

# Chemical Delivery System of MIBG to the Central Nervous System: Synthesis, 11 C-Radiosynthesis, and in Vivo Evaluation

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## ACS Medicinal Chemistry Letters

Letter

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MIRG

(MetalodoBenzvlGuanidine)

NH<sub>2</sub>

Specific radiotracer of norepinephrine transporter (NET)

[<sup>123</sup>I/<sup>131</sup>I]MIBG : diagnosis and therapy of peripheral

Study of the noradrenergic system involved in

depression, attention deficit hyperactivity disorders

### <sup>1</sup> Chemical Delivery System of MIBG to the Central Nervous System: <sup>2</sup> Synthesis, <sup>11</sup>C-Radiosynthesis, and *in Vivo* Evaluation

<sup>3</sup> Fabienne Gourand,<sup>\*,‡</sup>
 <sup>a</sup> Delphine Patin,<sup>‡</sup> Axelle Henry,<sup>†</sup> Méziane Ibazizène,<sup>‡</sup> Martine Dhilly,<sup>‡</sup>
 <sup>4</sup> Fabien Fillesoye,<sup>‡</sup> Olivier Tirel,<sup>‡</sup> Mihaela-Liliana Tintas,<sup>‡</sup> Cyril Papamicaël,<sup>†</sup> Vincent Levacher,<sup>\*,†</sup>
 <sup>5</sup> and Louisa Barré<sup>‡</sup>

6 <sup>‡</sup>Normandie Univ, UNICAEN, CEA, CNRS, UMR 6030 ISTCT/LDM-TEP group, Bd Henri Becquerel, BP 5229, 14074 Cedex 7 Caen, France

8 <sup>†</sup>Normandie Univ, COBRA, UMR 6014 et FR 3038; Univ Rouen; INSA Rouen; CNRS, IRCOF, 1 rue Tesnière, 76821 Mont Saint
 9 Aignan Cedex, France

10 Supporting Information

**ABSTRACT:** The norepinephrine transporter (NET) plays an impor-11 tant role in neurotransmission and is involved in a multitude of 12 psychiatric and neurodegenerative diseases. [123I/131I]meta-iodobenzyl-13 guanidine (MIBG) is a widely used radiotracer in the diagnosis and 14 follow-up of peripheral neuroendocrine tumors overexpressing the 15 16 norepinephrine transporter. MIBG does not cross the blood-brain barrier (BBB), and we have demonstrated the "proof-of-concept" that 1,4-17 dihydroquinoline/quinolinium salt as chemical delivery system (CDS) is 18 a promising tool to deliver MIBG to the brain. To improve BBB passage, 19

20 various substituents on the 1,4-dihydroquinoline moiety and a linker

21 between CDS and MIBG were added. A series of CDS-MIBGs 1a-d was synthesized, labeled with carbon-11, and evaluated in

22 vivo into rats. The in vivo results demonstrated that, although adding substituents on CDS in 1a-c is of no benefit for brain

23 delivery of MIBG, the presence of a linker in CDS-MIBG 1d greatly improved both brain penetration and the release rate of

24 MIBG in the central nervous system.

25 **KEYWORDS:** Central nervous system, norepinephrine transporter, MIBG, radiosynthesis, redox chemical delivery system,

26 1,4-dihydroquinolines carriers

<sup>27</sup> T he *in vivo* expression of norepinephrine transporter <sup>28</sup> (NET) is mostly established in the central and peripheral <sup>29</sup> sympathetic nervous system. Several different radiotracers for <sup>30</sup> clinical imaging of NET expression were developed.

Among them, *meta*-iodobenzylguanidine (MIBG) is structurally similar to the neurotransmitter norepinephrine, and [<sup>123</sup>I]MIBG single photon emission computed tomography (SPECT) imaging studies are the most accurate method for s detection of catecholamine-secreting tumors including neuroendocrine tumors such as pheochromocytoma and neuroplastoma.<sup>1-3</sup>

<sup>38</sup> Moreover, MIBG was also radiolabeled with iodine-131 for <sup>39</sup> radiotherapy to treat neuroendocrine tumors. Positron <sup>40</sup> emission tomography (PET) is more accurate and has the <sup>41</sup> potential to be more sensitive and to provide better image <sup>42</sup> resolution. In this context, efforts to develop MIBG analogs <sup>43</sup> labeled with a positron emitter remain of great interest, and <sup>44</sup> several <sup>18</sup>F-labeled benzylguanidine analogs have already been <sup>45</sup> developed for PET imaging of NET expression. Recently, the <sup>46</sup> radiotracer *meta*-[<sup>18</sup>F]Fluorobenzylguanidine ([<sup>18</sup>F]MFBG) <sup>47</sup> has shown to be a very promising PET candidate leading to <sup>48</sup> successful clinical investigations.<sup>4–7</sup> Dysregulation of NET is <sup>49</sup> implicated in various neuropsychiatric disorders such as

depression, anxiety, attention deficit hyperactivity disorders 50 (ADHD), Parkinson's disease, Alzheimer's disease, and 51 epilepsy. As the NET plays an important role in the central 52 nervous system (CNS), the use of MIBG or MIBG analogs in 53 brain imaging needs to be explored. However, MIBG is unable 54 to cross the blood-brain-barrier (BBB). Guilloteau et al. have 55 compared the uptake and release of radioiodinated meta- 56 iodobenzylguanidine ([125I]MIBG) and tritiated norepinephr- 57 ine ( $[^{3}H]NE$ ) in different regions of the rat brain. The authors 58 found comparable regional distribution of [<sup>3</sup>H]NE and 59 [<sup>125</sup>I]MIBG uptake in the rat brain.<sup>8</sup> A chemical delivery 60 system (CDS) designed for MIBG able to cross the BBB would 61 provide a potential imaging marker to visualize the NET in the 62 brain (Figure 1). In the literature, Bodor et al. have developed 63 fl an interesting CDS based on a lipophilic 1,4-dihydropyridine 64 able to cross the lipophilic BBB.9,10 Then, the 1,4-65 dihydropyridine system is oxidized into the CNS to a 66 hydrophilic pyridinium species. which cannot cross back the 67 BBB (named as "the locked in effect"). A subsequent 68

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**Peripheral System** 

**Central Nervous System** 

adrenergic tumors

d Brain B



Figure 1. Development of a <sup>11</sup>C-chemical delivery system of MIBG into the CNS.

69 hydrolysis releases the active compound, which can then act 70 directly on the target into the CNS. By using this approach, 71 Bodor et al. have targeted many drugs to the CNS.<sup>11–14</sup> Later, 72 Levacher et al. have solved many drawbacks related to this 73 CDS by means of 1,4-dihydroquinolines instead of 1,4-74 dihydropyridines. However, although mainly drugs were 75 successfully targeted using this strategy, very few reports deal 76 with the use of this CDS to target radiotracers into the brain. A 77 survey of the literature indicated that, aside from our previous 78 work on MIBG,<sup>15,16</sup> only a single research article<sup>17</sup> explored 79 the potential of this appealing CDS approach to deliver a 80 radiolabeled agent into the CNS. As far as our preliminary 81 research work on MIBG is concerned, our initial work focused s2 on the radiolabeling with carbon-11 of the CDS in order to 83 validate the concept described previously. The results of the in 84 vivo studies were highly encouraging, supporting our working 85 hypothesis that the dihydroquinoline system may possibly be a 86 promising CDS to target MIBG to brain tissues. Indeed, after 87 in vivo injection into rats of [<sup>11</sup>C]CDS-MIBG ([<sup>11</sup>C]1a), the 88 passage of  $[^{11}C]$  1a through the BBB has been demonstrated as 89 well as the presence of MIBG in the brain. However, this 90 chemical delivery system has some limitations: (1) a moderate 91 brain penetration has been measured, and (2) the oxidation 92 kinetics of  $\begin{bmatrix} 11 \\ C \end{bmatrix}$  1a was quite slow since more than 50% was 93 still present in rat brain at 45 min post injection. For these 94 reasons, this CDS still needed to be optimized before being 95 applied to radioiodinated MIBG. This Letter will focus on the 96 preparation and in vivo evaluation of new 1,4-dihydroquino-97 line-MIBG systems [<sup>11</sup>C]1b,c bearing methoxy groups to tune 98 the redox potential of the CDS. The preparation and in vivo 99 evaluation of a 1,4-dihydroquinoline  $[11\overline{C}]$ 1d having a self-100 immolative linker between the CDS and MIBG will be also 101 reported (Figure 1).

To perform the radiosynthesis and *in vivo* study of our systems, it was first necessary to synthesize the precursors for radiolabeling and references that will be used to identify compounds in radio-HPLC. We have previously described the synthesis of the targeting system **1a** starting from quinoline **4a** rof (Scheme 1).<sup>15</sup> We decided to adopt the same approach to prepare **1b,c**. Thus, a coupling reaction from quinolines **4b,c**<sup>18,19</sup> and MIBG using CDI led to the corresponding runolines **5b,c** in moderate yields (36% and 30%, 111 respectively). Alternatively, quinoline **5c** could be prepared

s1

Scheme 1. Synthesis of the Redox CDS-MIBG  $1a-c^{a}$ 



<sup>a</sup>Reagents and conditions: (i) CDI, DMF, 20 °C, 1 h then MIBG, 20 °C, 1 h for  $5a^*$  (60%) and 5b (36%) and 5c (30%); (ii) NBI, NEt<sub>3</sub>, DMF, 20 °C, 12 h (74%); (iii) MIBG, DMF, 140 °C, 7 h (76%); (iv) CH<sub>3</sub>OTf, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 2 h for  $2a^*$  (50%), 3 h for 2b (60%) and 2c (81%); (v) BNAH, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 12 h for  $1a^*$  (95%), 1b (32%), 1c (70%).  $1a^*$ ,  $2a^*$  and  $5a^*$  results are from ref 15.

by reacting MIBG with the activated enol ester<sup>20</sup> **4d** (76%), <sup>112</sup> the latter having been obtained by reacting **4c** with NBI (74%). <sup>113</sup> Then, quinolines **5b,c** were easily transformed into their <sup>114</sup> corresponding quinolinium salts **2b,c** (60% and 81%, <sup>115</sup> respectively) in the presence of methyl triflate. Finally, the <sup>116</sup> desired CDS-MIBG **1b,c** were successfully obtained after <sup>117</sup> regioselective reduction of quinolinium salts **2b,c** by means of <sup>118</sup> BNAH (32% and 70%, respectively). <sup>119</sup>

We next turned our attention to the synthesis of a CDS 120 having a  $\gamma$ -aminobutyric acid (GABA) self-immolative linker 121 group.<sup>21–23</sup> We envisaged the synthesis of quinoline **9** from 122 GABA derivative **6a** (Scheme 2, route A). So, neutralization of 123 s2 hydrochloride amine salt **6a** and subsequent coupling reaction 124 with carboxylic acid **4a** using BOP reagent led to quinoline **7a** 125 Scheme 2. Initial Routes To Synthesize the Targeting System  $1d^a$ 



<sup>a</sup>Reagents and conditions: (i) NaOH then 4a, BOP, NEt<sub>3</sub>, DMF, 20 °C, 12 h (79% for 7a, 25% for 9); (ii) LiOH, THF, MeOH, H<sub>2</sub>O, 20 °C, 3 h (96%); (iii) BOP, MIBG, NEt<sub>3</sub>, DMF, 20 °C, 12 h (25% for 8a, 4% for 9); (iv) CH<sub>3</sub>COCl, MeOH, 20 °C, 1 h for 8b (95%) or TFA, CH<sub>2</sub>Cl<sub>2</sub>, -5 °C, 1 h for 8b' (98%); (v) CH<sub>3</sub>OTf, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 12 h (44% for 2d and 23% for 2e determined by <sup>1</sup>H NMR); (vi) BNAH, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 12 h.

126 (79% yield). The methyl ester functional group was hydrolyzed 127 by LiOH to give carboxylic acid 7b (96% yield). The latter was 128 subsequently involved in a coupling reaction with MIBG using 129 BOP to give 9 in a very low yield (4% yield). We also 130 investigated other activation strategies of carboxylic acid 7b by 131 means of CDI, ClCOOEt, (COCl), NBI, or NHS/DCC. 132 Unfortunately, we failed to obtain 9 by using these reagents. 133 Alternatively, N-protected GABA 6b and MIBG were reacted 134 in the presence of BOP reagent to furnish the coupling product 135 8a in 25% yield (Scheme 2, route B). Then, N-Boc 136 deprotection was carried out by using either acetyl chloride/ 137 MeOH or TFA to lead, respectively, to the desired ammonium 138 salts 8b and 8b' (95% and 98% yields). One may note that 20 139 equiv of acetyl chloride/MeOH or TFA were required during 140 the course of the N-Boc deprotection to prevent from the 141 formation of the undesired  $\gamma$ -lactam ring resulting from the 142 cyclization reaction of the self-immolative linker. Thereafter, 143 ammonium 8b was neutralized back to pH 7 with sodium 144 hydroxide before being converted into the desired amide 9 in 145 25% yield by means of a coupling reaction between 4a and 146 BOP reagent. The quaternization reaction of 9 with methyl 147 triflate afforded a mixture of 2d,e (44% and 23%, respectively, 148 estimated by <sup>1</sup>H NMR). We then proceeded to a classical 149 reduction of the mixture of quinolinium salts 2d,e with BNAH. 150 However, LC/MS analysis of the crude reaction medium 151 revealed the presence of both 1,4-dihydroquinolines 1d,e and

quinolinium salts 2d,e, which turned out to be extremely 152 difficult to separate. Given this result, we decided to explore 153 another route to obtain exclusively 1,4-dihydroquinoline 1d. 154 To overcome the alkylation reaction leading to undesirable 155 compound 2e, quinoline 4e was first quaternized with methyl 156 triflate to give the key intermediate 10 in 96% yield (Scheme 157 s3 3). The resulting NHS-activated quinolinium 10<sup>24</sup> was 158 s3

### Scheme 3. Alternative Route to the Redox CDS-MIBG 1d<sup>a</sup>



<sup>*a*</sup>Reagents and conditions: (i) CH<sub>3</sub>OTf, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 4 h (96%); (ii) polymer-bound DBU, **8b**<sup>'</sup>, THF, 20 °C, 12 h (58%); (iii) BNAH, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 4 h (77% determined by <sup>1</sup>H NMR).

smoothly reacted with linker-MIBG derivative 8b' to yield 159 compound 2d (58%). Finally, a classical reduction reaction 160 with BNAH led to the desired MIBG-targeting system 1d 161 (77% determined by <sup>1</sup>H NMR).

Radiosyntheses of  $[^{11}C]$ **1b**,c were carried out as depicted in 163 Scheme 4 according to a two-step synthetic procedure.<sup>15,16,25</sup> 164 s4 The structures of the <sup>11</sup>C-labeled products were confirmed by 165 comparing their retention time with the corresponding 166 nonradioactive standard compounds using reverse-phase 167 HPLC. Thus, the quaternization reaction of quinolines 5b,c 168 with  $\begin{bmatrix} {}^{11}C \end{bmatrix}$  methyl triflate afforded quinolinium salts  $\begin{bmatrix} {}^{11}C \end{bmatrix}$  **2b,c.** 169 Reduction of  $[{}^{11}C]$ **2b,c** was conducted with BNAH for 5 min 170 at 100 °C to provide the corresponding 1,4-dihydroquinolines 171 [<sup>11</sup>C]1b,c (respectively, 68% and 61% relative percentages 172 determined by radio-HPLC). The same procedure was applied 173 to the radiosynthesis of  $[^{11}C]$ 1d. However, radio-HPLC 174 analyses demonstrated that  $[^{11}C]$ 2d was not stable enough 175 under these high dilution reaction conditions. To circumvent 176 the poor stability of [<sup>11</sup>C]2d, we decided to add the reducing 177 agent BNAH and the alkylating agent [<sup>11</sup>C]CH<sub>3</sub>OTf 178 simultaneously. Then, the reaction mixture was left to react 179 5 min at 20 °C. To prevent [<sup>11</sup>C]1d from oxidation during the 180 purification step, basic HPLC conditions were required. So, by 181 adding triethylamine in HPLC eluent, 1,4-dihydroquinoline 182 <sup>[11</sup>C]1d was obtained with a radiochemical purity of 50% 183 (based on HPLC analysis of the crude product). A 184 TRACERlab FX-MeI and FX-M radiosynthesis module was 185 used to achieve a fully automated radiosynthesis of  $[^{11}C]$ 1b-d 186 using a two-step reaction as shown in Scheme 4. The total 187 synthesis time of the fully automated process was approx- 188 imately 50 min. Activity levels in the final product ranged from 189 592 to 814 MBq for  $[^{11}C]$ 1b; 259–444 MBq for  $[^{11}C]$ 1c; and 190 148–518 MBq for  $[^{11}C]$ 1d. The radiochemical purities of 191  $[^{11}C]$ **1b**-d were >95%.

Then, biological studies were conducted in rats to 193 determine, *in vivo*, the cerebral penetration through the BBB 194 of the different MIBG-targeting systems  $[^{11}C]$ **1b**-**d** by 195 measuring the radioactivity of the cerebral samples obtained 196 after sacrifice of the animals (Figure 2). Last but not least, we 197 f2

#### Scheme 4. Radiosyntheses of [<sup>11</sup>C]1b-d<sup>a</sup>



<sup>*a*</sup>Reagents and conditions: for [<sup>11</sup>C]**1b**,c from **5b**,c: (i) [<sup>11</sup>C]CH<sub>3</sub>OTf, CH<sub>3</sub>CN, 20 °C, 5 min; (ii) BNAH, CH<sub>3</sub>CN, 100 °C, 5 min; for [<sup>11</sup>C]**1d** from **9**: (iii) [<sup>11</sup>C]CH<sub>3</sub>OTf, CH<sub>3</sub>CN, 20 °C and BNAH, then 10 min, 20 °C.



**Figure 2.** *Ex vivo* biodistribution of the radioactivity in rat brain at different time intervals following tail vein injection of  $[^{11}C]\mathbf{1a-d}$  (5, 10, 30, and 45 min for  $[^{11}C]\mathbf{1a-c}$ ; 5 and 10 min for  $[^{11}C]\mathbf{1d}$ ). Results are expressed in percent of injected dose per gram (%ID/g, mean, n = 2 for each point).  $[^{11}C]\mathbf{1a^*}$  results are from ref 15.

198 were also interested (both in brain and plasma) in the 199 oxidation rates of  $[^{11}C]\mathbf{1b-d}$  into the corresponding

quinolinium salts  $[^{11}C]$ **2b**-d, which subsequently led to the <sup>200</sup> cleavage of MIBG from the carrier through hydrolysis. The <sup>201</sup> results will be compared to those already obtained from  $[^{11}C]$  <sup>202</sup> **1a**<sup>15</sup> in order to select the most promising CDS to target <sup>203</sup> MIBG to the CNS. <sup>204</sup>

Then, the monitoring of both oxidation and MIBG cleavage 205 steps in the CNS were investigated from brain samples, which 206 were analyzed by radio-HPLC after radiotracer injection. Both 207 CDS-MIBG [<sup>11</sup>C]1b and [<sup>11</sup>C]1c proved to be rather stable 208 since 87% and 90% of 1,4-dihydroquinolines [<sup>11</sup>C]1b,c, 209 respectively, were detected at 10 min after injection, together 210 with 12% and 5% of quinolinium salts  $[^{11}C]$ 2b,c, respectively, 211 but with no traces of carboxylic acids  $[^{11}C]$ 3b,c (Figure 3b,c). 212 f3 Regarding CDS-MIBG [<sup>11</sup>C]1a previously investigated,<sup>15</sup> the 213 percentage of carboxylic acid [<sup>11</sup>C]3a reached 11% at 10 min 214 after injection, highlighting a faster cleavage of MIBG from the 215 quinolinium salt 2a (Figure 3a). We can therefore draw the 216 conclusion that the presence of methoxy groups on the carrier 217 do not increase the oxidation rates of  $\begin{bmatrix} 11\\ C \end{bmatrix}$ **1**b,c in the brain 218 compared to  $[^{11}C]$  1a and even seems to delay the cleavage of 219 MIBG from the resulting quinolinium salts  $[^{11}C]$ **2b,c**. 2.2.0

At this stage, it seems that in terms of brain uptake, 221 oxidation, and hydrolysis rates, CDS-MIBG  $[^{11}C]$ 1a remains 222 the best candidate among the three CDS-MIBG  $[^{11}C]$ 1a-c. In 223



Figure 3. Percentage of the expected  $[^{11}C]$  radioactive species in brain after injection into rat of (a)  $[^{11}C]$ 1a, (b)  $[^{11}C]$ 1b, (c)  $[^{11}C]$ 1c, and (d)  $[^{11}C]$ 1d (mean, n = 2 for each time point).  $[^{11}C]$ 1a\* results are from ref 15.

Scheme 5. Schematic Representation for MIBG Release from Carrier-linker-MIBG 1d



s5

224 contrast, HPLC analyses of both brain and plasma samples at 5 225 min after injection of 1,4-dihydroquinoline  $[^{11}C]$ 1d revealed 226 the presence of only one polar radioactive compound 227 corresponding to the carboxylic acid  $[^{11}C]$ 3a (Figure 3d). 228 These data indicate a fast *in vivo* oxidation of  $[^{11}C]$ 1d followed 229 by hydrolysis of the resulting quinolinium salt  $[^{11}C]$ 2d leading 230 to the release of carboxylic acid [<sup>11</sup>C]3a along with the linker-231 MIBG intermediate, which would undergo cyclization to 232 produce desired MIBG along with  $\gamma$ -lactam as byproduct. This 233 scenario depicted in Scheme 5 (route A) is backed up by the 234 fact that during the preparation of 8b,b', a fast cyclization 235 process of the corresponding free amine was observed leading 236 to MIBG and  $\gamma$ -lactam products. At this stage, a second 237 scenario cannot be ruled out in which hydrolysis would occur 238 at the carbonyl group attached to MIBG as shown in Scheme 5 239 (route B) to release MIBG in a single step. In light of our 240 results, it might be concluded that the presence of a linker 241 between the 1,4-dihydroquinoline moiety and MIBG increases 242 notably not only the BBB passage and oxidation rate of  $[^{11}C]$ 243 1d but also the release of MIBG from the carrier in the brain. 244 In this study, we successfully synthesized and labeled with 245 carbon-11 various  $\begin{bmatrix} 11 \\ C \end{bmatrix} CDS-MIBG$  ( $\begin{bmatrix} 11 \\ C \end{bmatrix} \mathbf{1b-d}$ ). We also 246 examined in vivo their potential to deliver MIBG into the 247 central nervous system. A preclinical evaluation showed high 248 BBB permeability of the carrier-linker-MIBG [<sup>11</sup>C]1d as 249 demonstrated by the high percentage of radioactivity measured 250 in the brain, whereas the two other CDS-MIBG  $[^{11}C]$ 1b,c 251 exhibited poor BBB passage. Once in the brain, fast oxidation 252 of the 1,4-dihydroquinoline  $[^{11}C]$ 1d and prompt cleavage of 253 MIBG from the resulting quinolinium salt [<sup>11</sup>C]2d take place 254 as evidenced by the only presence of carboxylic acid  $\begin{bmatrix} 11 \\ 23a \end{bmatrix}$  in 255 brain samples after 5 min. In light of these promising in vivo 256 profiles observed with  $[^{11}C]$ 1d, this work paves the way to the 257 use of the CDS-radiolabeled-MIBG as an appealing imaging 258 tool for the study of cerebral adrenergic nerve endings within 259 the brain.<sup>26272829</sup>

#### 260 **ASSOCIATED CONTENT**

#### 261 **Supporting Information**

262 The Supporting Information is available free of charge on the 263 ACS Publications website at DOI: 10.1021/acsmedchem-264 lett.8b00642.

Experimental procedures and characterization of all
 compounds, radiosyntheses and procedures for *in vivo* experiments (PDF)

#### **Corresponding Authors** 269 \*E-mail: gourand@cyceron.fr. 270 \*E-mail: vincent.levacher@insa-rouen.fr. 271 ORCID <sup>©</sup> 272 Fabienne Gourand: 0000-0002-3585-6437 273 Vincent Levacher: 0000-0002-6429-1965 274 Author Contributions 275 The manuscript was written through contributions of all 276 authors. All authors have given approval to the final version of 277 the manuscript; 278 Notes 279

The authors declare no competing financial interest. 280

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#### ABBREVIATIONS

MIBG, *meta*-iodobenzylguanidine; NET, norepinephrine trans- 291 porter; BBB, blood-brain barrier; CDS, chemical delivery 292 system; SPECT, single photon emission computed tomog- 293 raphy; PET, positron emission tomography; CNS, central 294 nervous system; ADHD, attention deficit hyperactivity 295 disorder 296

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