553 The most commonly used reactant of thiols is 5-IAF [256,257]. Preanalytical conditions
1554 were studied [258], and multicenter comparisons between CE-LIF studies and other techniques
1555 were also performed [259,260]. An ultrarapid CE-LIF method for the quantitation of total thiols
1556 in plasma was reported by Zinellu *et al* [261]; this method involved the use of 75 mM N-methyl-
1557 D-glucamine buffer (pH 11). The thiols reduced by tri-n-butylphosphine reacted with 5-IAF,
1558 and the baseline separation of total plasma Cys-Gly, Hcy, Cys, and GSH required 5 min. The
1559 same authors have published several articles on assays of thiols in biological media and
1560 described the quantification of reduced and total forms of thiols in erythrocytes. To minimize

1561 the oxidation of reduced thiols, the erythrocytes were lysed in water (15 min at 4 °C), following
1562 which protein precipitation was performed using acetonitrile. The supernatant was rapidly
1563 derivatized with 5-IAF to minimize auto-oxidation. Under these conditions, Cys-Gly, Cys,
1564 GSH, and γ -glutamylcysteine (Glu-Cys) were separated within 4 min. The influence of the
1565 acidic precipitation on intracellular thiol concentration was investigated, and the data suggested
1566 that sample acidification modified the measured redox thiol status owing to the establishment
1567 of a pro-oxidant environment. Similarly, the thiol redox status of erythrocytes was evaluated in
1568 22 healthy volunteers [262]. The thiol-containing AAs linked by disulfide bonds to low-density
1569 lipoprotein (LDL) were also quantitated [263], and the levels of Hcy linked to LDL were
1570 measured in 16 patients with acute myocardial infarction and 32 healthy volunteers [264]. In
1571 the subjects with acute myocardial infarction, an increase in the levels of apo-B Hcy and Cys
1572 linked to LDL was observed. This finding suggests that LDL S-homocysteinylated may serve
1573 as a marker for cardiovascular-risk evaluation. In a study on 104 healthy patients, Hcy, Cys,
1574 Cys-Gly, Glu-Cys, and GSH bound to LDL were quantitated. The study showed that among the
1575 thiol-containing AAs, only the total plasma Hcy content was related to apoB-Hcy
1576 concentrations [265]. The same separation method was used to quantitate Cys and Hcy in 124
1577 healthy patients (44 women and 80 men, age: 50 ± 10 years). The mean levels of Hcy and Cys
1578 were ~ 11 and $284 \mu\text{M}$, respectively. To be precise, 90% subjects in this group had Hcy levels
1579 $< 15 \mu\text{M}$, as the samples were obtained from a healthy population. Univariate Pearson's analysis
1580 revealed a correlation between the white blood cell count and serum Hcy and Cys levels in
1581 healthy subjects [266]. Similarly, Pinna *et al* [267] measured the plasma levels of Hcy and Cys
1582 in healthy subjects and patients with retinal vein occlusion. The mean plasma concentration of
1583 Cys was significantly higher in patients with retinal vein occlusion. Hypercysteinemia may have
1584 contributed to the pathogenesis of this disorder. Furthermore, using the same method, the levels
1585 of intracellular thiols in human umbilical vein endothelial cells, ECV304 cells, and R1 stem
1586 cells were investigated [268], and an increase in the injection volume was observed to be
1587 necessary.

1588 Total, reduced, and free (of protein) thiols, and for comparison, protein-bound plasma
1589 thiols, were quantified by varying the order of disulfide reduction and protein precipitation.
1590 After derivatization with 5-IAF, CE/LIF (at 488 nm) was performed to measure the total and
1591 oxidized Hcy, Cys, Cys-Gly, Glu-Cys, and GSH levels. More than of 50% of these thiols were
1592 shown to be protein-bound, except GSH (30%). It was found that 3% Hcy and 4.5% Cys
1593 molecules were in the reduced form (Fig. 8) [269].

1594 N-acetyl-L-cysteine (NAC), a widely used mucolytic agent, may alter the plasma levels of some
1595 low-molecular-mass thiols. Zinellu *et al* [270] described a CE method using which NAC was
1596 baseline-separated from other physiological thiols. The suggested method was used to measure
1597 the levels of this drug and those of Hcy, Cys, Cys-Gly, Glu-Cys, and GSH in NAC-treated
1598 patients with chronic obstructive bronchopneumopathy. There was no evidence of the effect of
1599 NAC on the concentration of plasma thiols.

1600 Other studies have also addressed this topic: in-column derivatization was designed for
1601 a fully automated assay of Hcy and other thiols. The method involved the direct injection of a
1602 sample containing Hcy and 4-aminosulfonyl-7-fluoro-2,1,3-benzoxadizole, which reacted for
1603 10 min at 50 °C. Hcy was detected within 7 min, and the LOD achieved for Hcy with LIF
1604 detection was 5.0 nM, as compared to 2.5 nM obtained using precolumn LIF detection [158].

1605

1606 **6.1.2. UV absorbance detection**

1607 Zinellu *et al* [271] reported an original application for the quantitation of biological
1608 thiols, including Cys, Hcy, cysteine, Hcy-thiolactone, and Hcy-cysteine. These molecules were
1609 reduced using CuSO₄, with thiolactone serving as an internal standard. CE/UV detection (at 190
1610 and 232 nm) was performed in 40 mM Tris solution (pH 1.6), and an overpressure of 0.1 psi
1611 was applied from the inlet to the outlet. The LOD obtained was ~1 μM. Furmaniak *et al* [272]
1612 analyzed Hcy-thiolactone in urine using CE/UV (at 240 nm). This molecule was found to be an
1613 efficient predictor of mortality of cardiovascular patients. Field-amplified sample injection and
1614 sweeping MEKC were performed for this application. The stacking method required two
1615 different BGE systems (including one with SDS).

1616 Zinellu *et al* [273] also published a method for detecting Met in samples where analyte
1617 derivatization should be avoided owing to low sample concentration. Met was detected by UV
1618 absorbance (204 nm) using an acidic Tris-phosphate buffer. The performance of the assay was
1619 evaluated by measuring Met concentrations in patients with retinal venous occlusion.

1620 UV absorbance was also used with 2,2'-dipyridyl disulfide for Hcy detection. Reaction
1621 with Hcy induced the equimolar formation of 2-thiopyridone, which was separated using
1622 MEKC and detected at 343 nm. The concentration of Hcy could be calculated from the result
1623 of 2-thiopyridone detection [274].

1624 Kubalczyk *et al* [275] proposed the derivatization of thiols using 2-chloro-1-
1625 methylquinolinium tetrafluoroborate and the separation (from plasma) and detection of a Hcy-
1626 2-S-quinolinium derivative using CE/UV with acetonitrile stacking. Zhang *et al* [276] reported

1627 a CE/UV method without Hcy derivatization. Significantly higher Hcy concentrations were
1628 detected in patients with Alzheimer's disease than in controls. The elevated plasma Hcy levels
1629 could be attributed to environmental factors than genetic ones, such as mutations in N⁵,N¹⁰-
1630 methylenetetrahydrofolate reductase or cystathionine β-synthase genes.

1631

1632 **6.2. Studies on dimethylarginines and other methylated species**

1633 Dimethylarginines are potent endogenous inhibitors of nitric oxide synthase (NOS) and
1634 accumulate in the plasma of patients with renal failure, peripheral arterial occlusive disease, or
1635 clinically asymptomatic hypercholesterolemia. These have been studied using CE/LIF, CE/UV,
1636 and CE/C⁴D.

1637 As Arg and its derivatives are basic molecules, they migrate more rapidly than most
1638 other AAs. This property is important because it facilitates their separation. Caussé *et al*
1639 reported a method for the separation of symmetric and asymmetric dimethylarginine (SDMA
1640 and ADMA), N^G-monomethyl-L-arginine, and Arg in a simple boric acid/CAPS buffer (pH 10)
1641 using homoarginine as an internal standard after derivatization with FITC (with LIF detection
1642 at 488 nm). The variation in ADMA levels was compared between serum samples collected
1643 from healthy subjects and subjects undergoing hemodialysis [277]. In another study, the
1644 separation of mixtures containing SDMA, ADMA, N^G-monomethyl-L-arginine, Arg,
1645 homoarginine, Orn, and L-citrulline, labeled as 4-fluoro-7-nitrobenzofurazan derivatives, was
1646 accomplished [278] using borate/deoxycholic acid at pH 9.4 as the BGE. ADMA levels were
1647 measured in plasma at 0.125 μM using LIF (at 488 nm).

1648 Zinellu *et al* [279] measured the ADMA, SDMA, and Arg concentrations in human
1649 plasma using CE/UV (200 nm, no derivatization) after acetonitrile/ammonia (90:10) protein
1650 precipitation, centrifugation, and filtration on a microconcentrator. The sample was evaporated
1651 and diluted in water prior to CE. A water plug was injected for 1 s (0.5 psi), followed by sample
1652 injection for 10 s (0.5 psi). Separation was performed in Tris-phosphate buffer. The recovery
1653 rates of plasma ADMA were between 101% and 104%.

1654 Methylarginines are potent vasoconstrictors present at elevated concentrations in the
1655 blood of patients with cardiovascular diseases, and must be rapidly quantified in serum. For this
1656 purpose, samples are rapidly heated (at 100 °C for 1.5 min) and NDA/CN-derivatized before
1657 separation by CE-LIF (using a 445-nm diode laser) [280].

1658 A CE technique was designed by Tuma *et al* [55] for assaying urinary methylhistidine
1659 (MH). 3-MH, 1-MH, and His were separated in both acidic and alkaline media, where these
1660 AAs form cations and anions, respectively. The effective mobility of all ionic forms was
1661 measured over a broad pH range (1.67–11.80). 3-MH and 1-MH were quantified along with
1662 creatinine in untreated urine samples with LODs of 2.4 and 3.0 μM , respectively. Separation
1663 was performed using an acetic acid/Tris/hydroxyethyl cellulose electrolyte. The analysis
1664 revealed differences between healthy individuals and patients, with more extensive degradation
1665 of muscle proteins observed in the second group.

1666

1667 **6.3. Other clinical studies**

1668 **6.3.1. CE/LIF studies**

1669 CE is also typically used for separating, characterizing, and quantifying AAs in
1670 inflammation. For instance, CE-LIF of NBD derivatives (488 nm) was performed to quantify
1671 Lys and cadaverine in dental and tongue biofilms and saliva before and after oral hygiene
1672 restriction [281,282]. NBD-F-derivatized GABA was quantitated in the CSF of 24
1673 neuropediatric patients receiving different antiepileptic treatments; the data were compared
1674 with those obtained from 55 healthy individuals. The investigators noticed an increase in GABA
1675 concentration when CSF was maintained at room temperature for 0.5 to 5 h. They established
1676 reference values for children of different age groups at less than or above 6 months of age: 48
1677 and 66 nM respectively. Higher concentrations were recorded in neuropediatric patients
1678 undergoing antiepileptic treatments [283].

1679 Sbrana *et al* [284] optimized a CE/LIF (He-Cd laser, 325 nm) method for the
1680 measurement of the ratio between S-adenosyl-L-Hcy and S-adenosyl-L-methionine, which can
1681 be used to assess antiviral potency *in vivo*. After chloroacetaldehyde derivatization, the
1682 separation and quantitation of S-adenosyl-L-Hcy and S-adenosyl-L-methionine in human
1683 plasma were achieved in less than 1 min. The same group of researchers also showed that in
1684 patients infected with human immunodeficiency virus (HIV), disease progression is associated
1685 with a decrease in GSH and Cys levels [285].

1686 Two sensitive and reproducible CE/LIF (488 nm) and HPLC-fluorescence procedures
1687 were designed for the quantitative detection of L-ergothioneine. Patients affected by
1688 autoimmune disorders such as rheumatoid arthritis and Crohn's disease present with high levels
1689 of L-ergothioneine in blood. In one study, 5-IAF was used for L-ergothioneine quantitation by

1690 precolumn derivatization in plasma, and an LOD of 0.27 μM was recorded [286]. Serum L-
1691 ergothioneine, taurine, Hcy, Cys, GSH, Cys-Gly, and Glu-Cys were quantitated in 439 subjects
1692 using the method mentioned last. The reference range of L-ergothioneine was established (0.36
1693 to 3.08 μM in healthy subjects), and the authors showed that age and plasma Glu-Cys levels are
1694 independent factors negatively associated with L-ergothioneine concentration [287].

1695 Bipolar disorder (BD) is a common psychiatric disorder. Literature data show that patients with
1696 BD have higher plasma concentrations of Glu, Gln, and Gly, and these AAs act as possible
1697 biomarkers of this pathology. A CE method was designed for measuring the levels of AAs in
1698 patients with BD and to monitor the effects of medical treatment. CE/LIF (488 nm) of NBD-F-
1699 derivatized plasma was performed for separating D-Ser, L-Ser, and nine other AAs. The method
1700 was successfully used for the diagnosis of BD and its progression [288].

1701 CE/LIF (488 nm) of CBQCA-labeled AAs from plasma (using a 488-nm Ar ion laser)
1702 of patients with phenylketonuria, tyrosinemia, maple syrup urinary disease, hyperomithinemia,
1703 or citrullinemia was performed in a study [111]. Twenty-nine AAs (barring Trp) were detected
1704 and could be reproducibly separated in 70 min. Existing literature shows that Trp is difficult to
1705 identify using CBQCA derivatization owing to its poor fluorescence properties [289]. The use
1706 of NDA was also proposed for the separation of 21 AAs using CE/LEDIF (405 nm) in plasma
1707 [290]. The authors used 5% polyvinylpyrrolidone as a sieving medium with acetonitrile and
1708 SDS in the BGE. Tyr and Trp have also been quantified using CE/UV-LIF (266 nm) in CSF
1709 [78]; native fluorescence can serve as an alternative to visible LIF for aromatic-AA detection.
1710 In a study, CE-LIF and a near-infrared laser (785 nm) were used to analyze Tyr and nitrotyrosine
1711 in biological media. A near-infrared dye was used to label these compounds and was compared
1712 to FITC and NBD-F (both using a 488-nm laser). Micromolar concentrations of the AAs were
1713 detected in sinus washes [291]. Inborn errors of metabolism were diagnosed using urine samples
1714 from children, as the early detection of the AAs implicated in metabolic diseases enables early
1715 initiation of compensatory therapies. In a CE/LIF (488 nm) experiment for the separation and
1716 quantification of FITC-labeled pyroglutamic acid, Tyr, Phe, Val, Pro, Gly, and sarcosine, 130
1717 mM 18C6H4 was used as the BGE [292].

1718 D-AAs play an important physiological role; as reviewed above, they have rarely been
1719 assayed in clinical studies. Yet, in rats, the concentration of D-Ala in the anterior pituitary and
1720 islets of Langerhans increased in response to glucose stimulation. NDA-labeled D-AAs were
1721 chirally separated and quantified using CE-LIF (440 nm, diode laser) in a formamide-based
1722 electrolyte containing hydroxypropyl γ -CD (nonaqueous CE separation); however, a D-amino

1723 acid oxidase pretreatment and preconcentration step was required [293]. CE-LIF has also been
1724 used to quantitate L-Met, L-Cys, taurine, and GSH in the livers of male and female rats to test
1725 whether the glutamyl cycle is gender-specific [294].

1726

1727 **6.3.2. CE/UV**

1728 2,4-Dinitrofluorobenzene, a AA reactant, has been used for the complete separation of 16 AAs
1729 and D-norleucine within 8 min. The running buffer contained 30 mM sodium tetraborate (pH
1730 9.8), isopropyl alcohol, and 30% Brij 35 (825:150:25, v/v/v), and UV detection was performed
1731 at 360 nm. The AA concentration was measured in the sera of 32 patients with chronic renal
1732 failure. Among them, the levels of Ser, Ile, and Val were significantly lower than those in
1733 healthy volunteers ($P < 0.01$), whereas the levels of cystine, Trp, and Phe were significantly
1734 higher ($P < 0.01$) [295]. A CE/UV method (not described in the article) helped evaluate the
1735 effect of a high-fat meal, orange juice, and antacids (which neutralize stomach acidity) on the
1736 absorption of a single oral dose of cycloserine and estimate its pharmacokinetic properties. The
1737 pharmacokinetic parameters were found to be minimally affected by orange juice and antacid
1738 intake, whereas the high-fat meal delayed the absorption. The administration of cycloserine
1739 without a high-fat meal prevented potential alterations in the pattern of absorption [296]. By the
1740 simultaneous quantification of multiple markers, better diagnostic value can be achieved for
1741 multiple renal function markers in human urine samples. The successful high-throughput
1742 separation of creatinine, creatine, uric acid, and *p*-aminohippuric acid was performed using
1743 CE/UV. *p*-Aminohippuric acid had an LOD of 1.5 μM and a linear detection range of 1.5–250
1744 μM [297]. Another interesting approach involved the analysis of mixtures containing
1745 aminolevulinic acid, porphobilinogen, levulinic acid, and Gly. These compounds were
1746 separated at pH 9.3–9.4 and detected using UV spectrophotometry at 205 nm. The method was
1747 applied to the culture broth of *Rhodopseudomonas sphaeroides* [298].

1748 Among other studies related to clinical studies, tryptophan derivatives were selectively
1749 separated from 24 types of nutraceuticals. A pretreatment system involving a combination of
1750 homogeneous liquid-liquid extraction and a sweeping method has been used to separate and
1751 quantitate four types of Trp derivatives: 5-hydroxy L-tryptophan, 5-methyl L-tryptophan, 1-
1752 methyl L-tryptophan, and L-tryptophan. The LODs following complete separation of the Trp
1753 derivatives were at 10-nM levels when UV detection was used [299]. Aromatic AAs (Phe, Tyr,
1754 and Trp) are indicative of liver and kidney function. Twenty patients with chronic kidney

1755 disease were shown to have decreased plasma Tyr concentration, with the Phe levels being
1756 normal or marginally increased. This simultaneous quantification was realized using CE/UV
1757 (200 nm; Fig. 9) [300].

1758 Zinellu *et al* [301] studied the development of a simple free-zone CE method for the
1759 simultaneous measurement of creatinine and creatine levels in human plasma. The effects of
1760 analytical parameters, such as concentration and pH of Tris-phosphate running buffer and
1761 cartridge temperature, on resolution, migration time, peak areas, and separation efficiency were
1762 investigated. Effective separation using CE/UV (190 nm) was achieved in less than 8 min. The
1763 plasma creatinine levels in 120 healthy subjects were assayed, with marginal changes observed
1764 in plasma creatinine and creatine levels after moderate physical exercise. Guanidinoacetic acid,
1765 creatinine, and creatine in plasma and urine were quantitated in less than 7.5 min using CE/UV
1766 (190 nm) with a BGE with acidic pH in 32 patients, using these molecules as markers of renal
1767 function [302]. Guanidinoacetic acid and creatine were quantified using CE/UV (190 nm),
1768 whereas total and reduced Hcy were quantified using CE/LIF (after derivatization with 5-IAF
1769 and detection at 488 nm) in 16 young volunteers categorized as sedentary individuals and
1770 athletes. It was shown that after exercise, the levels of reduced Hcy decreased, total Hcy levels
1771 remained unchanged, and the creatine concentration increased [303]. Transient
1772 isotachopheresis using MEKC for 3-nitro-tyrosine detection in urine was performed with an
1773 LOD of 70 nM; this experiment on AA detection was performed in biological media in one
1774 study [304].

1775

1776 **6.3.3. CE/C⁴D**

1777 CE/C⁴D was used by Tuma *et al* for the detection of free AAs in amniotic fluid [54].
1778 Twenty proteinogenic AAs and 12 other biogenic compounds, including ethanolamine, choline,
1779 Ala, 2-aminobutyric acid, GABA, creatinine, Orn, carnitine, citrulline, 4-hydroxyproline, 1-
1780 MH, and 3-MH, were identified in a separation run of 65 min. Acetic acid and
1781 hydroxyethylcellulose served as the running electrolyte. Addition of acetonitrile to the samples
1782 improved the separation of AAs. The LODs ranged between 1.5 μ M (Arg) and 6.7 μ M (Asp).
1783 The method was later applied to clinical assays of amniotic fluid samples collected from 20
1784 pregnant women aged above 35 years and 24 pregnant women in whom abnormal fetus
1785 development was suspected. The second group of women was found to show systematically
1786 enhanced amniotic levels of most AAs studied. More rapid separation was realized using 20%
1787 MeOH in the separation buffer, which led to the separation of four branched AAs from seven

1788 other AAs in less than 3 min [305,306]. Venous-arterial differences in Val, Ile, Leu, Ala, and
1789 Gln levels in skeletal muscles have also been evaluated [66].

1790 The detection of cystine using capillary isotachopheresis with on-line isotachopheresis
1791 sample pretreatment and conductivity detection was performed for monitoring cystine levels in
1792 urine samples without sample preparation [307].

1793 We believe that even though the importance of this detection technique is relatively low
1794 in clinical studies at present, the studies presented here show how it could be useful for the
1795 detection of some AAs associated with clinical diagnostics.

1796

1797 **7. AAs in neurochemistry applications**

1798 Because microdialysis can be performed on live and freely moving animals, it allows us
1799 to collect information regarding the chemical changes that occur in the region of the brain where
1800 the microdialysis probe is implanted during specific activities of the animal. As Ringer buffer
1801 flows in the probe at a flow rate of several $\mu\text{L}/\text{min}$, and consequently collects the
1802 neurotransmitter molecules, the small volumes to be analyzed are well suitable for CE.
1803 Accordingly, CE/LIF holds promise as an effective tool in neuroscience, and its applications in
1804 various subfields of neuroscience are of interest. In the 1990s, Hernandez *et al* [308] proposed
1805 the use microdialysis coupled with CE/LIF for monitoring the increase of Glu and Asp
1806 concentrations. The method gained significant and rapid popularity. The authors used NDA and
1807 claimed to quantitate AAs at ranges between 10 and 0.01 μM . The approach was then improved
1808 by Robert *et al* [309], who analyzed dopamine and noradrenaline in microdialysates using NDA
1809 derivatization and measured the basal level of noradrenaline (5 nM) in the rat medial frontal
1810 cortex. This was soon followed by the on-line derivatization of 0.5- μL volumes of
1811 microdialysates for detecting NDA derivatives of catecholamines, along with Asp and Glu.
1812 Using microdialysis, the temporal resolution of 2-min fractions was achieved for the
1813 simultaneous monitoring of noradrenaline and Glu concentrations in rat brain cortex
1814 microdialysates [310]. Several authors have devised on-line derivatization systems, including
1815 the above-mentioned one, in which OPA and BME were used [311,312], as well as another one
1816 in which NDA and KCN were used [313], the latter obviating the need for an expensive UV
1817 LED source. Using the OPA/BME system, Glu and Asp were assayed in the striatum of
1818 anesthetized rats during acute electrical stimulation in the rat brain; the temporal resolution (*i.e.*,
1819 the interval between two consecutive collections of a microdialysate) achieved was 12 s, with

1820 an LOD of 200 nM recorded [311]. Using MEKC analysis, Asp, Glu, Ile, Leu, Lys, Met, Phe,
1821 taurine, Tyr, and Val were detected at basal concentrations ranging from 1.9 μ M (Asp) to 5.3
1822 μ M (Val), with a temporal resolution of 3 min. The concentrations of these AAs in the striatum
1823 were monitored after K⁺ depolarization [312]. In another study, the concentrations of Glu and
1824 Asp were measured at 5-s intervals in the striatum of chloral hydrate–anesthetized rats after
1825 depolarizing electrical pulses were administered to the prefrontal cortex, followed by injections
1826 of tetrodotoxin or depletion of extracellular Ca²⁺, or after infusion of L-trans-pyrrolidine-2,4-
1827 dicarboxylic acid using the dialysis probe [314].

1828 The extracellular concentrations of Glu, Asp, and *O*-phosphoethanolamine have also
1829 been analyzed in hippocampal slice cultures and in the striatum of anesthetized rats treated by
1830 perfusion with a solution with high K⁺ levels or containing a Glu uptake inhibitor. With NDA
1831 labeling, basal concentrations of 33 nM for *O*-phosphoethanolamine, 4.4 μ M for Glu, and 210
1832 nM for Asp were recorded.

1833 The primary aim in these studies was to initiate microdialysate experiments using the
1834 CE/LIF technique, as it can be easily adapted to small sample volumes and low concentrations
1835 [315]. However, this idea has certain commercial limitations, as insufficient progress has been
1836 made in this area of research compared to that in LC/electrochemical detection. Yet, significant
1837 research advances have been realized in various subfields of neuroscience using CE, as recently
1838 reviewed by Lapainis and Sweedler [316]. Here, we shall primarily focus on microdialysis
1839 assays.

1840 Since the 2000s, state-of-the-art methods have been designed by Parrot *et al* [317] and
1841 Nandy and Lunte [318]. Some important studies have been discussed below.

1842 After MEKC optimization and pH adjustment for the separation of Glu, Asp, and GABA
1843 labeled with NDA, a dual-probe microdialysis system was used in the striatum of mice to detect
1844 nanomolar concentrations of AAs [319]. Two laboratory-made concentric microdialysis probes
1845 were glued together (spaced at 0.5 mm). Vigabatrin, an antiepileptic drug, was perfused through
1846 the “delivery probe”, and then diffused into the extracellular space. The effluent of this probe
1847 was directed toward waste. The second probe was continuously infused with artificial CSF
1848 collecting vigabatrin, Asp, Glu, GABA, and cysteic acid present in the extracellular space,
1849 which were then off-line-labeled with NDA. The authors mentioned that vigabatrin induces
1850 alterations in Glu and GABA levels in a drug concentration–dependent manner at the site of
1851 biochemical changes; these finding may help develop a better understanding of the mechanism
1852 underlying the action of the drug [320].

1853 Five neurotransmitters—dopamine, noradrenaline, GABA, Glu, and Asp—were labeled
1854 with NDA/KCN through direct mixing in a collection tube. The authors observed that the
1855 sampling time was limited by the minimal volume (5 μ L) required for analysis using the
1856 automated CE system. The neurotransmitters could be assayed in 667-nL dialysates (collection
1857 time: 20 s). The LODs in the dialysis probe were between 1 nM (noradrenaline) and 420 nM
1858 (Glu). Temporal resolution enabled the simultaneous monitoring of these molecules in rats,
1859 which revealed the increase in GABA concentrations concomitant with seizures, as indicated
1860 by the combined electroencephalographic recordings [321].

1861 To achieve better on-line derivatization of microdialysates and to prevent off-line
1862 derivatization during in-capillary derivatization, the samples were sandwiched between two
1863 plugs (at a reagent-to-sample plug length ratio of 4) of a reagent mixture (NDA/NaCN at 1:1
1864 ratio) at the capillary inlet and then separated. The initial electrophoretic mixing was followed
1865 by a zero-potential reaction step before the application of separation voltage. The LODs were
1866 found to be identical to those obtained with off-line derivatization, and Asp and Glu were
1867 identified in brain microdialysates [322].

1868 Kaul *et al* [323] monitored the levels of carbamathione (a partial noncompetitive
1869 inhibitor of N-methyl-D-aspartic acid glutamate receptor), GABA, and Glu in brain
1870 microdialysis samples collected from the nucleus accumbens. After the administration of an
1871 intravenous dose of carbamathione (200 mg·kg⁻¹), a change was observed in the GABA and Glu
1872 levels.

1873 On-line derivatization of a microdialysate using OPA/BME was performed using a
1874 large-sized and expensive Ar laser functional at 351 nm, and CE separation was performed
1875 using hydroxypropyl γ -CD in the BGE. O'Brien *et al* [324] demonstrated the contrasting
1876 changes in striatal GABA and D-serine neurotransmitter levels in mice with hyperglutamatergic
1877 Tourette's syndrome and obsessive-compulsive disorder-like pathology. This was followed by
1878 measurement of the changes in extracellular D-Ser concentrations in the rat striatum in response
1879 to stimulation with glutamate agonists and antagonists [325]. In the same manner, on-line
1880 microdialysis-CE-LIF analysis was performed with OPA/BME on-line derivatization of the
1881 supernatant across an intact larval tiger salamander retina to quantitate D-Ser (Fig. 10) [326].

1882 Li *et al* [327] used a similar on-line derivatization protocol by inserting microdialysis
1883 probes into the nucleus accumbens core of rats and achieved 15-s temporal resolution of the
1884 AAs in microdialysates. The researchers trained Sprague–Dawley rats to self-administer either
1885 10% ethanol-containing gelatin or nonalcoholic gelatin. An increase in taurine concentration

1886 correlated with the quantity of ethanol consumed ($R^2 = 0.81$), whereas no concentration changes
1887 were detectable in the rats that consumed the nonalcoholic gel. A considerable increase in Gly
1888 concentration in both groups correlated with the quantity of gel consumed. The highest increase
1889 in Gly concentration was observed during the longest time-out period after each delivery of the
1890 gel. The anticipation of reinforcement correlated with an increase in Gly levels in the nucleus
1891 accumbens. Kasper *et al* [328] performed the microdialysis of the nucleus accumbens core
1892 under basal conditions and after potassium stimulation, in response to a novel candidate drug,
1893 4-phenyl-2-N,N-dimethylaminotetralin, and other modulators of 5-HT_{2C} receptor, which were
1894 administered by reverse dialysis. The GABA concentrations were measured. The authors stated
1895 that the 5-HT_{2C} receptor agonists specifically attenuated a stimulated GABA release in the
1896 nucleus accumbens core, whereas 5-HT_{2C} antagonists or inverse agonists did not exert any
1897 effect. Under the same conditions but with LIF with a 351-nm diode-pumped solid-state laser,
1898 the changes in the time course of the detection of AAs and a neurotransmitter in the rat nucleus
1899 accumbens were investigated by Venton *et al* [329]. They showed that following exposure to a
1900 predator odor, a rapid and transient increase in the levels of AA neurotransmitters (Glu, Asp,
1901 GABA, Gly, and Taurine) correlated with behavioral reactivity to salient stimuli.

1902
1903 NBD-F has been used for the on-line labeling of Ile, Leu, Val, Ala, Gln, and Glu as
1904 important indicators of adipocyte lipogenesis. Microdialysis was performed to assess
1905 metabolism dynamics of 3T3-L1 cells. The LODs achieved were 400, 200, and 100 nM for Ile,
1906 Leu, and Val, respectively [330]. Arg, Lys, Ile, Leu, Met, Phe, Val, GABA, Gln, Ala, Gly, and
1907 taurine were studied under the same conditions, and the on-line derivatization was implemented
1908 in a 66-cm portion of the capillary (75 μ m ID) heated at 80 °C (resulting in a reaction time of 5
1909 min). The separation was realized in a short portion of the capillary in less than 16 s. In this
1910 case, the LODs ranged between 0.7 μ M (Val) and 6.5 μ M (Gln). The microdialysis probes were
1911 implanted into the inguinal adipose tissue depot of C57BL/6 mice to record dynamic *in vivo*
1912 changes under insulin stimulation via tail vein injection. In this case, the Val, Ala, and taurine
1913 concentrations increased by 37%–46% [331].

1914 Microdialysis sampling of cells (with temporal resolution of 20 s) from an immortalized
1915 astrocytic cell line (C8-D1A) cultured in direct contact with a porous probe was performed to
1916 measure the release of small AAs and amines (labeled with NBD-F) from astrocytes after on-
1917 line derivatization. The basal release of Phe, taurine, DL-serine, and Glu was evaluated. Upon
1918 stimulation with KCl, the levels of Gly, taurine, and DL-Ser increased drastically by 700%,

1919 185%, and 215%, respectively, whereas the levels of Phe and Val were unaffected. The results
1920 of microdialysis were compared with data from the traditional collection of aliquots from
1921 cultured cells, which are suitable for measuring static concentrations. While the data were in
1922 agreement, the higher temporal resolution of *in vitro* microdialysis-CE enabled measurements
1923 that better reflected the dynamic changes in the cells [332].

1924 A mixture of 8 mM heptakis(2,6-di-O-methyl)- β -cyclodextrin and 5 mM 6-monodeoxy-
1925 6-mono(3-hydroxy)propylamino- β -cyclo-dextrin was used as a CS to separate L-Glu, D-Asp,
1926 and L-Asp. D-Asp is of interest because it modulates adult neural plasticity and embryonic brain
1927 development. The extracellular concentrations of these AAs were measured in microdialysis
1928 samples from freely moving chicks. The D-Asp concentration decreased during the first week
1929 after birth. The potassium-evoked release of D-Asp was observed. D-Asp constituted a greater
1930 percentage of total Asp in the extracellular space than in whole-tissue extracts; therefore, the
1931 bulk of D-Asp detected in tissues was from the extracellular space [333].

1932 Some of the studies performed in this field were based on the strategy devised by
1933 Hernandez *et al* 30 years ago using FITC as a labeling dye [308]. Intracerebral microdialysis in
1934 the hippocampus can be used to measure variations in agmatine concentration in the
1935 extracellular environment. Even though detectable quantities of this amine were found in the
1936 dialysates from probes located in the hippocampus, it was not found in the probes located in the
1937 lateral ventricle. The extracellular agmatine levels were shown to be calcium- and impulse-
1938 dependent, and eventually, the depolarization of hippocampal neurons was shown to lead to an
1939 increase in the extracellular agmatine concentration [334]. Skirezowski *et al* [335] investigated
1940 the role of ventral pallidum GABAergic terminals in rats with depressive-like behavior induced
1941 by the forced swim test. Changes in GABA levels were monitored in the ventral pallidum during
1942 the test. The GABA levels increased significantly during days 1 and 2 during swimming and
1943 returned to pre-swimming levels after the test ended. In another study, the GABA, Glu, and
1944 agmatine levels in the hippocampus were measured in rats subjected to a ketogenic diet for 2
1945 weeks and were compared to the levels in rats fed a normal rat chow diet. The GABA and
1946 agmatine levels were found to increase, whereas there were no changes in Glu levels. The
1947 authors concluded that the ketogenic diet altered the levels of various transmitters by favoring
1948 inhibitory over excitatory neurotransmitters [336]. Putrescine is another molecule whose
1949 concentration was measured in blood droplets collected from patients with Parkinson's disease.
1950 A statistically significant increase in erythrocyte putrescine concentration was detected with a

1951 nonsignificant increase in its plasma concentration. This leads us to the following question: Is
1952 putrescine causally involved in the pathophysiology of Parkinson's disease [337]?

1953 The levels of FITC-labeled Arg and Glu in gingival crevicular fluid collected from adult
1954 patients with chronic periodontitis (versus periodontally healthy controls) were measured using
1955 two types of microdialysis probes (normal and U-shaped probes). The two probes yielded the
1956 same results, and the increase in Arg and decrease in Glu concentrations were associated with
1957 periodontitis [338]. Microdialysis in the medial striatum of young post-hatch domestic chicks
1958 suggested that Asp is co-released with Glu and may play a substantial role (distinct from that
1959 of Glu) in the striatum [339]. These data indicate that FITC derivatization can be suitable for
1960 microdialysate analysis after off-line derivatization, and even though FITC contains several
1961 impurities and has relatively low reactivity, it can be used to analyze AAs or biogenic amines
1962 present at nanomolar concentrations.

1963 DTAF derivatization has also been applied to investigate focal cerebral ischemia and
1964 reperfusion induced by middle cerebral artery occlusion. Microdialysis in the hypothalamus of
1965 rats was performed to investigate the dynamic changes in the levels of 14 AAs (Arg, Lys, Trp,
1966 Phe, Gln, GABA, Asn, Pro, Ser, Ala, Tau, Gly, Glu, and Asp) during cerebral
1967 ischemia/reperfusion. Middle cerebral artery occlusion and reperfusion led to a significant
1968 increase in the extracellular levels of these AAs [340]. Additionally, this strategy was adapted
1969 to quantitate Arg, Lys, Trp, GABA, l-Ser, Ala, Tau, Gly, Glu, Asp, dopamine, and the
1970 neuromodulators D-Ser and *O*-phosphoethanolamine. The levels of neurotransmitters and
1971 neuromodulators were observed to be elevated during cerebral ischemia/reperfusion [341].

1972 5-carboxyfluorescein N-succinimidyl ester was used for Glu and Asp quantitation in the
1973 microdialysates of rat periaqueductal gray matter. The LODs obtained were below 1 nM, and
1974 the basal concentrations of the AAs were measured in the microdialysates and after formalin
1975 injection [342].

1976 FQ has also been suggested for this application. Wu *et al* [343] monitored its reaction
1977 rates with five neurotransmitters (Ala, taurine, GABA, Gln, and Glu) in artificial CSF. The
1978 LODs ranged from 1 to 10 nM. FQ was also used in a study on microdialysates and brain
1979 homogenates from rats [344].

1980 In a particular study, microdialysis involving UV-LIF (266 nm) was performed for the
1981 detection of fluorescent molecules such as serotonin with pH-mediated in-capillary

1982 pre-concentration of samples and a buffer consisting of 80 mM citrate (pH 2.5) and 20 mM
1983 hydroxypropyl- β -CD. The reported LOD was 0.25 nM [345].

1984 MS with ESI has also been used to analyze neurotransmitters in microdialysates. This
1985 approach was first proposed 25 years ago by Takada *et al* [346], and was developed recently
1986 for a crustacean model, *Cancer borealis*. In an attempt to combine CE with MALDI, a simple
1987 tool was devised, named pressure-assisted capillary electrophoresis-mass spectrometric
1988 imaging platform, in which CE flow and matrix flow (α -cyano-4-hydroxycinnamic acid) from
1989 a second capillary were mixed at the tips [347–349]. The resulting flow gently touched the
1990 MALDI plate surface, which was controlled mechanically, and moved along the long axis of
1991 the plate. A straight and uniform trace was deposited on the MALDI plate and was analyzed
1992 using MALDI MS imaging. MALDI imaging of the eluent migrating off the capillary was
1993 performed, similar to the process used in CE-ion mobility-MS experiments. The obtained
1994 results were compared with LC/MS data. Seventy-one compounds were selectively detected
1995 using CE/MALDI [350].

1996
1997 Over the past 20 years, the progress in CE techniques performed using detectors of
1998 different types has improved our understanding of the functioning of the brain in animals and
1999 humans. Intensive research aimed at identifying and quantifying neurotransmitters associated
2000 with the studied functions is conducted almost exclusively through on-line derivatization using
2001 microdialysis-CE-LIF devices. However, the popularity of these important studies seems to be
2002 transient, as in recent times, virtually no new applications have been reported in neurochemistry.

2003

2004 **8. Food analyses**

2005 AAs are essential nutritional components in a balanced diet and are present in food either
2006 as free AAs or AA residues in proteins. Furthermore, they can help elucidate the origin of a
2007 food product. Enantiomeric separation, a single procedure for a complex mixture, rapidity,
2008 sensitivity, and repeatability are helpful qualities for identity control and quality control
2009 techniques for foods and plants. Enantiomeric separation procedures help determine the impact,
2010 if any, of the chiral composition of dietary components on health.

2011 Unfortunately, food product analysis requires the release of AAs from a complex matrix,
2012 separation of individual AAs, and AA quantification using calibration standards. Even if the
2013 principle remains unchanged, each step has to be adapted to the specifics of the sample at hand.

2014 Owing to this, publications on the development of electrophoretic methods for applications in
2015 the food industry have rarely gained ground. Following a spike in the number of publications
2016 in 2010, fewer than five studies have been published per year.

2017 Technical developments are mostly related to sample preparation, and in recent years,
2018 to the introduction of “omics” tools (CE-MS for food).

2019 Surprisingly, the number of reviews (not focused on the subject but addressing it) is
2020 comparatively high. The first review on the use of CE-MS for the determination of AAs in food
2021 was published in 2005 by Simo *et al* [351]. In 2007, a review was published that focused on the
2022 applications of CE to the analysis of small molecules (free AAs, carbohydrates, organic acids,
2023 vitamins, and a variety of antioxidants) in foods [352], which helped establish CE as a useful
2024 alternative to chromatographic methods such as HPLC and GC in this field. In 2010, a review
2025 focusing on grape-derived products was published, in which different chromatographic
2026 methodologies (including CE) as well as several derivatizing reagents used for enological
2027 purposes [353] were compared [354]. In the same year, enantiomeric CE separation methods
2028 for characterizing AAs, pesticides, and phenols in foods and beverages were studied [355]. A
2029 review with a special focus on electromigration methods for the analysis of food constituents,
2030 including AAs and biogenic amines, was also published [356]. In 2014, a review was published
2031 on CE-based assays (electromigration, microchips, CE/MS, and chiral CE) of biomolecules
2032 present in food and beverages [357]. The evolution of AA, protein, lipid, and carbohydrate
2033 analyses of food samples using electromigration techniques over a period of 20 years [358] and
2034 the use of CE for the analysis of nonproteinogenic AAs [359] were also reviewed.

2035 Last year, there was significant interest regarding methods for assessing food quality
2036 and authenticity based on AA determination [360]. Assays on nonproteinogenic AA
2037 determination were also reviewed for the period spanning 2015–2018 [361], while three
2038 detailed examples of enantioseparation were described by Castro-Puyana and Marina [362].

2039

2040 **8.1. AAs in beverages**

2041 Most studies on CE for analysis of food products have focused on beverages, and more
2042 specifically on fruit juice, tea, beer, and wine.

2043 **8.1.1. Juices**

2044 The simultaneous analysis of citrus juice components using CE was integrated into a
2045 single procedure using a BGE containing 5% of acetonitrile. Biogenic amines, flavonoids, and

2046 aromatic AAs (Trp, Phe, and Tyr) in citrus juice can be used to assess the quality, freshness,
2047 and possible adulteration of these products. Simo *et al* [363] successfully differentiated between
2048 three types of commercial orange juice (*i.e.*, nectars, orange juice reconstituted from
2049 concentrates, and pasteurized orange juices not manufactured using concentrates) by
2050 quantitating FITC-labeled L- and D-AAAs using MEKC-LIF and β -CD. In addition, the authors
2051 also described a new coaxial chiral CE-MS coupling method for separating D- and L-AAAs
2052 [364]. β -CD was used with a BGE with a coated capillary (ethylpyrrolidine methacrylate-N,N-
2053 dimethylacrylamide, a copolymer), which prevented contamination of the electrospray [365].
2054 Under optimum CE-MS conditions, the MS sensitivity levels obtained for FITC- and dansyl-
2055 AAAs are similar, whereas chiral resolution is more suitable for FITC-AAAs. Chiral CE-MS allows
2056 the detection of D/L-Asp, -Glu, -Ser, -Asn, -Ala, -Pro, -Arg, and GABA in commercial orange
2057 juices (Fig. 11).

2058 A rapid CE separation method was designed to analyze S-adenosyl-L-methionine in
2059 fruits and fruit juices without a pre-purification step; this method was found to be 50% more
2060 rapid and sensitive than the conventional HPLC technique [366].

2061 Cys and GSH were also quantified in orange juices and soft drinks at micromolar levels
2062 using a disulfide reduction step followed by quinolinium derivatization of thiols and separation
2063 using CE with acetonitrile stacking [367].

2064

2065 **8.1.2. Soft drinks**

2066 A rapid CE method was designed for the simultaneous detection of AAAs within 17 min
2067 in several beverages using 1,2-naphthoquinone-4-sulfonate derivatives ; The LOD obtained for
2068 all AAAs was 1 mg·L⁻¹ [368].

2069 In a particular study, a PMMA chip was used to quantitatively analyze AAAs in sports
2070 beverages, jelly-form beverages, and tablet-form functional foods. MEKC was coupled with
2071 LEDIF detection, and the sample labeling and analysis required less than 10 min [369].

2072

2073 **8.1.3. Tea**

2074 Seventeen NDA-AA derivatives were quantitatively analyzed within 16 min in tea
2075 (*Camellia sinensis*) leaves and beverages using CE/LEDIF (410 nm) [370].

2076 To decrease matrix interference, a methodology was published for the improved analysis
2077 of tea samples without pre-purification and pre-concentration. An in-capillary OPA/BME

2078 derivatization procedure combined with stacking CE was used to implement the analytical
2079 process at a subnanomolar detection level [371].

2080 Aroma is an essential factor that affects tea quality. Using CE, it was discovered that
2081 dark storage significantly raises the levels of most AAs, including L-Phe, a key precursor of
2082 phenylpropanoids/benzenoids [372].

2083 In a study, CE was coupled with evaporative light scattering detection. This was
2084 combined with a step for sample cleanup using carboxylated single-walled carbon nanotubes.
2085 The method was applied to white tea samples [373]. This technique is claimed to have an LOD
2086 in the micromolar range; however, a CE system based on this technique is not yet commercially
2087 available, nor are the carbon nanotubes.

2088

2089 **8.1.4. Beer and wine**

2090 Nine AAs, along with serotonin, were detected in wine samples of different origins and
2091 vintage using rapid CE/LIF. In the study, DTAF microwave-assisted derivatization was
2092 performed, and a direct hydrodynamic injection was applied to commercial Italian wines [374].
2093 An ionic liquid with β -CD and SDS was added to the BGE for a CE assay of AAs with in-
2094 capillary OPA/BME labeling of beer samples. Eleven AAs were detected and quantified,
2095 indicating the valuable potential applications of this method in food analysis [375].

2096 *Saccharomyces cerevisiae* growth is known to decrease significantly under acidic
2097 conditions. A metabolomics approach was adopted to understand this phenomenon [376]. *S.*
2098 *cerevisiae* was cultured in a lactic acid-containing medium (pH 2.5). The addition of Pro to the
2099 culture medium protected the proliferating cells from acid stress. A separation method based on
2100 CE/LIF was developed to evaluate AA consumption by yeast during beer fermentation [377].

2101 Trp detection in beer was performed using an isotachophoretic CE process between the
2102 leading electrolyte comprising 10 mM HCl, 1% HEC, 20 mM 1,3-
2103 bis[tris(hydroxymethyl)methylamino]propane, and 10 mM 6-aminocaproic acid, and the
2104 terminating electrolyte, which was 20 mM 2-amino-2-methyl-1,3-propanediol. An LOD of 2.6
2105 mg·L⁻¹ was achieved. The results were found to be comparable to those obtained using HPLC
2106 [378].

2107

2108 **8.1.5. Other beverages**

2109 Chiral ligand exchange CE with UV detection has been used for the selection of aromatic
2110 D- or L-AAAs in rice-brewed suspensions (Laozao) using a Zn(II) complex as a chiral selection
2111 agent [379]. Baseline separation of DL-aromatic AAAs and partial separation of some 9-
2112 fluorenylmethoxycarbonyl-labeled nonaromatic AAAs were achieved. Aromatic AAAs were
2113 found to be present in the millimolar range in Laozao from four different brands.

2114 Jayarajah *et al* [380] devised a portable microCE instrument that could detect biogenic
2115 amines with fluorescamine-labeled primary amino groups in fermented beverages within only
2116 120 s using a glass CE device containing 21.4 cm long separation channels.

2117 N-phenylpropenoyl-l-amino acids are important contributors to the astringent taste of cocoa.
2118 Crude extracts of defatted seeds were analyzed using CE in less than 30 min [381]. A CE-LIF
2119 (488 nm) assay for FITC-labeled Arg, Val, Trp, folic acid, and niacinamide, plus riboflavin
2120 (natively fluorescent) in roasted cocoa beans was reported and applied to four health drink
2121 samples [382].

2122 In a study, on-line coupling between liquid-liquid extraction and CE/C⁴D was tested on
2123 complex food matrices with high sodium contents. The sample was prepared in a dextran-rich
2124 phase (8% w/v 500 kDa Dextran), and 5.0 M acetic acid with 6% w/v of 6-kDa PEG (the second
2125 phase) was used as the BGE. Glu could be quantitated in soy sauces, and Lys, His, Arg, Gly,
2126 Ala, Ser, Val, Leu, Asn, Thr, Trp, Met, Tyr, Pro, and Cys could be detected in less than 12.5
2127 min. The LOD for Glu was ~10 μM [383].

2128 An interesting approach was designed using a portable battery-operated CE instrument.
2129 The instrument had two capillaries, each equipped with a C⁴D detector and different buffers to
2130 quantify taurine, niacin (vitamin B3), and choline in energy drinks, fresh and powdered milk,
2131 and probiotic green rice. LODs of ~2 μM were achieved [384,385].

2132 In a study, baseline separation of the enantiomers of 11 DL-AAAs, detectable as
2133 [AA+18C6H4+H]⁺ ions (*i.e.*, complexed with 18C6H4) was performed successfully using CE-
2134 MS, whereas five other AAAs were only partially separated. The identification of several D
2135 enantiomers in balsamic and red vinegars correlates with fermentation during the manufacturing
2136 process. The taste quality of fermented foods can be assessed based on the concentration of D-
2137 AAAs [386]. Similarly, a CE/MS approach was used successfully to distinguish between low-
2138 and high-quality Japanese Ginjo sake [387].

2139

2140 **8.2. Milk products**

2141 The detection of furosine (ϵ -N-2-furoylmethyl-L-lysine) in food using CE has been
2142 optimized for analyses of pasteurized milk and Mozzarella cheese [388]. Later, a CE method
2143 for assaying AAs was developed and validated. The method enabled the separation and
2144 detection of important metabolic acids and AAs in yogurt and commercial cheeses. Using this
2145 method, 10 AAs were resolved, with an LOD of 2 mM achieved for Gly [389]. A CE/MS
2146 metabolomic approach was used to compare a type strain of *Lactococcus lactis* and a GABA-
2147 producing strain, *L. lactis* 01-7 [390]. This approach showed that the GABA content was higher
2148 in *L. lactis* 01-7-fermented milk. Furthermore, the study also revealed that the Orn levels were
2149 27-fold higher than those in control milk.

2150 AAs from alternative nutritive sources are of interest to some authors. A cheap method
2151 was proposed for analyzing FITC-labeled AAs based on CE/LEDIF in Cucurbitaceae milk from
2152 Sub-Saharan Africa. Six essential AAs (Phe, Thr, Val, Trp, Ile, and Leu) were detected in the
2153 extracts; however, lysine was not detected [391]. *Lathyrus* plants, also known as peavines,
2154 represent an alternative protein source; however, excess consumption of these can lead to
2155 lathyrism caused by β -N-oxalyl-L- α,β -diaminopropionic acid. A relevant CE/UV (195 nm)
2156 detection method was published for its analysis [392].

2157

2158 **8.3. Miscellaneous**

2159 1-aminocyclopropane-1-carboxylic acid present in apple tissues was detected using
2160 MEKC/LIF [393], in which the compound was baseline-separated from other AAs. An LOD of
2161 10 nM was documented without extra purification and enrichment procedures.

2162 MEKC/UV (265 nm) detection of S-alk(en)ylcysteine-S-oxides in 12 commonly
2163 consumed alliaceous and cruciferous vegetables (*e.g.*, garlic, onion, leek, chive, cabbage,
2164 radish, cauliflower, and broccoli) was developed using FMOc derivatization [394]. The total
2165 content of these oxides in the analyzed *Allium* species varied between 0.59 and 12.3 mg·g⁻¹
2166 fresh weight.

2167 Cereals are major sources of Phe. A MEKC/UV (200 nm) method was devised to assess
2168 the Phe content in cereals [395]. The obtained selectivity and accuracy were found to be
2169 comparable with those of an LC-MS/MS method, and the new method could be applied to some
2170 cereal products.

2171 A CE/C⁴D technique was used to detect free AAs in *Nicotiana tabacum* leaves [396].
2172 Although LODs in the lower micromolar range for the 20 proteinogenic AAs made this system
2173 suitable for metabolic studies, Met and Cys could not be detected using this method. In another

2174 study, LC-MS, CE-MS, and GC-MS were utilized for metabolomic analysis of tobacco leaves
2175 [397]. Leaf aging clearly led to reduced AA concentrations, especially for Gln or Asn. A similar
2176 approach was adopted to investigate the interactions between carbon and nitrogen metabolic
2177 pathways in mature tobacco leaves [398].

2178 A metabolomic investigation was performed to analyze glucosinolates, isothiocyanates,
2179 sugars, and AAs along with the bacterial loads in rocket salad [399]. CE/MS was employed to
2180 simultaneously assay the effects of carbon dioxide supply, nutrient formulation, and LED
2181 irradiation on head lettuce production [400].

2182 A novel method for furosine detection in food products using CE-MS/MS was optimized
2183 and validated. Solid-phase extraction treatment was applied to different flours and different
2184 food products (pasta, milk). Appropriate LOD, recovery, and intraday repeatability values were
2185 obtained [401].

2186 A CE-MS/MS method was developed to detect seed-oil adulteration in extra virgin olive
2187 oils. This approach enabled the determination of Orn, β -Ala, GABA, alloisoleucine, citrulline,
2188 and pyroglutamic acid levels [191]. The suggested method was validated and applied to the
2189 identification of the selected nonproteinogenic AAs in various oils. The method was also used
2190 for analyzing olive oil adulteration with soybean oil.

2191 The presence of AAs in fermented soy sauce was investigated with a focus on food
2192 safety [402] using a Förster resonance energy transfer detection approach with OPA/BME
2193 derivatives. Trp concentration was selectively determined, because Trp decomposes when soy
2194 is treated by acidic hydrolysis instead of natural fermentation. A sensitivity of approximately
2195 10 nM was achieved for Trp.

2196

2197 **9. Conclusion**

2198 In conclusion, the most pertinent question is why CE is used instead of LC. The limitations
2199 of CE concerning the repeatability are well known. They can be due to the buffering capacities of the
2200 electrolyte and to the buffer replenishment. The capillary cutting, the precision of the injection volume
2201 and the rinsing steps are also very important. The temperature needs also to be controlled. The
2202 commercial instruments, especially those coupled to MS, have cooling capacities for an optimized
2203 temperature regulation. When controlling these different parameters, CE will have repeatabilities
2204 comparable to LC. Then, CE is more compatible with lower sample volumes than usual LC (few nL vs.
2205 few μ L). Moreover, it may also be argued that the working cost of a CE run is considerably lower than
2206 that of an LC run, in particular because of low buffer volumes (few mL per day for CE vs. few hundred
2207 mL for LC). Additionally, in most studies, a simple fused silica capillary is used in CE (costing 10€/m),

2208 which is considerably less expensive than an LC column. Enantiomers are also easier to separate using
2209 CE than LC. Lastly, by coupling CE with C⁴D detection, the analysis and quantification of AAs in the
2210 μM range (and at times in the sub-μM range) can be realized without derivatization, whereas LC-UV
2211 requires a derivatization step.

2212 We would like to focus on the learnings from this review. A significant body of
2213 research exists on the determination of AAs using CE. Several authors have investigated
2214 different means of separation and various method of detection of AAs, using UV, LIF or LEDIF,
2215 C⁴D, or MS. Therefore, researchers who wish to use CE for AA determination will have access
2216 to a lot of information, maybe even excess. This review was our attempt to assist future users
2217 of CE in the selection of an appropriate CE method.

2218 For detection of molecules at nanomolar concentrations using CE, CE/LEDIF should
2219 be used, and based on the excitation wavelength, one has to select the suitable dye from different
2220 dyes, which have also been discussed in this review. Moreover, specificity for the target AA
2221 should be considered during selection. Some of these AAs are difficult to detect (*e.g.*, Trp). If
2222 AA concentrations are in the micromolar range, C⁴D is considerably effective and has been
2223 proved to be the best detection method candidate, as the method does not require derivatization
2224 and the sample preparation process is simple. The buffers used primarily contain acetic acid at
2225 high concentrations with different adjuvants to improve separation. Several other weakly
2226 charged molecules, including lactic acid, citric acid, Tris, Ches, MES, and CAPS, can also be
2227 used in BGEs for CE-C⁴D. In the near future, this detection technique will assist AA
2228 applications in clinical biochemistry laboratories. As for CE/UV, its major limitation is the
2229 necessity for derivatization, which is not a prerequisite for CE/C⁴D. This makes CE/C⁴D the
2230 preferred method.

2231 When AAs and other small-molecule compounds in micromolar and submicromolar
2232 ranges are to be detected using CE, MS is the detection method of choice owing to its selectivity
2233 and mass measurement resolution, even though the choice of volatile buffers available is
2234 considerably limited. Sensitivity, selectivity, and easily operable devices make MS an
2235 impressive detection method even for small ions from AAs. In studies on metabolomics, the
2236 use of CE/MS is usually discussed passively. Analytical conditions are usually not presented,
2237 and this technique is gradually becoming redundant, even though the impressive results
2238 obtained using this method are well-reported.

2239

2240 **10. References**

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3379 **Figure 1:** Normalized number of publications related to CE and AA in reports published since
 3380 2000 (source Web of science). The obtained curves are polynomes of the third degree. The data
 3381 for each curve are normalized to obtain a clear presentation. The maximum number of yearly
 3382 publications related to the different curves are indicated in parentheses: CE (994), CE and AA
 3383 (227), CE/MS and AA (57), CE/fluorescence and AA (65), CE/C⁴D and AA (16).

3384

3385 **Figure 2:** Electropherograms of five-fold diluted deproteinized plasma samples without A) and
 3386 spiked with B) 100 mM standard-free AA/peptide mixture. Electropherograms of 30 AAs.
 3387 BGE: 8 mM *p*-aminosalicylic acid –2 mM NaCO₃ at pH 10.15, 87 cm long 75 μm ID capillary
 3388 (effective length: 80 cm), 15 kV. Detection: UV absorption at 254 nm. (1) Arg, (2) Lys, (3)
 3389 Orn, (4) Pro, (5) GABA, (6) hydroxy-Lys, (7) Ala, (8) carnosine, (9) Leu/ Ile, (10) Trp, (11)
 3390 Citruline, (12) Val, (13) Phe, (14) Ala, (15) His, (16) Met, (17) Gln, (18) Thr, (19) Asn, (20)
 3391 Gly, (21) Ser, (22) Tyr, (23) homocystine, (24) Hcy, (25) cystine (26) oxydated glutathione
 3392 (GSSG), (27) Glu, (28), reduced glutathione (GSH), (29) Asp. Ref [37], with permission.

3393

3394 **Figure 3:** AA determination using CE-C⁴D in DBS eluate of five individuals (20 μL of DBS
 3395 eluted with methanol/water (50/50, v/v)). The separation was realized using 1.6 M acetic acid,
 3396 1 mM 18-crown-6, 0.1% (v/v), Tween 20, pH 2.1. 30 kV. (1) Choline, (2) Creatinine, (3) Orn,

3397 (4) Lys, (5) Arg, (6) His, (7) Gly, (8) Ala, (9) Val, (10) Ile, (11) Leu, (12) Ser, (13) Thr, (14)
3398 Gln, (15) Glu, (16) Phe, (17) Tyr, (18) Pro; *, unknown. Ref [58], with permission.

3399

3400 **Figure 4:** Electropherogram of diluted cerebrospinal fluid (20× in water) (1) Trp, (2) Tyr, (3)
3401 hydroxyindole acetic acid; (u) represent unidentified compounds. The separation was realized
3402 using 10 mM CAPS, 15 mM sodium tetraborate, pH 9.2, 15 kV with a 75 μm ID capillary of
3403 length 60 cm (effective length 53 cm). Detection was performed using a UV-LIF detector
3404 equipped with a 266-nm pulsed laser. Ref [78], with permission

3405

3406 **Figure 5: I)** Schematic illustration of processes occurring in EMMA. Step A) Injection of
3407 “sweeping plug” and reactants. The depicted plug length ratios are equal to the real plug length
3408 ratios. Step B) Mixing of reactants using EMMA. The injected plug of NaCN is pushed out
3409 from the capillary by the EOF, whereas the merged plugs of reactants (derivatization plug) are
3410 retained within the capillary. Step C) Reaction incubation at zero potential allowing a high
3411 reaction yield. Step D) SDS from the “sweeping plug” sweeps NDA-labeled AAs and results in
3412 improved peak shapes. Step E) Separation of NDA-labeled AAs. Steps D and E occur
3413 simultaneously. The inlet capillary end was immersed either in NaCN solution or in the BGE,
3414 and in all cases, the outlet capillary end was immersed in the BGE. [NaCN] = 250 mM [NDA]
3415 = 8 mM in MeOH/isopropanol (4/1, v/v), BGE: 73 mM SDS, 6.7% (v/v) 1-propanol, 0.5 mM
3416 HP-β-CD, 135 mM H₃BO₃/NaOH, pH 9. **II) A)** Electropherograms of model samples of AAs
3417 recorded after on-capillary derivatization with NDA/NaCN using EMMA mixing strategy. Peak
3418 order differences and migration time shifts between the electropherograms originate from the
3419 sweeping performed in EMMA, which provides additional selectivity. Capillary 50 μm ID
3420 66.0/45.0 cm total/effective length, 30 kV; (1) Asn, (2) Ser, (3),Gln, (4) Thr, (5) His, (6) cystine-
3421 mono-labelled, (7) Glu, (8) Gly, (9) Tyr, (10) Ala, (11) Asp, (12) Tau, (13) Ala-Gln, (14) Val,
3422 (15) Met, (16) norVal, (17) Trp, (18) Ile, (19) Leu, (20) Phe, (21) Arg, (22) cysteine di-labelled
3423 NDA, and (23) Lys. Imp.: Impurity from the Tau standard. Cond. benzoin-type condensation
3424 products of NDA catalyzed by the cyanide anion. B) Same electropherogram as that depicted
3425 in A without peak identification. C) 100× diluted pooled human plasma, D) 100× diluted culture
3426 medium. The peak corresponding to NDA-labeled-Ile was the only peak identified by the
3427 standard addition method in all samples (and the only one selected for the matrix effect study).
3428 Ref [102], with permission

3429

3430 **Figure 6:** (A) Plot of 22 consecutive electropherograms collected on-line during step change in
3431 Glu and Asp concentrations. These AAs were labelled using a low-gated injection interface and
3432 BME. UV-LEDIF detection (100 mW, $\lambda_{\max} = 365$ nm) was performed. Analyte concentration
3433 changed from 0.5 to 2 μ M and back to 0.5 μ M. Reaction conditions: injection, 1 s; crossflow,
3434 1 mL/min (10 mM phosphate, pH 7.4); capillary ID, 25 μ m; EL, 8 cm. Ref [119], with
3435 permission

3436
3437 **Figure 7:** A) Extracted-ion electropherograms for evaluating the separation efficiency achieved
3438 for human-plasma extract. (1) Orn, (2) Lys, (3) Arg, (4) His, (5) β -Ala, (6) Ala, (7) sarcosine,
3439 (8) GABA, (9) N,N-dimethyl-Gly, (10) Gly, (11) creatine, (12) Val, (13) betaine, (14) Ser, (15)
3440 homo-Ser, (16) Thr, (17) iso-Leu, (18) Leu, (19) Asn, (20) Met, (21) Gln, (22) Pro, (23) Glu,
3441 (24) Trp, (25) citrulline, (26) Phe, (27) Tyr, and (28) Asp were detected during cation analysis.
3442 The electropherograms of (29) 3-hydroxybutyric acid, (30) 2-hydroxybutyric acid, (31) lactic
3443 acid, (32) fumaric acid, (33) citric acid, and (34) isocitric acid were detected during anion
3444 analysis. B) Overview of the 270 metabolites identified during metabolome analysis of human
3445 plasma extract using CE-high resolution MS. Ref [187] with permission.

3446
3447 **Figure 8:** CE/LIF (488 nm) of plasma samples derivatized using 5-IAF. The analysis presents
3448 the electropherograms of A) total; B) free; C) reduced thiols of healthy (thick black line) and
3449 hyperhomocysteinemic subjects (dotted line). Reagents used: 5 mmol/L sodium phosphate, 5
3450 mM boric acid as electrolyte solution with 75 mM N-methyl-D-glucamine, pH 11. 45 °C, 30
3451 kV. Ref [269], with permission.

3452
3453 **Figure 9:** CE/UV of Phe, Trp, methyl-Trp (IS, 200 μ M), and Tyr in human plasma using 80
3454 mM Tris phosphate solution titrated at pH 1.4 with 85% m/m phosphoric acid. UV absorbance:
3455 200 nm. The samples were prepared using 50 μ L of plasma, to which 50 μ L of water was added,
3456 along with 20 μ L of 200 μ M of methyl-Trp and 25 μ L of sulfosalicylic acid (15% m/v). After
3457 centrifugation, 50 μ L of the supernatant was use for CE. Unk= unknown compounds. Ref [300],
3458 with permission.

3459
3460 **Figure 10:** Schematic of the A) microdialysis-capillary electrophoresis instrument; B) flow gate
3461 (with 43 mM OPA (9/1 methanol/75 mM borate, pH 10.5, 10 μ L/h)/114 mM BME (in artificial

3462 CSF (aCSF), (10 $\mu\text{L}/\text{h}$) capillary and CE/UV-LIF (351 nm) separation capillary); C)
3463 microdialysis probe (0.33 $\mu\text{L}/\text{min}$) with aCSF. The mix exited the cross into a 9 cm long, 150
3464 μm ID capillary. The derivatized dialysate was injected into the CE capillary using a flow-gated
3465 interface, comprising an acrylic block that held the reaction capillary and the separation
3466 capillary (8 cm long, 5 μm ID end-to-end with a 50- μm gap between them; the BGE was
3467 pumped through this gap at a rate of 40 mL/h). D) Electropherograms of dialysate sampled from
3468 the rat striatum under normal conditions. The labeled peaks represent (1) L-2-aminoadipic acid
3469 (internal standard), (2) glutamate, (3) GABA, (4) taurine, (5) D-Ser, and (6) L-Ser. BGE: 100
3470 mM borate/20 mM HP- β -CD, pH 10.5; 20 kV. (E) Maximum percent change in Glu, GABA,
3471 D-Ser, and L-Ser concentrations observed during a 3-min application of 100 μM N-methyl-D-
3472 aspartate (NMDA) and 100 μM NMDA+ 200 μM MK-801 (a NMDA receptor antagonist). * p
3473 < 0.05 compared to 100 μM NMDA. ** p = 0.08 compared to 100 μM NMDA. p -values were
3474 determined using the t -test. Ref [325], with permission

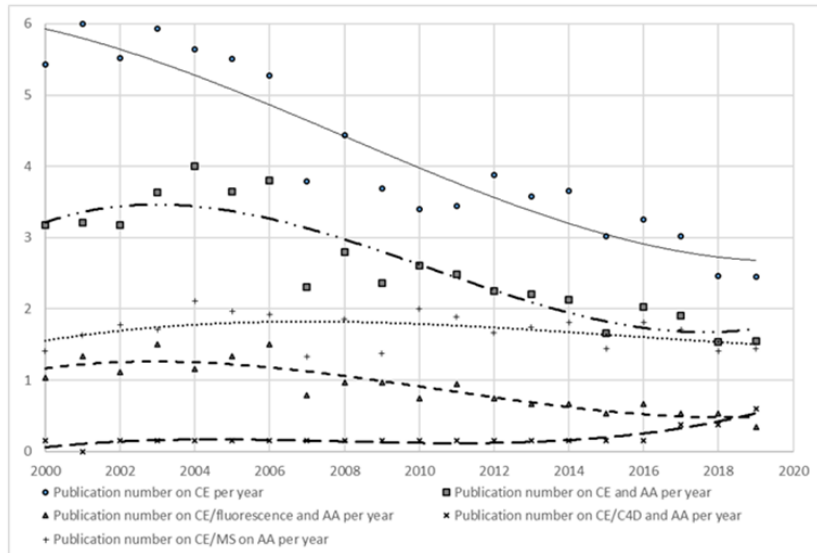
3475

3476 **Figure 11:** Extracted ion electropherogram of CE-ESI⁺-MS of: A) standard D/L-Asp, -Glu, -
3477 Ser, -Ala, -Asn, -Pro, -Arg, and GABA derivatized with FITC at 125 μM of each AA, B) orange
3478 juice sample adulterated with 0.8% D/L Asp. CE conditions: polymer-coated capillary (87 cm
3479 ID, 50 μm ID); BGE, 100 mM ammonium acetate, pH 6, 5 mM β -CD; 15 kV. Sheath liquid:
3480 MeOH/water (1/1 v/v) with 25% BGE without β -CD, flow rate 3.5 $\mu\text{L}/\text{min}$. Ref [364], with
3481 permission.

3482

3483 Fig1

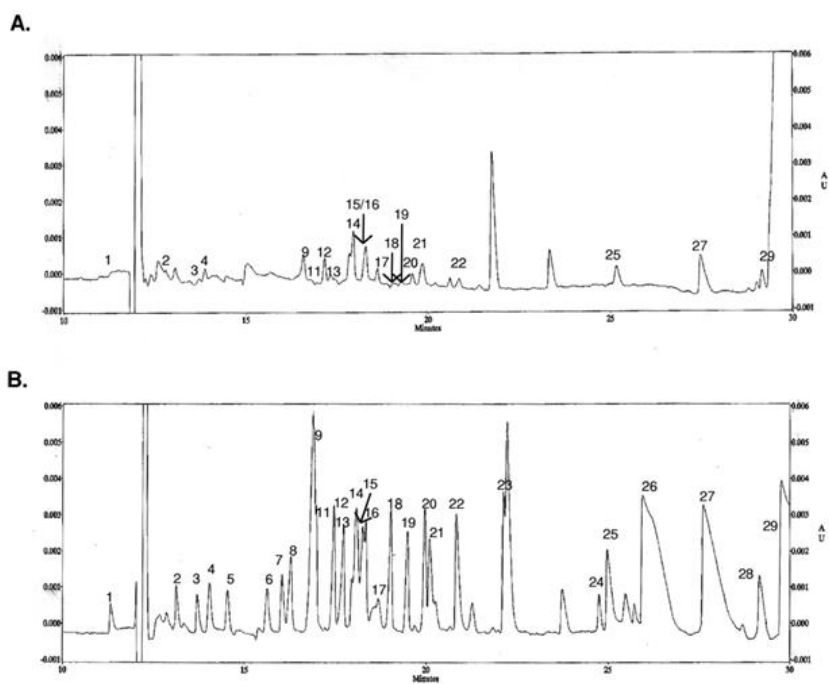
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3486 Fig 1

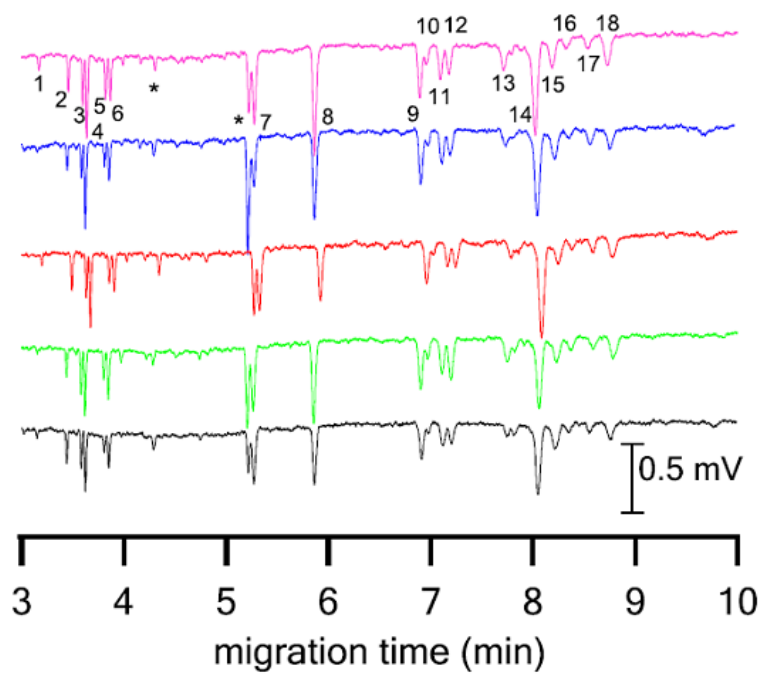
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3489 Fig 2

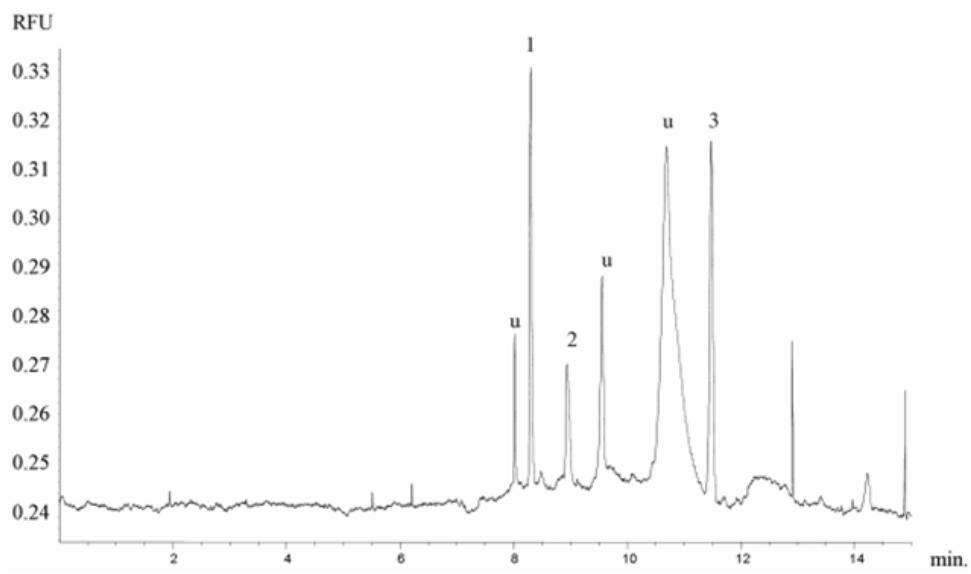
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3492 Fig 3

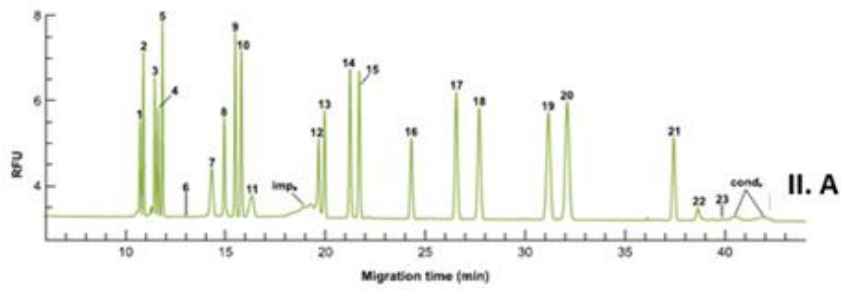
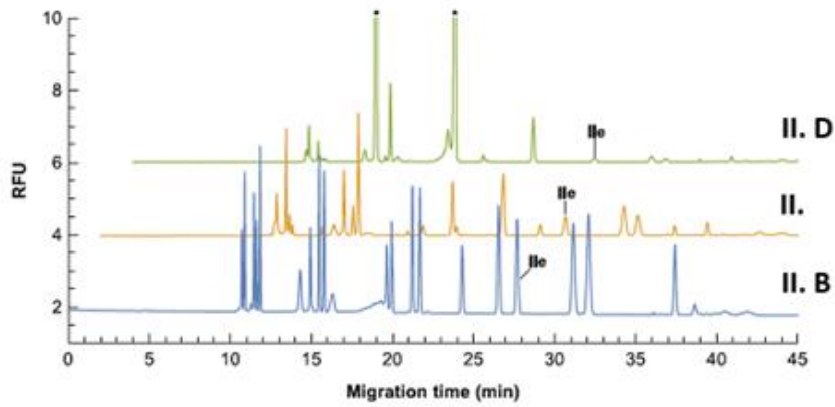
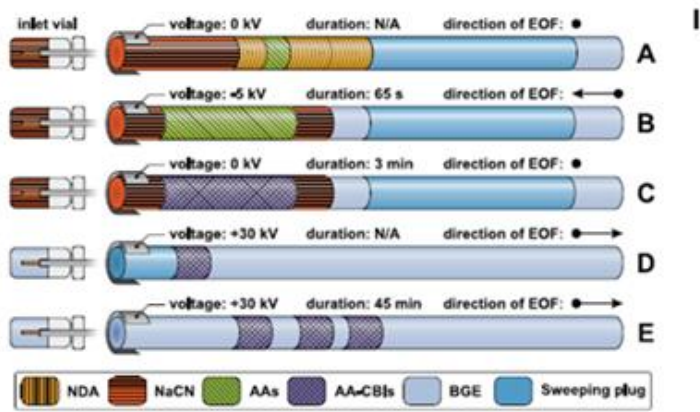
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3495 Fig 4

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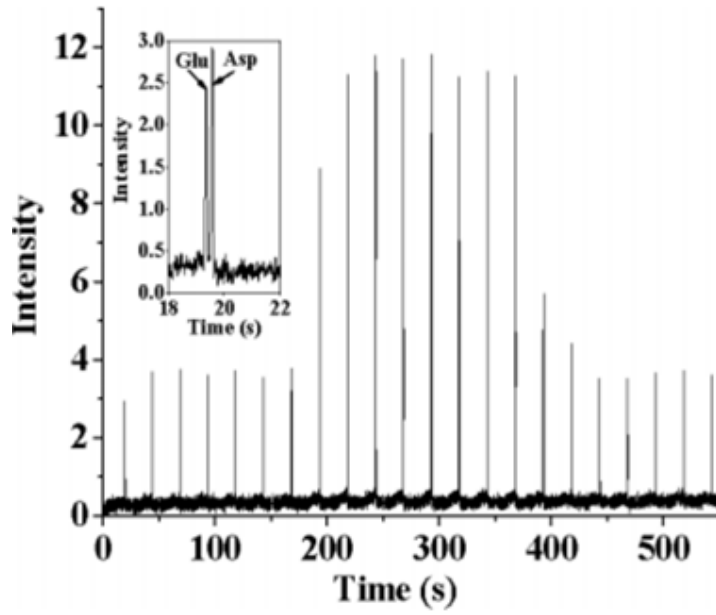


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3498 Fig 5

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3500 Fig 6



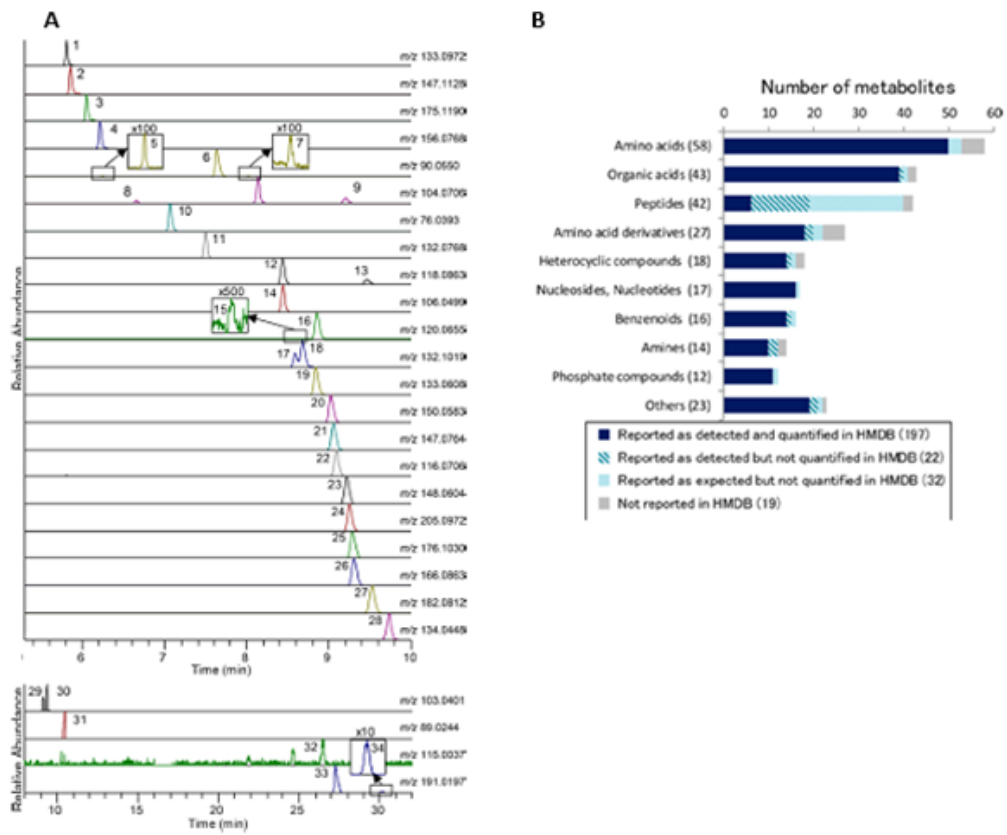
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3504 Fig 7

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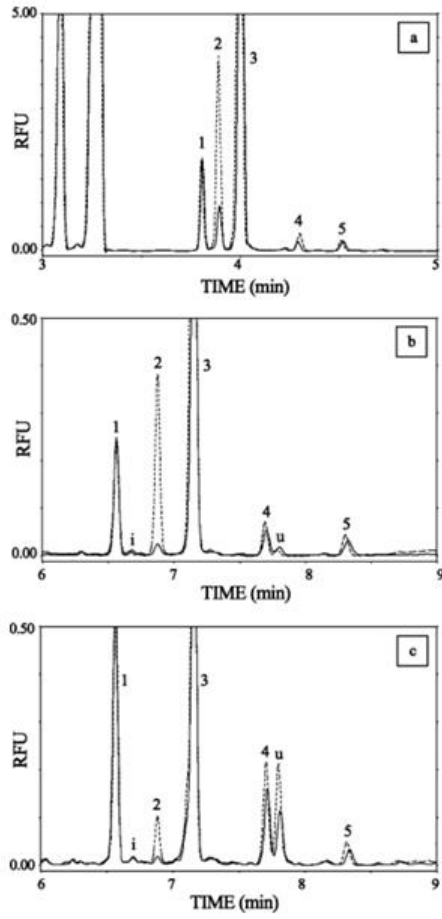


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3508 Fig 8

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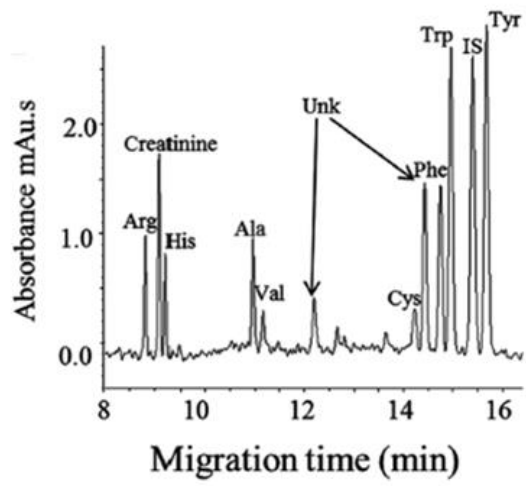
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3514 Fig 9

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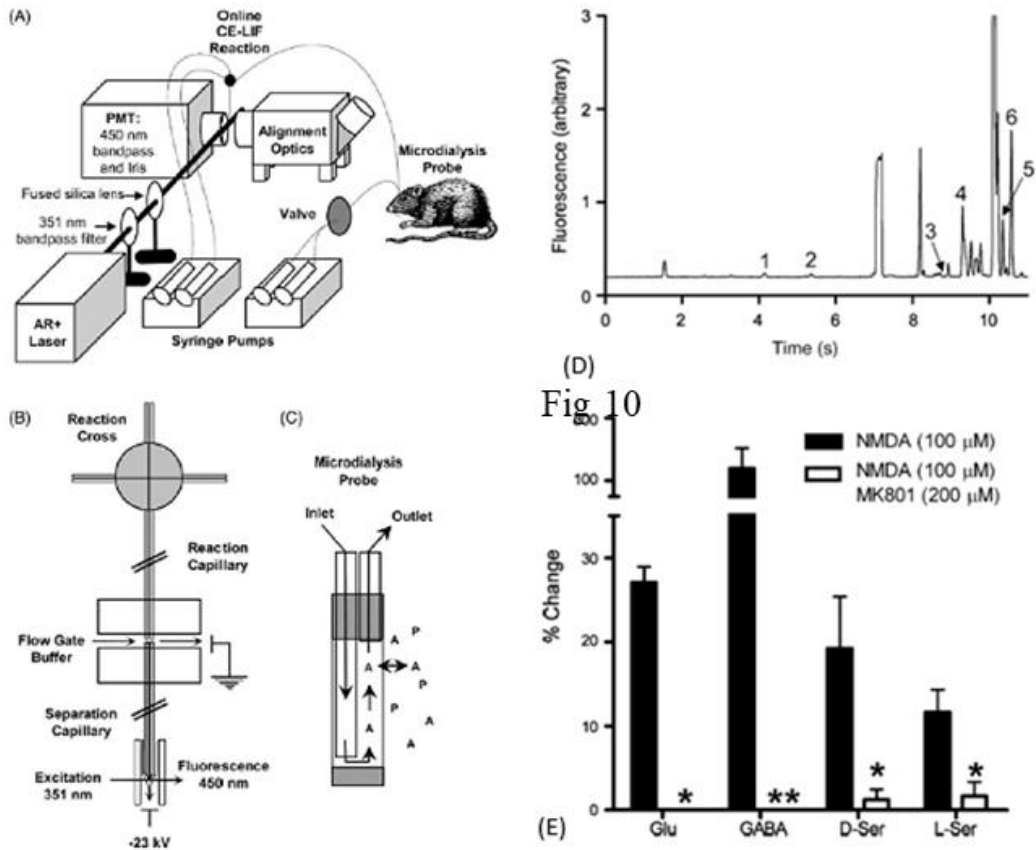
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3518 Fig 10

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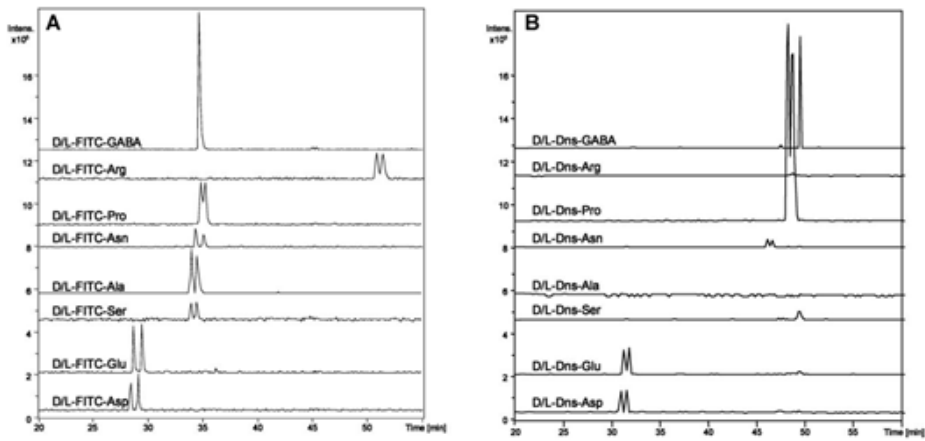
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3524 Fig 11

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Table 1: Separation and detection parameters adopted in the major publications reviewed in the chapter CE/UV

(AA, amino acid; nd, not determined; ID, inner diameter of the capillary; EL, effective length of the capillary; TL, total length of capillary; IS, internal standard)

AA	Sample and sample treatment	Separation conditions	Detection λ (nm)	LOD	Ref
Taurine, homotaurine (IS)	100 μ L human, (or feline, or bovine) plasma + 150 μ L ACN vortexed, then centrifuged. 200 μ L supernatant react with 20 μ L fluorescamine (5 mg/L) in ACN.	75 μ m ID, 50 cm TL, 40 cm EL capillary. Citric acid pH=3. -27.5 kV	266	nd	[13]
All proteinogenic AA (except Trp)	16 hours, 6 M HCl hydrolysis (110 °C) of 100 mg fish flour, filtered, evaporated. 500 μ L water diluted. 100 μ L were reacted with 100 μ L Na ₂ CO ₃ (0.1 M). 300 μ L isopropanol, 5 μ L PITC , 35 min. Excess PITC removed with hexane.	50 μ m ID, 65 cm TL, 55 cm EL capillary, phosphate (30 mM, pH 7.4), 4 mM β -CD, +25 kV. Leu/ Ile not separated	254	1 μ M	[14]
D/L-Glu, D/L-Ser, D/L-Met, D/L α -amino-n-butyric acid, D/L Trp, D/L norLeu, D/L Asp, D/L Ser	Standard dansylated AAs diluted in BGE.	50 μ m ID, 55 cm TL, 40 cm EL capillary. 10 mM Cu(CH ₃ COO) ₂ , 20 mM L-phenylalaninamide, 20 mM CH ₃ COONH ₄ , pH 5. 15 kV.	254	nd	[16]
D/L-Glu, D/L-Leu, D/L-Val, D/L-Met, D/L-Thr, D/L-Ser, D/L-norVal, D/L-Asp, D/L α -amino-n-butyric acid, D/L-Trp, D/L-Phe, D/L-norLeu	Standard dansylated AAs diluted in BGE.	50 μ m ID, 50 cm TL, 36.5 cm EL capillary. 10 mM Cu(CH ₃ COO) ₂ , 20 mM L-prolinamide, 20 mM CH ₃ COONH ₄ , at pH 6 or 5. +13.6 kV.	254	nd	[17]
D/L-Asn, D/L-Met, D/L-Thr, D/L-Ser, D/L-Asp, D/L-Trp, D/L-Phe, D/L-Ile, D/L-Tyr	100 μ L standards AA + 200 μ L 40.0 mM Li ₂ CO ₃ +100 μ L dansyl chloride , 35.0 min, then 5 μ L 2.0% ethylamine.	50 μ m ID, 65 cm TL, 50 cm EL capillary. 5 mM CH ₃ COONH ₄ , 100 mM boric acid, 4 mM Zn(II), 8 mM L-phenylalaninamide, pH 8.2. -23 kV.	254	nd	[18]
D/L proteinogenic AA, D/L Orn	20 μ L AA (+ 20 μ L 40.0 mM Li ₂ CO ₃ + 20 μ L dansyl chloride (5.6 mM in acetone), 35.0 min, then 5 μ L 2.0% ethylamine. Test applied for screening tyrosinase inhibitors	75 μ m ID, 60 cm TL, 45 cm EL capillary. 100 mM boric acid, 5 mM CH ₃ COONH ₄ , 2.5 mM Mn(II), 5 mM [1-butyl-3-methylimidazolium][L-Ala] and 5.0 mM β -CD at pH 8.3. -23 kV.	254	3 μ M	[20]

D-Ser	Standard dansylated AAs diluted in BGE.	75 μ m ID, 35 cm TL, 28 cm EL capillary coated with a linear polyacrylamide. 200 mM β -alanine/acetate (pH 4.20) – MeOH (1/1, v/v); 20 mM (+)-1-allyl-(5R,8S,10R)-terguride. 20 kV.	254	Below 0.01% D-Ser	[22]
D/L-Trp, D/L-Phe, D/L-Tyr, D/L-His, D/L Cys, D/L-Ala	200 μ L standards AA (1 mg/L) in 40.0 mM Li ₂ CO ₃ + 300 μ L dansyl chloride (5.6 mM in ACN), 35.0 min, then 50 μ L 2.0% ethylamine.	50 μ m ID, 40 cm TL, 32 cm EL capillary. 100 mM β -CD, 10 mM tetramethylammonium-L-Arg in N -methylformamide containing 50 mM Tris and 35 mM citric acid (pH 7.85). 30 kV;	254	nd	[23]
Phe, Ile, Tyr, His, Leu	0.03 M 1,2-naphthoquinone-4-sulfonate in HCl 0.1 M, reacted with AAs in 50 mM sodium borate/90 mM NaCl pH=10.	75 μ m ID, 70 cm TL, 58 cm EL capillary. 40 mM sodium tetraborate–isopropanol (3:1, v/v)	DAD 225-550	nd	[24]
Pro, Gly, Trp, Val, Thr, Ser, Phe, Asn, Ala, Ile, Leu, Glu, Asp, Cys	0.1 g of commercial pharmaceuticals or 10 g of feed dissolved in 0.1 L 10 mM HCl. Diluted in water, filtered. In-capillary derivatization using 1,2-naphthoquinone-4-sulfonate .	75 μ m ID, 50 cm TL, 43 cm EL capillary. Sandwiched in-capillary derivatization: 0.03 M 1,2-naphthoquinone-4-sulfonate in HCl 0.1 M/sample/0.03 M 1,2-naphthoquinone-4-sulfonate in HCl 0.1 M. (Pressure.time: Pa.s: 166/103/166) BGE: 40 mM sodium tetraborate (pH=9,2)/isopropanol (4:1 v/v). Stacking process 3 min, -20 kV. Separation +20 kV	230	0.7 μ M (Pro) to 2.1 μ M (Cys)	[27]
His, Trp, Leu, Met, Thr, Ser, Gly, and nine aliphatic amines.	Standard AAs, on-column derivatization using phthalic anhydride .	50 μ m ID, 47 cm TL, 40.5 cm EL capillary. 1 s pressure injection of 10 mM phallic acid in ACN, 1 s injection AA in ACN/water 9:1. Separation: 20 mM phosphate pH=10. 24 kV	200	nd	[28]
Arg, histamine, serotonin, tyramine, putrescine, and cadaverine among 16 AAs	5 g pieces of mackerel or tuna (fish) in 20 mL HCl (0.5 M) homogenized, 1 M NaOH neutralized diluted in 50 mL water. Injection: 5 kV for 3 s, specific injection of neutral biogenic amines for in-capillary OPA/BM labeling.	On column derivatization with OPA/BME and separation in a capillary filled with Capcell Pak C18 (5 μ m) type UG 120 (Shiseido, Tokyo, Japan). Capillary filled with 5 mM OPA/2ME and 70% acetonitrile/10 mM borate (pH 10). Cathode vial 70% acetonitrile/10 mM borate (pH 10).	340	50-100 μ M	[32]
D/L Ser, Gly (IS)	100 μ L of serine racemase reaction media, containing 20 μ M pyridoxal-5'-phosphate, 1 mM MgCl ₂ , 1 mM ATP, 5 mM DTT, 0.5 mM enzyme+20 μ L 30 mM EDTA, 6 mM	75 μ m ID, 40 cm TL, 30 cm EL capillary. In-capillary derivatization: 5 s hydrodynamic injection (1 kPa) of 50 μ L sample + 50 μ L 200 μ M Gly, followed by any one of OPA/BME	230	3 μ M D-Ser.	[33]

	aminoxyacetic acid hemihydrochloride; were injected in CE for in capillary OPA/BME labeling.	(30/60 mM, in 25% ACN), 6 kV, 1 min. BGE: 50 mM sodium tetraborate (pH 9.7), 40 mM 2-hydroxypropyl- γ -CD. 12 kV			
L-carnosine, mimosine, 6-aminonicotinic acid (ANA), 3-ANA, 2-ANA, 4-aminobenzoic acid, 2-aminobenzoic acid, 5-aminosalicylic acid, D/L Trp, D/L-homoPhe, D/L Phe, 5-hydroxy D/L Trp, D/L Tyr, 3,4 dihydroxy-L-Phe	Free standard AAs	50 μ m ID, 57 cm TL, 50 cm EL capillary. 100 mM sodium phosphate, pH 2.0	200	0.2-0.4 μ M	[35]
Lys, Pro, Trp, OH-Pro, Leu, His, Phe, Val, Met, Gln, Ala, Thr, Ser, Asn, Cys, and Glu	Free AAs from plant extracts in 25% ethanol.	75 μ m ID, 40 cm TL, 30 cm EL capillary. 10 mM benzoic acid + 1 mM myrisityltrimethylammonium bromide at pH of 11.20. -15 kV.	225 (indirect)	10 μ M (Val) 45 μ M (Lys)	[36]
20 AAs, Om, GABA, β -Ala, 3-Me-His, Hcys, cystine, glutathione, anserine, carnosine, Hcys, δ -hydroxylysine, citruline	100 μ L plasma or supernatant of cultivated macrophages + acetone, centrifuged, supernatant 5 \times diluted in water.	75 μ m ID, 87 cm TL, 80.5 cm EL, capillary. 8 mM <i>p</i> -aminosalicylic acid + 2 mM NaCO ₃ , pH 10.15. 15 kV.	254 (indirect)	1.9 μ M (Glu) 20.1 μ M (Gly)	[37]
Gabapentin	bulk drug, diluted in water and filtered.	75 μ m ID, 74 cm TL, 62.5 cm EL capillary. 5 mM 5-sulphosalicylic acid and 0.5 mM cetyltrimethylammonium bromide (CTAB), pH 11. -20 kV.	215 (indirect)	5 μ M	[38]
Glu, Asp	100 μ L human serum + 200 μ L methanol/ACN, centrifuged. Supernatant was dried, then mixed with 3 mM H ₃ PO ₄ 6% methanol.	50 μ m ID, 50 cm TL, 42 cm EL, capillary. 10 mM Tris–8 mM benzoic acid–10 mM β -CD pH 7.5. 12 kV	214 (indirect)	0.4 μ M	[40]
3-nitro-Tyr	Urine was centrifuged, filtered, and 1 mL spiked with 1 mL of 0.1 M NaCl.	75 μ m ID, 48.5 cm TL, 40 cm EL, capillary. 50 mM HEPES/105 mM Tris	426	0.07 μ M	[41]
Lys, His, Ser, Leu, Phe, Glu, Pro	100% human saliva + 5 μ L sulfosalicylic acid (50% in water) centrifuged, supernatant filtered and diluted in water. 0.5 g green tea in 100 mL	50 μ m ID, 65 cm TL, 57 cm EL, capillary. 50 mM CuSO ₄ 0.05% acetic acid (pH 4.5) 15 V.	254	0.1-0.5 μ M	[43]

	boiled water, infused 1 h filtered and diluted in water.				
Phe, Tyr	Phe- and Tyr-spiked urine diluted in BGE 1/1.	50 μm ID, 100 cm TL, 91.5 cm EL capillary coated with a bilayer of polybrene (hexadimethrine bromide), and 25% (m/v) aqueous solution of poly(vinylsulfonate). Injection: 1) 12.5% NH_4OH , 25 s 50 mbar. 2) sample diluted 1:1 in BGE 228 s at 50 mbar. BGE, 1 M formic acid. 30 kV	200	54 nM (Phe) 19 nM (Tyr)	[44]

Table 2: Separation and detection parameters adopted in the major publications reviewed in the chapter CE/C⁴D.

(AA, amino acid; nd, not determined; ID, inner diameter of the capillary; EL, effective length of the capillary; TL, capillary total length; IS, internal standard)

AA	Sample and sample treatment	Separation conditions	LOD	Ref
20 proteinogenic AAs and Cys-Cys	Human urine and saliva, alcoholic extracts from herbs (veronica and scouring rush) Budvar beer, water solution of Panganin yeast, sonicated and then filtered.	50 μm ID, 80 cm TL, 66.5 cm EL capillary. 2.3 M acetic acid (pH 2.1) and 0.1% w/w hydroxyethylcellulose. 30 kV	9.1 μM (Lys) - 29 μM (Asp)	[51]
20 proteinogenic AAs	Urine samples were diluted 10 \times in BGE buffer. Beer was diluted 5 \times in BGE, then ultrasonicated and filtered.	0.25 μm ID, 60 cm TL capillary. Electrokinetic injection 5 kV, 7 s. 50 mM 2-amino-2-methyl-1-propanol/10 mM 3-(cyclohexylamino)-1-propanesulfonic acid (CAPS), pH 10.8. 25 kV	0.2 μM (Arg), 0.4 μM (His)	[52]
Thr, Met, Leu	Standards of AAs in standards of carbohydrate mixtures.	15 μm ID, 40 cm TL, 25 cm EL capillary. Electrokinetic injection 20 kV, 2 s. 10 mM NaOH, 4.5 mM Na_2HPO_4 , 1 mM cetyltrimethyl-ammonium bromide, pH >12; 20 kV	\approx 1 μM	[53]

18 proteinogenic AAs, Orn citruline, creatinine, 3-Me-His	100 μ L human plasma+100 μ L acetone, centrifuged, supernatant, injected.	75 μ m ID, 80 cm TL, 67 cm EL capillary. 1.7 M acetic acid 0.1% hydroxyethylcellulose, pH 2.2. 20 kV	4.3 μ M (Arg) 42.9 μ M (Cys)	[54]
3-Me-His, 1-Me-His, His	Urine diluted 1/1 in ACN, filtered.	75 μ m ID, 80 cm TL, 65 cm EL capillary. 0.5 M acetic acid, 20 mM NH ₄ OH, 0.1% m/v hydroxyethyl- cellulose (pH 3.4). 20 kV.	\approx 7 μ M	[55]
20 proteinogenic AAs, 3-Me-His, 1-Me-His, b-Ala, citruline, creatinine, choline, Orn, 4- hydroxy-Pro, Cys-Cys	50 μ L human plasma + 100 μ L CAN, centrifuged, supernatant filtered. Cerebrospinal fluid, urine, and saliva, filtered. 50 μ L of these fluids+50 μ L ACN.	25 μ m ID, 33 cm TL, 18 cm EL capillary. 4 M acetic acid. 20 kV.	0.2 μ M (Lys) 0.6 μ M (Asp)	[56]
Carnitine, acetyl-carnitine, propionyl-carnitine, isovaleryl- carnitine, hexanoyl-carnitine, valproyl-carnitine, octanoyl- carnitine	50 μ L human plasma + 50 μ L ACN/methanol (3/1) centrifuged. Supernatant diluted 4 \times in BGE. Human urine samples centrifuged, diluted 4 \times in BGE.	50 μ m ID, 40 cm TL, 32 cm EL capillary. 0.5 M acetic acid, 1 mM hydroxypropyl- β -cyclodextrin; 0.05% Tween, pH 2.6. 15 kV.	1 μ M carnitine 3.2 μ M octa- noylcarnitine	[57]
β -Ala, His, GABA, Gly, Ala, 2- amino-isobutyric acid, Val, Ser, isovaline, Leu, Glu, Asp	Subcritical extraction of ocean water.	50 μ m ID, 64 cm TL, 43 cm EL capillary. 5 M acetic acid. 30 kV	nd	[59]
D/L-Arg, D/L-Val, D/L-Ser, D/L- Phe, D/L-Tyr, D/L-Aps, D/L-Thr, D/L-Met, D/L Trp	Standard AAs	10 μ m ID, 48 cm TL, 43 cm EL capillary. 10 mM (+)-(18-crown-6)-2, 3, 11, 12-tetracarboxylic acid, 10 mM citrate/Tris at pH 2.2. 15 kV	2.5-20 μ M	[60]
cis-1,2-diaminocyclohexane, 3- cyclohexyl-D-Ala, prolinol, 2- adamantanamine, 1- cyclohexylethylamine	Amines and non proteinogenic standard AAs.	25 μ m ID, 60 cm TL, 55 cm EL capillary. Electrokinetic injection 5 kV, 7 s. 0.5 M acetic acid, 50 mM(+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid, pH 2.5. 15 kV	\approx 1 μ M	[61]
Lys, His, Arg, Gly, Ala, Leu, Glu. (Gly solely quantitated)	2.5 μ L periaqueductal gray matter microdialysate (2.5 mM KCl, 125 mM NaCl, 1.18 mM MgCl ₂ and 1.26 mM CaCl ₂) + 7.5 μ L, shaken and analyzed.	75 μ m ID, 43 cm TL, 30 cm EL capillary. 1.7 M acetic acid 12% m/v PEG (pH 2.1).	3.3 μ M	[63]
GABA, Gly, Glu, 2-amino- isobutyric acid	2.5 μ L periaqueductal gray matter microdialysate (2.5 mM KCl, 125 mM NaCl, 1.18 mM MgCl ₂ and 1.26 mM CaCl ₂) + 7.5 μ L, shaken and analyzed.	50 μ m ID, 43 cm TL, 28 cm EL capillary. Injection 100 s, 50 mbar. The ACN sample zone was forced out at 50 mbar, 100 s at 25 kV. 4.0 M acetic acid (pH 1.9). 25 kV.	29 nM (GABA, Gly), 37 nM (Glu)	[64]

Ala, Val, Ile, Leu, Ser, Gln, Glu, Phe, Pro, Tyr	10 μ L plasma+30 μ L 10 mM HCl in ACN, 30 μ L supernatant injected.	25 μ m ID, 31 cm TL, 14.5 cm EL coated capillary with poly(acrylamide-co-(3-acrylamidopropyl) trimethyl-ammonium chloride) (PAMAPTAC) containing 1% m/m (3-acrylamidopropyl) trimethylammonium chloride (APTAC). 3.2 M acetic acid +10% v/v MeOH. -30 kV	\approx 0.6 μ M	[66]
Lys, Ala, Pro, Glu, Asp	1 g honey/50 mL water, centrifuged, supernatant filtered.	50 μ m ID, 60 cm TL, 48 cm EL capillary. 2 M lactic acid (pH 1.4)	39 ng/g (Lys) 90 ng/g (Asp)	[67]
Choline, taurine	Milk (powdered, fresh), rice, energy drink. 1 g powder in 10 mL water, sonicated, filtered, diluted with water. Liquids filtered, diluted with water.	50 μ m ID, 60 cm TL, 45 cm EL for the two capillaries. Capillary 1 (taurine) 150 mM Tris/Lac (pH 8.96). Capillary 2 (choline) 150 mM Tris/Ace (pH 9.5). -10 kV	0.27 mg/L taurine 0.35 mg/L choline	[68]

Table 3: Separation and detection parameters adopted in the major publications reviewed in the chapter CE/fluorescence.

(AA, amino acid; nd, not determined; ID, inner diameter of the capillary; EL, effective length of the capillary; TL, total length of capillary; SFC, sheath flow cell; IS, internal standard; SR, serotonin; DP, dopamine; NP, norepinephrine; NA, noradrenaline)

AA	Sample and sample treatment	Separation conditions	Excitation λ (nm)	LOD	Ref
Serotonin, Trp, hydroxy-indole-3-acetic acid	Standard	50 μ m ID, 67 cm TL, 60 cm EL capillary. 20 mM borate buffer, pH=9. 23 kV	Pulsed 266	5 nM (SR) 2 nM (Trp)	[77]
Tyr, Trp	CSF, filtered, diluted 20 \times in water .	75 μ m ID, 60 cm TL, 57 cm EL capillary. 10 mM CAPS, 15 mM sodium tetraborate, pH 9.2. 15 kV.	Pulsed 266	0.15 nM (Trp)	[78]
Trp, tryptamine, SR acetyl-serotonin, 5-hydroxyindole-3-acetic acid, melatonin, Tyr, DP, octopamine, epinephrine,	Single metacerebral cell in microvial, homogenized with tungsten needle manipulation and damages of the BGE as hypoosmotic buffer.	150 μ m ID, 80 cm TL, capillary. SFC. Electrokinetic injection 2.1 kV 10 s. 50 mM borate pH=8.7. 21 kV	Pulsed 248,6 ¹	27 nM(SR) 8 μ M (DP)	[79]

¹ Wavelength-resolved fluorescence

5,6,7,8-tetrahydrobiopterin, flavin mono-nucleotide), Flavin adenine dinucleotide, β -nicotinamide adenine dinucleotide, β -nicotinamide adenine dinucleotide phosphate.					
D/L Trp	Standards: D-Trp/L-Trp=1/400	50 μ m ID, 10 cm TL, 5 cm EL capillary. 1.0 mM phosphate with 0.15% HS- γ -CD at 6 kV.	Pulsed 266	70 pM	[80]
Tryptamine, SR, NR, octopamine, N-acetylserotonin, DP epinephrine, Trp, Tyr, Phe, 3,4-dihydroxyphenylalanine, NP	Individual cerebral ganglion neurons in the 300-nL vial homogenized with BGE	50 μ m ID, 80 cm TL, capillary. SFC. Electrokinetic injection 2.1 kV 10 s. 50 mM citrate buffer at pH 3. 21 kV	257 ¹	4.4 nM tryptamine 3.9 μ M NP	[82]
Trp and proteins	Standard	75 μ m ID, 60 cm TL, 50 cm EL capillary. 40 mM sodium phosphate. pH 11.3.	XeHg lamp 280	6.7 nM	[84]
DP, 3,4-dihydroxy-DL-phenylalanine (DOPA), epinephrine, 5-hydroxyindole-3-acetic acid, 5-hydroxytryptamine 3-indoxyl sulfate	10 μ L urine diluted in 100 mM citric acid and 89% ACN.	75 μ m ID capillary. Electrokinetic injection 15 kV, 360 s. 400 mM propanoic acid 20% glycerol.	Pulsed 266	0.3 nM (epinephrine), 17 pM (tryptamine)	[88]
DP, NA, dihydroxybenzylamine (SI)	0.5 μ L 500 mM borate (pH 8.6) + 0.45 μ L, 10 mM NaCN + 3.6 μ L (3.25 μ L microdialysate + 0.35 μ L 0.1 M perchloric acid) + 0.1 μ L 5 mM NDA.	50 μ m ID, 72 cm TL, 52.5 cm EL capillary. 110 mM phosphate buffer, pH 7. 15 kV	442	0.37 nM (NP)	[93]
Asp, Glu, GABA, Gly, NA, DP, Ser	5 μ L microdialysate + 160 μ L 125 mM borate pH 8.7, 40 μ L 43 mM KCN + 33 μ L 5 mM NDA.	50 μ m ID, 65 cm TL, 50 cm EL capillary. 22.5 mM lithium tetraborate, 20 mM lithium dodecylsulfate. 10 kV/7 min then 20 kV/8 min.	442	0.22nM (Gly) 0.42nM (GABA)	[95]
Ser, Thr, His, Glu, Ala, Asp, Tyr, Val, Met, Ile, Leu, Phe, Lys, Arg	700 μ L 100 mM borate buffer pH 9.5 + 100 μ L (10 mM NaCN, 10 mM borate buffer) + 100 μ L 2.5 μ M standard AA + 100 μ L 1 mM NDA in ACN	50 μ m ID, 57 cm TL, 50 cm EL capillary. 100 mM borate, pH 9.5, 50 mM SDS	LED 405	\approx 10 nM	[96]

Arg, histamine, agmatine, methylamine; His; Gln, Ser, propylamine, GABA; Gly, Thr, Ala; Tyr, Val, Glu	Beer diluted 50×. 100 µL mixed with 900 µL (0.6 mM NDA, 1 mM sodium tetraborate, 0.6 mM NaCN). Water diluted 10× prior to injection.	75 µm ID, 40 cm TL, 30 cm EL capillary. 100 mM Tris–borate pH 7, 14 mM CTAB, 25% CAN, 1.2% PEO.-15 kV.	LED 405	9.5 nM (GABA) 50.5 (Thr)	[97]
Phosphorylated Ser (P-Ser), Phosphorylated Tyr (P-Tyr), Phosphorylated Thr (P-Thr)	80 µL standard phospho-AA + 20 µL 20 mM sodium tetraborate (pH 10.0) + 20 µL 40 mM KCN + 20 µL 3.5 mM, 15 min at 65 °C	75 µm ID, 40.5 cm TL, capillary. 30 mM sodium tetraborate 2 mM β-CD. pH 9.2. 18 kV.	Hg Lamp 400-490	P-Tyr 5.6 nM P-Ser 7.2 nM	[101]
Asn, Ser, Gln, Thr, His, cystine, Glu, Gly, Tyr, Ala, Asp, Taurine, Ala-Gln, Val, Met, norVal, Trp, Ile, Leu, Phe, Arg, Lys	2 µL human plasma (or culture media of in vitro cultivation of human embryos) + 8 µL MeOH/2-propanol (IPA) (4/1), centrifuged. Supernatant diluted 1/1 in 100 mM H ₃ BO ₃ /NaOH, pH 9.8, 2 µM norvaline.	50 µm ID, 66 cm TL, 45 cm EL capillary. BR: 200 mM H ₃ BO ₃ /NaOH, pH 9.8 EMMA: i) injection 30 s 100 mbar (3000 bar.s), 100 mM SDS in BR, ii) 1200 mbar.s, 1 mM NDA in (BR, 12.5% (v/v) MeOH/IPA (4:1)), iii) 350 mbar.s AA sample, iv) 400 mbar.s 1 mM NDA in (BR, 12.5% (v/v) MeOH/IPA (4:1)), v) 1900 mbar.s 2.5 mM NaCN in BR. Then -5 kV for 65 s capillary inlet with 2.5 mM NaCN. No voltage for 3 min. BGE 73 mM SDS, 6.7% (v/v) 1 P, 0.5 mM HP-β-CD, 135 mM H ₃ BO ₃ /NaOH of pH 9.00. 30 kV.	488	5.6 nM (Tyr, His) 48 nM (Asp)	[103]
Asp, Glu	One blotted dry planarian, sonicated in 100 µL 0.1 M HCl + 150 µL ACN, centrifuged. 5 µL supernatant + 45 µL borax, 2 µL 0.1 M HCl, 3 µL ACN, 25 µL 12 mM KCN, then 10 µL 10 mM NDA in MeOH.	25 µm ID, 25 cm TL, 20 cm EL capillary. 10 mM sodium phosphate buffer, pH 7.5. 20 kV.	445	400 nM (Glu) 300 nM (Asp)	[108]
Lys; 1-Me-His, citruline, Gln; L-anserine, 3-Me–His, Tyr; Orn, β-Ala, camosine, Hcy, Ser; Gly; Ala; taurine, L/D-α-amino-butyric acid, Val, Hcy, Met; Thr; Nor-Val, Ile; Phe; Leu, L-α -aminoadipic acid; Nor-Leu; Glu; Arg, Asp	100 µL human plasma + 25 µL (160 g/L sulfosalicylic acid 200 µM norvaline). Vortexed, centrifuged; neutralized to pH 9 with 5 M NaOH. 30 µL sample + 30 µL 30 mM CBQCA (10-fold molar excess AA), + 6 µL 75 mM KCN, 65 °C. Diluted 7.5× in 10 mM borate.	50 µm ID, 67 cm TL, 60 cm EL capillary. 160 mM borate, 130 mM SDS, 20 mM NaCl, and 7.5 mM γ-CD. 30 kV	488	40 nM (Arg)	[111]

Arg	Standard Arg. 2.5 μ L AA, 11.5 μ L MeOH, 1 μ L 50 mM KCN, 10 μ L 10 mM CBQCA.	50 μ m ID, 41.5 cm TL capillary. SF. 18 mM Borate, 10 mM SDS, pH 9.3. 29 kV.	488	26 pM	[112]
Ser, Gln, Met, Asn, Thr, Tyr, Ala, Gly, Val, His, Pro, Cys, Ile, Leu, Phe, Norleucine, Glu, Arg, Asp.	Culture medium of <i>Brevibacterium linens</i> strain BL2 2 μ L sample, 10 μ L 420 μ M CBQCA (in MeOH), 5 μ L 420 μ M KCN, 6 μ L MeOH, 11 μ L H ₂ O, 0.5 μ L 1 mM norleucine.	75 μ m ID, 107 cm TL, 99 cm EL capillary. 6.25 mM sodium borate, 150 mM SDS, 10 mM THF, pH 9.66. 24 kV.	488	17 pM (Ile, Leu, Phe) 383 pM (Glu)	[113]
Arg, His, Ala, taurine, Gly, Glu, Asp	Tear sample collected via phenol red thread and inserted in a pipette tip, rinsed with 20 mM phosphate buffer pH 8. Centrifuged. 10 μ L sample + 10 μ L 10 mM CBQCA + 10 μ L 10 mM KCN	50 μ m ID, 50 cm TL, 40 cm EL capillary. 25 mM borate buffer, pH 9.2. 24 kV	LED 480	89 nM (taurine) 4.4 μ M (Asp)	[114]
Glu, Asp, taurine, GABA, O-methyl l-threonine (IS)	10 μ L microdialysate of suprachiasmatic nucleus of hamsters + (75 μ g FQ in 10 μ L MeOH), + 5 μ L (80 mM KCN 150 nM IS), 65 °C 60 min.	50 μ m ID, 60 cm TL, 50 cm EL capillary. 155 mM borate, 20 mM SDS. pH 9.5. 20 kV	488	8 nM GABA 110 nM (Glu)	[115]
Asp, Glu	Standards	25 μ m ID, 8 cm EL separation capillary. Flow-gated injection interface/mixing tee. 7.5 mM OPA/BME, and AA 1.2 μ L/min, in 100 μ m reaction capillary 30 cm long to interface. Crossflow interface 1 mL/min (10.0 mM phosphate, pH 7.40). 1 kV/cm	LED 365	11 nM (Asp) 10 nM (Glu)	[119]
Lys, Arg, Glu, Asp	Japanese beer.	50 μ m ID, 30 cm TL, 20 cm length for laser drilled hole for post column derivatization, 25 cm EL, capillary. BGE 10 mM SDS and 50 mM borate (pH 9.5). Derivatization reagents, 10 mM OPA, 1% BME 9% ethanol v/v in BGE, derivatization voltage 4 kV. Separation voltage 10 kV.	LED 365	\approx 5 μ M	[120]

Hcy	0.8 mL urine + 7 mL 20 mM CH ₃ COOH pH 4.7 + 200 µL 2.0× Tween 20-Au nanoparticles (aminothiols high selectivity). 2 h equilibration. Centrifuged, supernatant removed. 20 µL precipitate in 20 µL 2 mM thioglycolic acid. Supernatant in 0.1 mM OPA (no nucleophile addition)	75 µm ID, 50 cm TL, 40 cm EL capillary. 10 mM SDS, 10 mM phosphate buffer, pH 12. 10 kV	Diode laser 355	4 nM (Hcy)	[122]
Arg, Gln, His, Pro, Ala, Asp	Standards. 1 µL 5 mM FITC (in acetone) + 5 µL sample diluted 1/1 in 0.4 M carbonate buffer (pH 9.0) + 24 µL acetone + 20 µL 0.2 M carbonate buffer (pH 9.0). 40 °C 3 h	50 µm ID, 57 cm TL, 50 cm EL capillary. Phosphate/borate buffer pH 9. 20 kV	SFC 488	0.1 nM(Arg) 0.4 nM(Pro)	[125]
Ammonia, Ala, Asn, Asp, Arg, citruline, Gln, Glu, Gly, Leu, Lys, Orn, Phe, SEr, taurine, Thr, Tyr, tyramine, Val	50 µL cerebrospinal fluid + 50 µL 0.21 mM FITC (acetone). 2 h; diluted 1000× with water.	50 µm ID, 75 cm TL, 42 cm EL capillary. 100 mM boric acid, 100 mM SDS, pH = 9.3. 20 kV	488	≈5 pM each AA	[136]
Arg, cysteine, Ile, His, Pro, Tyr, Phe, Gln, Ala, Gly, Glu	Standards. Derivatization media 55.5 µM FITC + 10 µM AA in 0.022 M phosphate pH 9.4. 12 h. Extraction: 0.2 mL liquid ion-exchange Amberlite resin LA-2 (selective extract FITC excess).	75 µm ID, 57 cm TL, 50 cm EL capillary. 0.4% boric acid, 0.3% sodium tetraborate pH 9.5.	488	0.5 nM (Arg) 0.3 nM (Pro)	[138]
Homocysteic acid (IS), Ala, Ser, Gly, taurine, Glu, Asp	100 µL human plasma + 50 µL 200 µM IS filtered using Vivaspin 500. 50 µL supernatant + 40 µL 200 mM Na ₂ HPO ₄ pH 9.5 + 10 µL 80 mM FITC. 20 min, 100 °C. 100× water diluted. 100 µL cerebrospinal fluid, saliva, or vitreous humor was vacuum dried, and reswollen in 20 µL 200 mM Na ₂ HPO ₄ pH 9.5 + 10 µL 80 mM FITC. 20 min, 100 °C.	75 µm ID, 57 cm TL, 50 cm EL capillary. 18 mM Na ₃ PO ₄ , pH 11.8. 28 kV.	488	25 nM (Gly) 67 nM (Ser and Asp)	[139]
Gly, Ala, methylamine, tyramine, hexylamine, dibutylamine, putrescine,	800 µL sonicated beer + 495 µL 0.2 M carbonate buffer (pH 9), 1 mL 10 mM FITC + 1 mL acetone. 50 °C, 2 h, 5× water diluted	75 µm ID, 40.5 cm TL, 40 cm EL capillary. 30 mM sodium borate, 0.001% hexadimethrin bromide, 15% isopropanol, pH 9.3. -25 kV.	488, LED 470	0.9 µM (Ala) 3 µM (putrescine)	[143]

cadaverine, 1,6 hexanodiamine, agmatine					
Glu, Asp, P-Tyr, P-Thr, P-Ser. (P= phosphorylated)	0.2 g <i>Nicotiana tabacum</i> calcium/calmodulin-binding protein kinase (NtCBK2) from Tobacco cells, in 100 µL 25 mM Tris-HCl (pH 7.5), 0.5 mM dithiothreitol, 10 mM magnesium acetate, 100 µM ATP and 1 mM CaCl ₂ , 30 min, 30 °C. Hydrolyzed in 6 M HCl at 110 °C for 4 h. Aliquot dried and dissolved in 100 µL of 10 mM borate (pH 9.3). 5 µL sample + 5 µL 0.2 M borate buffer (pH 9) and 2 µL 5 mM DTAF. 50× diluted in water.	50 µm ID, 65 cm TL, 50 cm EL capillary. Borate buffer (20 mM, pH 9.35), Brij35 (10 mM). 25 kV	488	0.5 nM (P-Tyr), 5 nM (Asp)	[146]
Gabapentin, Phenylpropanolamine (IS)	0.5 mL plasma + 1 mL ACN, vortexed, centrifuged. 90 µL supernatant + 10 µL 15 µM IS. 50 µL of this solution + 10 µL 10 mM 6-carboxyfluorescein succinimidyl ester + 40 µL 50 mM borate buffer, pH 9.5.	50 µm ID, 60 cm TL, 40 cm EL capillary. 50 mM sodium borate, pH 9.5; 25 kV.	488	60 nM gabapentin	[150]
ethylamine; ethanolamine; n-hexylamine; methylamine; n-pentylamine; n-propylamine	Filtered beer. 50 µL + 10 µL 1 mM 6-oxy-(N-succinimidyl acetate)-9-(2'-methoxy carbonyl) fluorescein (SAMF) +75 µL H ₃ BO ₃ pH 8.	75 µm ID, 57 cm TL, 50 cm EL capillary. 25 mM boric acid, 24 mM SDS, pH 9. 22.5 kV	488	80 pM (methylamine) 400 pM (n-butylamine)	[151]
Hcy, D-penicillamine, cysteamine, Cys, glutathione	100 µL plasma + 10 µL 35 mmol/L tris(2-carboxy ethyl)phosphine + 5 µL 10 mM IS, Vortexed. + 60 µL 0.8 M 5-sulfosalicylic acid. Vortexed, centrifuged. 100 µL supernatant + 50 µL 1 g/L 6-IAF(in DMSO), 2 h, 5000× diluted in water.	50 µm ID, 75 cm TL, 43 cm EL capillary. 10 mM SDS, 50 mM boric acid, 20 mM 3-(cyclohexylamino)-1 propanesulfonic acid pH 9.5. 25 kV	488	nd	[152]
Glutathione, Hcy, N-acetyl-Cys, cystamine (IS)	0.5 mL plasma + 50 µL 500 µM IS + 250 µL dithiothreitol (in 0.9% NaCl), vortexed 15 min. + 100 µL (2.34 M perchloric acid, 2 mM EDTA), vortexed, centrifuged. 100 µL supernatant + 1 mL (0.42 mM fluorescein-5-maleimide, 50 mM phosphate, pH 7.5), 15 min., 100× diluted with water.	75 µm ID, 57 cm TL, 50 cm EL capillary. Acetonitrile/10 mM phosphate, 50 mM SDS [27:73 (v/v); pH 7.0], 45 °C, 25 kV.	488	3 µM	[153]

Homocysteine, Cys glutathione, Cys-Gly, γ -Glu-Cys, penicillamine, mercaptopropionyl Gly, cysteamine, mercapto acetic acid (IS)	75 μ L urine + 125 μ L 16 μ M IS + 30 μ L 17.5 mM tris(carboxyethyl)phosphine. 100 μ L of this solution + 100 μ L 1.5 M perchloric acid, vortexed, centrifuged. 50 μ L supernatant + 33 μ L 1M NaOH + 10 μ L 5 mM 5-bromo methylfluorescein (in N,N-dimethyl formamide). 10 min reaction.	25 μ m ID, 27 cm TL, 20 cm EL capillary. 60 mM borate, 15 mM SDS, 2-amino-2-methyl-1-propanol, pH 10. 30 kV.	488	76 nM (Hcy) 183 nM (penicillamine)	[154]
D/L Val, D/L Ala, D/LAsp, D/L Glu, Gly	10 μ L AA Mars7 standard with 40 μ L 50 mM borate buffer (pH 9.5), 10 μ L of water and 50 μ L 1.8 mM fluorescamine (in acetone).	72 μ m ID, 6.2 cm EL microchip; 10 mM Na ₂ CO ₃ , 15 mM HP- β -CD, pH 8.9. 700V/cm	Diode laser 404	83 nM (Val)	[156]
Hcy, Cys, glutathione	100 μ M AA standards in 100 mM borate pH 8, 2 mM EDTA. 2 Na. 400 μ M 4-aminosulfonyl-7-fluoro-2,1,3-benzoxadizole (ABDF) in 100 mM borate pH 8.	50 μ m ID, 45 cm TL, 30 cm EL capillary. On-column derivatization: injection ABDF 30 s (15 cm siphoning), sample AA 15 s (15 cm siphoning), ABDF 20 s (15 cm siphoning). Voltage 1 min each +1 kV, -1 kV, +1 kV, 38 °C, 10 min. Separation: 20 mM Tris, 0.1 M H ₃ PO ₄ pH 2.1; 15 kV	363.8	2.5 nM (Hcy) 5 nM (Cys)	[158]
methylamine, dimethylamine, ethylamine pyrrolidine, isobutyl amine, isoamylamine, ammonia	20 μ L beer + 20 μ L (MeOH, CH ₃ COONa saturated) + 20 μ L 7-chloro-4-nitrobenzo-2-oxa-1,3-diazole (NBD-Cl) 5 mM in MeOH. 60 °C 2 h, 4 \times diluted with water.	75 μ m ID, 81 cm TL, 74.5 cm EL capillary. 50 mM SDS, 10 mM borate pH 9.3. 24 kV.	488	10 μ M (isoamylamine)	[160]
Val, Ala, Glu, Asp, buccaline, amyloid- β	Standard	75 μ m ID, 47 cm TL, 40 cm EL capillary. In capillary derivatization: 4s (0.1 psi) injection (0.1psi) AA in BGE, 1 s (0.1psi) ethanol, 2 s (0.1 psi) 52 mM NBD-F (in ethanol) Separation: BGE: 20 mM borate buffer pH ranging from 7.7 to 10.0. 15 kV. 45 °C	488	0.1 μ M (Ala) 0.6 μ M (Asp)	[162]
D/L-Ser	30–60 mg male rat cerebrum tissue in 150 μ L 0.1 M HCl, homogenized, sonicated, centrifuged. 100 μ L supernatant + 30 μ L 30% (w/v) trichloro acetic acid solution vortexed, centrifuged, + 20 μ L 1 M NaOH to pH 9. 10 μ L	50 μ m ID, 75 cm TL, 50 cm EL capillary. Separation 100 mM borate, pH 10, 40 mM HP- β -CD. 15 kV	457.9	0.3 μ M (D-Ser)	[163]

	of this solution + 40 μ L 0.1 M borate pH 9 + 50 μ L 2 mM NBDF. 60 °C, 5 min.				
Gly, Ser, Val, Gln	Standards. Molar ratio AA/NBDF = 0.1.	75 μ m ID, 45 cm TL, 25 cm EL capillary. EMMA on column injection with inkjet microchip. Two droplets 25 \times times of 180 pL (44 V 20- μ s injections) of 1 mM NBDF (in ethanol) (droplet 1) and AA in 10 mM borate pH 8.5 (droplet 2) 3 kV, 2 s incubation 5 min.	473	0.2 nM(Gln) 5 nM(Val, Ser)	[165]
D/L Tyr, L-Lys, L-His, L-Val, Gly, L-Glu, L-Asp	100 μ L commercial pharmaceutical preparation of AA, 880 μ L ACN/water (1:1, v/v) + 20 μ L trimethylamine, vortexed, sonicated, centrifuged. 10 μ L supernatant + 10 μ L 10 mM R(-)-4-(3-iso thiocyanatopyrrolidin-1-yl)-7-(N,N dimethylaminosulfonyl)-2,1,3-benzoxadiazole. 55 °C 20 min. 30 μ L 1 mM CH ₃ COOH (in 1/1, ACN/water)	75 μ m ID, 45 cm TL capillary. 15 mM borate pH 10.5. 14 kV.	LED 460	2.9 μ M D-Tyr	[166]
glutathione	20 μ L centrifuged saliva, or exhaled breath condensate + 1 μ L 10 μ M eosin-5-maleimide (in DMF)	50 μ m ID, 50 cm TL, 25 cm EL capillary. 15 mM HEPES, pH 7. 15 kV.	Diode laser 515	0.59 nM (glutathione)	[167]

Table 4: Separation and detection parameters of the main publications cited in the chapter CE/MS generalities.

(AA, amino acid; nd, not determined; ID, inner diameter of the capillary; TL, total length of capillary; SF, sheath liquid flow rate; AmAc, ammonium acetate; IS, internal standard; SR, serotonin; DP, dopamine; NP, norepinephrine; NA, noradrenaline)

AA	Sample and sample treatment	Separation conditions	ESI +/-	LOD	Ref
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All proteinogenic AAs (except Gln), β -Ala, sarcosine, GABA, hydroxyPro, Orn, α -aminoadipic acid, allo- δ -hydroxylysine, 1-methylHis, citrulline, cystathionine, carnosine, anserine	Soy sauce, beer, sake, and human urine.	50 μ m ID, 100 cm TL capillary. 1 M FA, 30 kV. SF 10 μ L/min 5 mM AmAc in 50% (v/v) MeOH/water	+	0.3 μ M (Arg, His) 11 μ M (Asp)	[170]
All proteinogenic AAs	Infant food samples, 10 \times diluted with water, vortexed, centrifuged. Supernatant injected for CE.	50 μ m ID, 70 cm TL capillary. 300 mM FA, 100 mM trimethylamine. 20 kV. SF 4 μ L/min 0.0%–1.0% FA 2-propanol/water 80:20% v/v	+	\approx 1 μ M	[173]
D/L Arg, D/L Thr, D/L Val, D/L Trp, D/L Leu, D/L Tyr, D/L Lys, D/L Phe.	Standard	20 μ m ID, 130 cm TL capillary. 30 mM 18-C-6-TCA. 30 kV	+	nd	[175]
All proteinogenic AAs, L- canavanine	Dried blood spot + 100 μ L water (10 min.). 20 μ L this solution + 180 μ L (ACN/water/FA, 49.9/49.9/0.2; v/v/v).	20 μ m ID, 115 cm TL capillary. 1 M FA. 30 kV	+	2.5 μ M (Tyr) 35 μ M (Gly)	[176]
All proteinogenic AAs and 80 other molecules	<i>Xenopus</i> embryo + 55 μ L (ACM/water/MeOH, 2/2/1), triturated, vortexed, centrifuged. Supernatant collected.	50 μ m ID, 45 cm TL capillary. 1 M acetic acid. 26.5 kV. SF 10 mM ammonium acetate/MeOH, electrokinetically driven	-	nd	[178]
All proteinogenic AAs + methionine sulfone (IS), β -Ala, Orn, sarcosine, GABA, hydroxy-Pro	Human urine, diluted in water.	50 μ m ID, 100 cm TL capillary. 1 M FA, 30 kV. SF 10 μ L/min 5 mM ammonium acetate (50% MeOH-water, v/v)	+	0.7 μ M (Ser) 11 μ M sarcosine	[180]
Ng-nitroso-Arg, citrulline, cyano-Orn, Ng-Hydroxy-Arg, 1-3 cyclo-hexadiene	50 μ L Ng-hydroxy-l-Arg (10g/L) in PBS, +/- 10 μ L 1-3-cyclohexadiene (formamide 50/50)	50 μ m ID, 105 cm TL capillary. 50 mM. 30 kV. FA 10 μ L/min, 0.1% FA (50% water–MeOH, v/v)	+	nd	[181]
All proteinogenic AAs, methionine sulfone (IS)	50 mg preweighed deep-frozen human tissue homogenized in 500 μ L 20 μ M IS in MeOH. Then + (200 μ L water/500 μ L chloroform), vortexed, centrifuged. 480 μ L supernatant filtered (using a 5-kDa filter) + 50 μ L water.	50 μ m ID, 100 cm TL capillary SF 10 μ L/min 0.1 μ M hexakis(2,2-difluoroethoxy) phosphazene in (50% MeOH-water, v/v)	+	0.1 μ M (Ile, Leu, Phe, Arg...) 1.4 μ M (Gln)	[182]
All proteinogenic AAs, GABA, tyramine	<i>E. coli</i> (BL-21) in Luria-Bertani broth, centrifuged. Supernatant 20 \times diluted in 200 mM ammonium acetate	50 μ m ID, 80 cm TL capillary. 1 M FA, 23 kV. SF 10 μ L/min 5 mM ammonium acetate (50% MeOH/water, v/v)	+	1 nM (Lys) 25 nM (Glu)	[184]

Pro, uridine, hippuric acid, pyroglutamic acid, flavin adenine dinucleotide, glucose-6-phosphate, uric acid, glutathione, glutaric acid, citrate	Human urine, centrifuged, mixed 1/1 in 25 mM trimethylamine (TEA)	50 µm ID, 100 cm TL capillary. 25 mM trimethylamine. 30 kV. SF 5 µL/min 5 mM TEA (50% MeOH/water, v/v)	-	3.2 µM (Pyro-Glu) 4 µM (Pro)	[185]
¹³ C labelled AA	10 flaxseed embryos cultured with ¹³ C-glutamine, washed, extracted in 1 mL 0.01% HCl 95 °C. Lyophilized, resuspended in 1 mL sodium acetate (50 mM pH 5.5), loaded on Dowed 50×8, lyophilized, resuspended in 500 µL water.	50 µm ID, 125 cm TL capillary. 1 M FA, 25 kV. SF 8 µL/min 2.5 mM ammonium acetate (50% MeOH/water, v/v)	+	nd	[186]
All proteinogenic AAs, Orn, β-Ala, sarcosine, GABA, N,N-dimethylglycine, creatinine, betaine, homo-Ser, citrulline, homo-Arg, N ⁶ -trimethyl-Lys, 3-hydroxybutyrate, 2-hydroxybutyrate, lactate, fumarate	350 µL plasma + 3.15 mL 10 µM 2 AM in MeOH + 3.5 mL chloroform + 1.4 mL water, vortexed, centrifuged. Aqueous layer collected. AM: authentic material for migration-time alignment	50 µm ID, 80 cm TL capillary. Anions: 50 mM ammonium acetate (pH 8.5). Cations: 1 M FA. 30 kV SF 10 µL/min.	+/-	3.3 nM (Arg) 473 nM (Gly)	[187]
All proteinogenic AAs, acyl-carnitine, L-allo-Ile, 4-OH-Pro, pyro-Glu	100 µL (1/1 MeOH/H ₂ O) on Dried Blood Spot from Guthrie card, 20 min. Directly CE injected	50 µm ID, 80 cm TL capillary; 1.4 M FA, 30 kV. SF 10 µL 0.1% FA (50% MeOH/ water, v/v)	+	60 nM (Arg) 11.7 µM (Val)	[188]
All proteinogenic AAs, atenolol, O-butyryl-L-carnitine, L-carnitine, L-carnosine, creatinine, <i>p</i> -chloro-L-Tyr, L-citrulline, L-cystathionine, 2,3-dihydroxy-L-phenylalanine (DOPA), DP, guanosine, histamine, Hcy, Orn, 5-hydroxyl-L-tryptophan, metoprolol, N-methyl-L-Asp, 3-methyl-L-His, 1-methyl-adenosine, L-methionine sulfone, nicotinamide, nicotinic acid, <i>p</i> -nitro-L-tyrosine, O-octoyl-L carnitine, oxytetracycline, tyramine, <i>m</i> -L Tyr, <i>o</i> -L-Tyr, SR, L-theanine, glutathione	Washed RBC lysed in 3-fold-volume excess water (0 °C) vortexed, centrifuged. Supernatant ultracentrifugation using 3-kDa filter (protein removing). Filtrate diluted 1:1 with 400 mM ammonium acetate, pH 7.0.	50 µm ID, 80 cm TL capillary; 1.4 M FA, 30 kV. SF 10 µL 0.1% FA (50% MeOH/ water, v/v)	+	nd	[189]
All proteinogenic AAs, Orn, N,N-diaminobutane, ethanolamine, carnosine, β-Ala, GABA, sarcosine, α	50 mg pineapple leaves were ground + 500 µL MeOH/water 1/1 (v/v), vortexed, centrifuged. Supernatant ultracentrifuged in 5-kDa ultrafilter.	50 µm ID, 100 cm TL capillary. 1 M FA 30 kV. SF 10 µL/min (50% MeOH/ water, v/v)	+/-	≈1 µM	[190]

aminobutyrate, cystathionine, homo-Ser, methionine sulfone, hydroxy-Pro, Phe-Gly, phosphoethanolamine, urea, taurine, succinate, lactate, malate, isocitrate, fumarate, tartrate, cis-aconitate					
Orn, β -Ala, Allo-Ile, citrulline, pyro-Glu.	40 g vegetable oils + 160 mL of methanol:chloroform (2:1, v/v) vortexed, left overnight, centrifuged. Upper phase collected + (40 mL chloroform, 100 mL water), vortexed centrifuged. Supernatant dried. + 1 mL Butanolic-HCl, vortexed, 80 °C, 30 min., dry and diluted in 500 μ L of acetonitrile/water (40:60, v/v)	50 μ m ID, 60 cm TL capillary. 0.1 M FA, 25 kV. SF 3.3 μ L/min 0.1% FA (isopropanol/water, 1/1, v/v)	+	40 pg/g (Orn, β -Ala, GABA). 190 pg/g (citrulline)	[191]
All proteinogenic AAs, Chloro-Tyr (IS), 4 hydroxy-Pro,	Clean Mylar strips (10 \times 2 cm) + 8 μ L 1.6 mM IS in BGE, left to dry + 1 mL (EtOH/water, 6/4, v/v), filtered, dry. + 50 μ L BGE	50 μ m ID, 100 cm TL capillary. 1 M FA, 25 kV. SF 10 μ L/min 0.1% FA (methanol /water, 1/1, v/v)	+	20 ng/strip (Lys) 180 ng/strip (Met)	[192]
D/L proteinogenic AAs without Asn, Arg, Allo-Ile	500 μ L vinegar filtered (3 kDa filter), water diluted (1/1).	50 μ m ID, 100 cm TL capillary. 1 M FA 30 mM 18C6H4, 24 kV. SF 10 μ L/min (50% MeOH/ water, v/v)	+	0.15 μ g/mL (Met) 0.83 μ g/mL (Val)	[194]
D/L Ser, D/L Glu, D/L Gln, D/L Asn, D/L Asp	100 μ L artificial cerebrospinal fluid, + 10 μ L 30 mM sodium tetraborate (pH 9.2) + 90 μ L 6 mM (+)-1-(9-fluorenyl)ethyl chloroformate (in acetone/ACN, 1/2, v/v)). Vortexed 1 h. Diluted in 0.5 mL water.	50 μ m ID, 80 cm TL capillary. BGE 150 mM acetic acid, pH 3.7 (NH ₄ OH), 30 kV. Inlet: 17 mbar negative pressure. SF 3 μ L/min 0.1% NH ₄ OH in (50% MeOH/ water, v/v)	-		[195]
D/L Arg, D/L Lys, D/L Ala, D/L Glu, D/L Asp	100 mg grounded soya kernels + 1 mL 0.37 M trichloroacetic acid, vortexed. + 0.2 mL 3.6 mM sodium deoxycholate. Centrifugation. 625 μ L supernatant + 675 μ L water + 1.5 mL 355 mM	50 μ m ID, 85 cm TL, capillary. 5 mM 3-monodeoxy-3-monoamino- β -CD, 50 mM, HCO ₃ , NH ₄ pH 8. 30	+	nd	[197]

	sodium tetraborate (pH 10). + 1 M NaOH pH 10 + water to final volume = 10 mL. 250 µL of this solution + 50 µL 3.75 mM FITC (in acetone). Reaction overnight.	kV. SF 4 µL/min (50% isopropanol/water, v/v).			
Zn-Gly, Zn Met, Zn galacturonate, Zn caffeate, Zn pterostilbene, Zn piceatannol, Zn isorhamnetin, Zn zeaxanthin glucoside	50 mg grounded goji berry + 2 mL 30 mM Tris-HCl pH 7.4. Vortexed 2 h. Ultrafiltrated (10 kDa filter) immediately analyzed.	50 µm ID, 100 cm TL, capillary. 20 mM ammonium formate (pH 9), 10 kV. SF 10 µL/min 5 mM ammonium formate, in 50% methanol/water (v/v)	+/-	nd	[199]
17 AAs	Standards	20 µm ID, 120 cm TL, porous tip capillary. 1 M FA 15 mM 18C6H4, 20 kV.	+	nd	[200]
D/L Asp, D/L Phe, D/L Tyr	~20 µg silk digested in 6 N HCl at 110 °C, 2 h, dried, resuspended in 0.1 N HCl.	20 µm ID, 120 cm TL, porous tip capillary. 30 mM 18C6H4. 30 kV	+	nd	[201]
Proteinogenic AA, spermine, hypoxanthine, glutathione, adenosine, creatine, hydroxyl-Pro, anthranilate, spermidine, cytosine, adenine, homo-Ser, tyramine	50 µL of known HepG2 cell lysate (in MeOH/water, 4/1, v/v) + 50 µL 0.2 µg/mL isotope-labeled AAs + 100 µL cold water/chloroform (1.5/1 v/v), vortex, centrifuged, supernatant ultrafiltered (5 kDa filter), dried + 50 µL 250 mM ammonium acetate, pH 7.	30 µm ID, 91 cm TL, porous tip capillary. 10% acetic acid pH 2.2, 30 kV	+	1-42 nM, except for Asp 412 nM	[203]
All proteinogenic AAs (except Cys, Asn, Gln) D ₃ -Met (IS), α-keto-glutarate, pyruvate, succinate, fumarate, lactate	2×10 ⁶ washed bovine aortic endothelial cells (or human tissue from sternotomy) + 600 µL cold [MeOH/water (4/1), 5 µM IS], sonicated, centrifuged. 20 µL supernatant were dried. Dry sample + 100 µL anhydrous DMF with (300 mM 1-chloro-N,N,2-trimethyl-1-propenylamine, 300 mM 3-(diethylamino) propionic acid) + 4 µL pyridine.	50 µm ID, 80 cm TL capillary. 5 mM ammonium formate, 10% MeOH, pH of FA adjusted to 2.5.	+	9 nM (Ile, Leu) 225 nM (His)	[205]
Trp, Tyr, Phe, Ala, Pro, Val, The, Leu, Ile, Arg, Met	Standards	50 µm ID, 40 cm TL capillary fitted in union comprising a conductive-hole. 5 mM ammonium acetate, pH 10.8. 25 kV.		0.11 µM (Phe) 1.62 µM (Ala)	[206]