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The metabolic status and olfactory function

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Part IV: Flavor perception and physiological status

Chapter 15: The metabolic status and olfactory function.

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Abstract

Olfaction interferes with various vital activities throughout the detection and processing of environmental odours related to feeding, social behaviour and reproduction. Particularly, animals strongly rely on olfaction to locate, choose, consume and stop to eat food. Thus, the olfactory system does contribute to adjustments in food intake regulation according to the physiological needs, leading to the concept of a multi-layered modulation acting from the periphery to higher brain centres. Indeed, both the olfactory mucosa and bulb are under the direct influence of metabolic hormones, peptides and nutrients which modulate odour processing according to the internal energetic status at short- and long-term. In mammals, an increasing number of food intake-related factors that modulate neuronal activity has been identified in the last two decades, reinforcing their putative roles as circulating factors acting at the molecular interface between environmental and nutritional cues. Indeed, pioneer works have shown that these factors could modulate olfactory sensitivity, acting directly or indirectly on neuronal activity. Examination of more integrated physiological conditions, e.g. metabolic state or hunger, has confirmed the tight and complex link between olfaction and endocrine systems, pointing out long-term modulatory effects in cell dynamics and tissue homeostasis related to nutritional imbalances in adulthood. Recently, the maternal metabolic status has even been shown to influence olfactory capabilities and associated behaviours – such as food intake- in offspring. This suggests a programming effect of the maternal nutritional context that could participate to the vicious circle of food intake deregulation, giving rise to a renewed interest of this topic.

Keys words: olfactory mucosa, olfactory bulb, odour sensitivity, hormones, neuropeptides, obesity, maternal trajectory,

In humans and animals, eating behaviour, comprising food seeking, onset and end consumption, is mainly triggered by internal metabolic needs, signalled by fluctuating levels of metabolic-related hormones and peptides (leptin, insulin, ghrelin, orexin), and of nutriments, such as glucose. However, the food consumption is also regulated by hedonic and sensory signals, including olfaction (Rolls, 2012), this making food-related odours as essentially involved in the food intake control (Le Magnen, 1959).

An intuitive perception from everyone experience, is that the olfactory function can be modulated by the metabolic state. Indeed, both the olfactory mucosa and bulb are influenced by metabolic hormones, peptides and nutrients which modulate odour processing according to the internal energetic status at short- and long-term. This chapter aims to shed light on how endogenous signals linked with the feeding or metabolic state, regulate olfactory sensitivity and olfactory-driven behaviours in humans and animals, with a special emphasis on the impacts of metabolic disorders, such as obesity, diabetes and eating disorders. It also gives insights in a programming effect of the maternal metabolic context as a way to support long-term effects on offspring's olfactory capacities.

15.1. How is the olfactory function under the influence of metabolic-related hormones and peptides and of nutriments: neuroanatomical evidences

For fifty years, numerous efforts have been done to localize hormones/peptides and their receptors by immunohistochemistry, radioimmunoassay, radioactive, or not, hormone binding assays and more recently molecular biology. The demonstration that most metabolic anorexigenic and orexigenic hormones and peptides receptors traditionally considered to be feeding related are expressed in the olfactory system in many species strongly came to support the findings that odour processing can be modulated by the nutritional status; this especially in the first two levels of the olfactory system, the olfactory mucosa (OM) and the olfactory bulb (OB), thus well before the involvement of cortical integration (Lucero, 2013; AlKoborssy et al., 2014; Nogi et al., 2020).

15.1.1. Anatomical distribution of receptors to metabolic related hormones and peptides along the olfactory pathways.

The olfactory mucosa

In mammalian OM¹, mature olfactory sensory neurons (OSNs), key cells interacting with odorant molecules and transducing the odorant signal, express a large array of receptors dedicated to major anorexigenic or orexigenic metabolic hormones: orexin receptor (OXR) have been localized in the apical ends of the sensory neurons (Caillol et al., 2003, Gorojankina et al., 2007), leptin receptor (Ob-R) (Baly et al., 2007) and insulin receptor (IR) (Lacroix et al., 2008) in dendritic knobs, ghrelin receptor (Ghr1a) (Loch et al., 2015), and endocannabinoid receptor CB1 in mature OSN (Hutch et al., 2015). In a less extend, neuropeptide Y receptor (NPY-Y1R) is expressed in a subset of OSNs dispersed within the OM (Negrioni et al., 2012). Moreover, the adiponectin receptor (AdipoR1), throughout which adiponectin regulates glucose levels and fatty acid catabolism, is also present in mature OSNs (Hass et al., 2008). Immature neurons for their part, only express Ob-R and IR. Moreover, the non-neuronal sustaining cells, ensheathing OSNs, express most of the so far mentioned receptors, except NPY-Y1Rs. Finally, the basal cells that ensure the OSN's renewing express IR, Ob-R, NPY-Y1R and CB1. In the *lamina propria*, Ob-R has been reported in the Bowman glands and IR in the endothelium of microvessels (Getchell et al., 2006; Baly et al., 2007; Lacroix et al., 2008).

The olfactory bulb

OB being the first olfactory structure of the central nervous system, a great effort has been done in localizing metabolic related receptors expression since decades in this tissue. The mitral-tufted cells (MTC) that receive direct sensory inputs from OSNs and transfer it to next brain olfactory area, express a large number of metabolic related receptors, including some of those reported in the OM such as IR (Fadool et al., 2000; Lacroix et al., 2008; Marks et al., 1990), Ob-R (Baly et al., 2007; Prud'homme et al., 2009), OXR (Caillol et al., 2003; Hardy et al., 2005; Shibata et al., 2008), CB1 (Tsou et al., 1998; Wang et al., 2012) and, additional ones such as Growth Hormone Secretagogue Receptor for ghrelin (GHSR) or Cholecystinin 2 receptor (CCK2R). More precisely, Ob-R, OXR, GHSR, CCK2R are expressed in the periglomerular area (OB peripheral layer where OSNs' axons synapse with MTCs' dendrites) while IR, Ob-R, ORX, GHSR and, in a less extend NPYR2, are present in the granular cells layer (Mercer et al., 1990; Tong et al., 2011; Aimé et al., 2012; Okuhara et al., 2018).

¹ The olfactory mucosa is located in the upper region of the nasal cavity and comprises the olfactory epithelium and the underlying lamina propria, connective tissue containing fibroblasts, blood vessels, Bowman's glands and bundles of fine axons from the olfactory neurons.

15.1.2 Local synthesis of metabolic-related hormones/peptides in olfactory tissues.

Metabolic hormones/peptides related to the receptors mentioned above mostly originate from peripheral organs (pancreas, adipocytes, gastro intestinal tract), and reach OM and OB by the general circulation thanks to the rich vascularisation of the *lamina propria*. Some others are synthesized and secreted in brain areas and released at the OB level via centrifugal fibre connections. Besides these sources for metabolic factors, local synthesis in the olfactory tissues has also been reported for orexin, leptin, insulin, NPY, endocannabinoids. In OM, some of them are synthesized by OSNs themselves (Caillol et al., 2003; Getchell et al., 2006; Baly et al., 2007; Lacroix et al., 2008) or by supporting cells (Montani et al., 2006; Jia et al., 2013; Hutch et al., 2015). Insulin has also been detected in the mucus that bathes the ORNs' cilia and sustaining cells' microvilli, suggesting a local production by nasal glands (Henkin, 2010). Similarly, in OB, several hypothalamic peptides and hormones are locally synthesized as putative key neuromodulators in regulating olfactory processing (Palouzier-Paulignan et al., 2012; Russo et al., 2018; Thiebaud et al., 2019). The reasons for the local synthesis are not yet understood, but the fact is that its level varies upon feeding conditions modifications (see 15.2 section) suggesting that a sustained paracrine synthesis would benefit to the tissue homeostasis.

15.1.3 The olfactory system, a target for circulating nutrients

In addition to be sensitive to metabolic hormones and peptides involved in food intake regulation, a large body of evidence indicates that the olfactory system would be also directly targeted by blood circulating nutrients, such as glucose, amino acids and lipids as recently reviewed (Julliard et al., 2017; Wu, 2020).

Glucose is the main energy source for cells, and glucose/lactate is essential in metabolic exchanges in the brain, between astrocytes and neurons (Benarroch, 2014). Glucose and lactate transporters or sodium glucose co-transporters (GLUTs, MCTs, SGLT1) have been described in various cell types of the OM and OB (Choeiri et al., 2002; Nunez-Parra et al., 2011; Aimé et al., 2014; Al Koborssy et al., 2014; Lacroix et al., 2015). GLUTs (1, 3 and 4) have been reported in the OB (mainly in the MTC and granular cell layers) and OM (GLUT1 in OSNs, Bowman glands and endothelial cells; GLUT1 and 3 in sustentacular cells). Moreover, GLUT4, transporter of particular interest since being an insulin-responsive glucose transporter, likely involved in obesity and insulin resistance pathology (Lumeng et al., 2007), is also expressed in the OM (Lacroix et al., 2015). Thanks to these transporters and to glucose metabolizing enzymes, sustentacular and Bowman's gland cells could participate to the transport of glucose from the blood vessels to the mucus to sustain OSN chemotransduction (Acevedo et al., 2019).

Fatty acid receptors, such as CD36 or GPR40, are expressed in neurons of olfactory structures, which raises the question of their role(s) in lipid olfactory sensing (Lee et al., 2015; Nakamoto et al., 2012). CD36, which is involved in oleic aldehyde perception, is prominently present in OSN cilia during the suckling period where it could fix oleic acid, a major milk component (Oberland et al., 2015; Lee et al., 2017).

In OB, the recent localization of GLUT5, GLUT9 and elements of the primary metabolic pathway for fructose, a major sweetener in processed foods, has also opened the possibility for its active metabolism in this structure (Oppelt et al., 2017).

Regarding more particularly the interactions between the metabolic signals and olfactory function, the expression of a myriad of metabolic receptors in various cell types of the OM obviously makes the olfactory tissue a privileged target of chemical nutritional cues from the systemic circulation (this point will be largely discussed in the next sections). However, in OM, the presence of metabolic receptors means that these receptors can be also targeted by inhaled molecules, not a priori devoted to the transmission of metabolic information. Indeed, it has been reported that odorants could bind some metabolic receptors as CB1 cannabinoid receptor (Audouze et al., 2014). Here, we are on the edge on the pure olfactory function and the next question is: would such odorant-metabolic receptor interactions extend the role of odorant molecules from the role of olfactory stimuli to other functions?

In any case, putative roles for feeding-related hormones and peptides probably differ between species. For example, in amphibians, OM endocannabinoid receptors (CB1 and CB2) modulate OSN sensitivity, thus contributing to the food intake control (Czesnik et al., 2007; Breunig et al., 2010). However, in mice unlike amphibians, OM endocannabinoids would not directly modulate the peripheral odorant detection, but would rather influence the cell homeostasis (Hutch et al., 2015).

The potential cross-over effects between the purely olfactory and/or modulatory function of odorants on hormone receptors and the species-differential effects of hormones on neuronal receptor function give us insight into the multiplexing between pure odorant and metabolic drug signalling, making the peripheral olfactory stage a strategic site for metabolic influences.

15.2 Prandial state and olfactory function

From all the neuroanatomical observations, it becomes evident that the myriad of internal physiological hormonal fluctuations due to the modification of the metabolic status linked to food intake rhythms, putatively modulates the odorant signalling. Such a metabolic modulation of the olfactory processing could be induced, either directly throughout the modification of local synthesis of metabolic related-factors, or indirectly through endocrine signals released in the general circulation. Accordingly, the effect of fasting has been largely investigated in the past years.

15.2.1. In humans

Since the 1950s, many studies have been designed to investigate the influence of the nutritional state on the olfactory perception processing at the peripheral level, a question that is still a matter of debate. Most studies used experimental devices or protocols allowing a broad evaluation of the olfactory performances by scoring several dimensions, such as threshold, discrimination, identification and pleasantness of various odorants. Earliest studies concluded, as intuitively expected, that fasting increased olfactory sensitivity (Goetzl et al., 1950; Schneider and Wolf, 1955), and were confirmed by later ones (Furchtgott and Friedman, 1960). Besides, other studies were less conclusive. Indeed, some data described a trend for lowered odour threshold under hunger state, but failed to achieve statistical significance due to individual variations (Furchtgott and Friedman, 1960), while others reported no link between the modulation of the olfactory perception and the feeding state (Koelega, 1994). These discrepancies can be mostly attributable to the fact that results have been gathered from very different conditions and paradigms methodologies: practice trial or

not before the experimental investigation, size and age of the cohorts, within or between subject design, pre-evaluation or not, of the hunger and mood state of the subject, nature and administration mode of the stimulus, duration of the fasting, time of the day at which the tests were performed, type of meal...

More recent studies, in which experimental paradigms have been roughly standardized, further emphasized the need to make a distinction between the sensitivity towards food versus non-food odours. Here lies the general common question of the classification of odours as strictly food-related or not. Indeed, by using the n-butanol generally considered as a non-food odour, the olfactory sensitivity is mostly found to be increased by fasting (Stafford and Welbeck, 2011; Cameron et al., 2012; Hanci and Altun, 2015), except in Albrecht's study (Albrecht et al., 2009) where it was unchanged. For food related-odours (2-heptanone/ blue cheese odour, isoamyl acetate/banana odour, herb odour), different studies reported that the olfactory sensitivity was increased, but, unexpectedly, only in satiated conditions (Berg et al., 1963; Albrecht et al., 2009; Stafford and Welbeck, 2011). The last study suggested that such an increased sensitivity following the meal might help the subject to detect and reject spot foods that are no longer required since they have been consumed at satiety. However, this observation was only concerned with high body mass index (BMI) subjects, suggesting that maintained sensitivity for food odours after meal rather reflects a decrease in the sensory-specific satiety (Cabanac, 1971) and would sustain food intake at the expense of the physiological needs.

Other studies reported that general chemosensory performances for non-food odours - here lies the general common question of the classification of odours as strictly food related or not- are improved in hunger state (Cameron et al., 2012) and decreased in satiety state (Hanci and Altun, 2015). In agreement with these results, the administration of insulin, mimicking a post-feeding episode in normosmic human, led to a decrease in sensitivity for non-food odours (Ketterer et al., 2011; Brunner et al., 2013) while it could also otherwise improve odour-cue spatial memorisation (Brunner et al., 2013; Brunner et al., 2015). In the same line, in patients with post-infectious loss of smell, the intranasal insulin application could immediately improve their olfactory performances: both detection and cognitive recognition (Schopf et al., 2015). Similarly, increase in odour detection was observed at high insulin doses, for neutral odours in normal and over-weighted subjects (Thanarajah et al., 2019). Thus, according to the task, the type/concentration of odours and the status of the subjects, healthy or with pathology, insulin could induce effects on the olfactory-driven performances that seem paradoxical. For completeness, the demonstration of a differential effect of insulin on olfactory sensitivity according to the sex, a parameter which has been neglected in most studies, complicates the investigations (Rodriguez-Raecke et al., 2018). Moreover, it must be stressed here that the physiological satiation state cannot be limited to the only insulin secretion.

With regard to the hunger state, Tong and co-workers (2011) reported that fasted subjects, systemically injected with ghrelin (aiming at reinforcing the physiological increase of this appetite-stimulating peptide before a meal), displayed increased sniffing rates for both food and non-food odorants (Tong et al., 2011). Indeed, sniffing behaviour is a crucial element of the olfactory function, which mirrors the olfactory exploration, high nostril flow rate being associated with enhanced odorant detection (Laing, 1983; Sobel et al., 2000).

In conclusion, in healthy and normal BMI humans, a specific decrease in food odour sensitivity is mainly observed after a meal and is associated with an hedonic value decrease

for a food consumed to satiety, as described earlier (Rolls and Rolls, 1997). It could participate to the food intake regulation by reducing the olfactory pleasantness in humans, but this effect depends on various parameters.

15.2.2. In animals

Important data were obtained by exploring global odour-driven behavioural responses in relation to hormonal regulation in animals, mainly in rats and mice (Pager et al., 1972; Gervais and Pager, 1982; Mulligan et al., 2002; Apfelbaum and Chaput, 2003). These experiments, by ensuring a better standardization in experimental conditions, broadly led to the same conclusion, namely that olfactory sensitivity is strongly modulated by the satiety state, and further, allowed to unravel some of the neuronal underlying mechanisms. The introduction of a food odour in the environment of satiated rats increased their basal activity (moving around, grooming) and sniffing activity. Such behaviours are amplified in fasted animals and might be mimicked by intracerebroventricular administration of orexigenic chemicals as orexin (Prud'homme et al., 2009) or insulin (Lacroix et al., 2015) in satiated animals. Conversely, the administration of anorexigenic chemicals, such as leptin or orexin antagonist, decreases food odour exploration times of fasted rats (Prud'homme et al., 2009). Olfactory behavioural tests in rat, based on conditioned olfactory aversions, also clearly showed that nutritional status and metabolic related hormones/peptides modulate odour sensitivity. Furthermore, the odour sensitivity increase, observed upon physiological fasting (Aimé et al., 2007; Ferry and Duchamp-Viret, 2014), was mimicked in satiated rats by injection of orexigenic factors, such as ghrelin (Tong et al., 2011) or orexin (Julliard et al., 2007; Ferry and Duchamp-Viret, 2014). Conversely, the decrease in odour sensitivity observed in satiated animals could be mimicked by administration anorexigenic factors, such as leptin (Julliard et al., 2007) or insulin (Marks et al., 2009). However, the effects of fasting on enhancement of olfactory behaviours also depend on the metabolic context of animals, since rodents models displaying low energetic backgrounds, such as the lean Lou/C rats, boost their olfactory sensitivity upon fasting, whereas obese Zucker rats do not (Badonnel et al., 2014).

The introduction of a familiar food odour in the environment of a fasted animal increases the OSNs electrical activity leading to enhance c-fos labelling (immediate-early gene) in OB. The same effect on c-fos labelling was obtained in satiated rats by intracerebroventricular injection of orexin (Prud'homme et al., 2009). Inversely, leptin and orexin antagonist administrations decreased c-fos response to a food odour (Prud'homme et al., 2009). Therefore, the opposite effects obtained with the appetite-stimulating and appetite-suppressing peptides on the olfactory system are in line with their expected impacts on behaviours linked to food consumption.

The direct demonstration of the action of metabolic hormones and the ways by which they modulate food odour processing, has been brought by electrophysiological studies that allowed unambiguous identification of the targeted neurons and mechanisms in the past few years. At the olfactory system peripheral level, as intuitively expected, a local application of anorexigenic or orexigenic factors has been shown to impact the amplitude of electro-olfactogram (EOGs: odorant-induced electrical response of a population of OSNs). The two potent anorectic peptides, insulin and leptin, decreased the amplitude of EOGs (Lacroix et al., 2008; Savigner et al., 2009) whereas, conversely, the orexinergic neuropeptide Y increased it, but only in fasted animals in which Y1 receptors are over expressed (Negroni et al., 2012). Another starvation signal, adiponectin, increased EOG responses (Loch et al., 2013) and then

OB responses (Loch et al., 2015), independently from the feeding state. In addition, the endocannabinoid system (CB1) was found as being involved in the regulation of food intake and odorant detection in fasted mice. Indeed, CB1 receptors endow centrifugal cortical fibers that project on OB inhibitory granule cells, their activation would inhibit these interneurons resulting in turn in a dis-inhibition of the MTCs (Soria-Gomez et al., 2014). Thus, such a CB1 system control, involving cortical feedback on OB, could couple metabolic states and perception abilities (see Terral et al., 2020 for a review).

In OB, patch-clamp recordings showed that the circulating hormones exert directly their effects on MTCs (Fadool et al., 2000; Apelbaum et al., 2005; Hardy et al., 2005; Kuczewski et al., 2014). More precisely, Kuczewski and co-workers showed that insulin can act on mitral cells both directly and indirectly, throughout the GABAergic interneuron network. By doing so, insulin could alter both rest and evoked activities of mitral cells. The use of these data to construct a mathematical model demonstrated that such an insulin action could differentially either increase or decrease the olfactory discrimination abilities of the OB network. This led Kuczewski and colleagues to propose that insulin, as one of the major hormones involved in feeding behaviours, would put the olfactory function under feeding signal control, according to the alimentary/ethological valence of the olfactory stimulus. However, if intranasal insulin administration impacts short-term olfactory processing, by modulating MTC firing in the OB in animals (Fadool et al., 2000; Tucker et al., 2013; Kuczewski et al., 2014), it displays negligible long-term effects, suggesting adaptive processes (Bell and Fadool, 2017). As for the anorectic hormone leptin, it reduces odour discrimination by decreasing the spontaneous firing of single MTCs and the odour- evoked beta and high gamma local field potential response (Sun et al., 2019). Moreover, application of prokineticin 2, a hypothalamic anorexigenic neuropeptide, significantly decreases food intake by lowering olfactory sensitivity (Cheng et al., 2006; Mortreux et al., 2019). Data on awake, head-fixed mice confirm that fasting enhances spontaneous firing rate of MTCs and the number of cells showing an excitatory response following food and non-food odours administration while it slightly decreases the neural discrimination (Wu et al., 2020).

The strong consensus that the olfactory performances rely on feeding conditions, through the feeding-state dependent metabolic-related factors, is in full agreement with the fact that the expression of these factors and their receptors are modulated in the olfactory system, according to the nutritional state. Indeed, after 48h of fasting, Ob-R and IR expressions in the OM are increased in rat (Baly et al., 2007; Lacroix et al., 2008). However, such an increase is not observed in the OB, suggesting that the modulation is tissue-specific and might answer to specific needs (Baly et al., 2007; Lacroix et al., 2008; Aimé et al., 2012). Moreover, the nutritional status impacts the local synthesis of these metabolic-related factors. Fasting increases leptin and insulin concentrations in the OM (Baly et al., 2007; Lacroix et al., 2011) or insulin in the mucus (Henkin, 2010) whereas decreases orexin (OXB) and prokineticin levels in the OB (Shibata et al., 2008; Mortreux et al., 2019). Even if these variations are small regarding the circulating concentrations, such paracrine control within the local environment of neurons may have functional repercussions. Moreover, due to the pleiotropic roles of these hormones and peptides in other tissues, they probably also more broadly target and impact some cellular processes, such as neuronal proliferation, apoptosis and neuronal plasticity, as it has been shown for NPY and insulin in OM (Hansel et al., 2001; Doyle et al., 2008; Jia and Hegg, 2010; Lacroix et al., 2011), or for ghrelin in the OB, that could participate to interneurons' differentiation (Li et al., 2014) or to synaptic reinforcement between OSN and mitral cells (Russo et al., 2020). In the same way, in OM, NPY secreted by microvillar cells is not only essential for their own differentiation, but also to send

neuroproliferative signals to basal precursor cells, thus participating to neo-neurogenesis, in basal conditions and after injury (Jia et al., 2013; Doyle et al., 2018; Huang et al., 2019). In addition, in mice, endocannabinoids are involved in the homeostatic regulation of cell proliferation of the basal cell population in the OM (Hutch et al., 2015; Hutch and Hegg, 2016). At last, leptin, by regulating OM mucus secretion, may modulate odorant-receptor interactions (Badonnel et al., 2009).

In comparison with the acute endocrine variations linked to fasting, the experimental modification of food-intake pattern of rats, i.e. a chronic food restriction, leading to long-term slight modifications of metabolic hormone circulating levels, also altered food-odour-driven behaviours and metabolic genes expression in the olfactory system (Badonnel et al., 2012). This result reflects the adaptation of both food searching behaviour and olfactory signal processing to the metabolic state. Such long-term effects which also could result from ground hormones imbalances could be involved in some olfactory deficits (see the next section, 15.3., on metabolic disorders). Such an adaptation of feeding related neuromodulators expression was also reported when mice are trained with odour-food association (Nogi et al., 2020).

Finally, the olfactory system functioning is not only impacted by metabolic hormones but also upstream by some circulating nutrients associated to food intake and digestion. Among these, glucose is a reliable indicator of the nutritional status, since its concentration rapidly fluctuates around meal, its fluctuations being critical for glucose sensing neurons. In rat OB, a patch-clamp study showed that changes in glucose concentration could rapidly alter MTCs' firing frequency (Tucker et al., 2013). In agreement with this result, the expression and regionalization of GLUT4 in OB is described as being feeding-state dependent (Aimé et al., 2014; Al Koborssy et al., 2014), suggesting that GLUT4, in addition to peptides involved in food intake regulation, could account, at least partly, for the olfactory sensitivity variations observed between satiated and fasted rats (Aimé et al., 2007; Al Koborssy et al., 2014). At last, OB glomerular astrocytes also participate in the regulation of metabolic sensing upon fasting thanks to an astroglial morphological plasticity controlled by anorexigenic and orexigenic peptides (Daumas-Meyer et al., 2018).

15.3 Metabolic disorders linked, or not, to eating disorders and olfactory function

In absence of metabolic diseases, the previous section showed that metabolic-related hormones/peptides and nutrients individually participate to the regulation of the olfactory signalling. However, it is still unclear if, and how, they interact in a complex metabolic environment in order to modify the olfactory function, particularly in case of severe pathologies characterized by chronic energy imbalance and food intake deregulation. A meta-analysis review in humans highlights the difficulties to definitely conclude on the association between the olfactory performances and abnormal eating behaviours, but underlines that data support an alteration of olfactory performances in obesity and anorexia nervosa disorders (Islam et al., 2015). Furthermore, the bidirectionality of such a relation is supported by a study reporting that, in mice, experience-induced loss of smell seems to prevent diet-induced obesity or block weight gain (Riera et al., 2017).

15.3.1 Obesity

Worldwide, obesity is becoming a major challenge for public health in westernized societies over the past decades, since causing a well-defined risk of cardiometabolic disease, osteoarthritis and different types of cancer. Obese individuals display increased weight gain, metabolic disorders and deregulated food intake (Paquot et al., 2012). It can be hypothesized that, facing highly palatable foods, the homeostatic mechanisms that regulate the energy balance are overwhelmed and changes in brain reward-circuitry probably occur. The last decade researches were undertaken to evaluate the olfactory function in obese subject, its modifications and impacts in food intake deregulation.

In humans

In humans, data are difficult to synthesize due to large heterogeneity in social origins, food habits, lifestyle and moods of people, as well as, biological differences, heredity, level of adiposity, experimental conditions (olfactory stimuli and metabolic state), age, gender and severity of obesity. Moreover, the studies exploring the effects of obesity on olfaction often consider a combination of parameters involving simultaneously the olfactory sensitivity, odorant identification and discrimination, reward evaluation and lastly, food intake quantification and preferences. The higher cortical processing, which is largely and directly affected by obesity too, also influences most of the resulting behaviours, but is not discussed here.

In cases of the extreme morbid obesity in adults, decreased odour detection abilities are clearly reported as compared to lean, age-matched, control subjects (Richardson et al., 2004; Richardson et al., 2012). Observational and clinical cases confirm that olfactory function is negatively correlated with body weight (Fernandez-Aranda et al., 2016; Peng, 2019). Obesity is associated to a smaller OB volume, but whether it is a cause or a consequence for obesity is unsolved (Poessel et al., 2020). When using BMI value as a risk factor of olfactory loss, predicting food intake disorders going with obesity development, data on olfactory performances are conflicting. Considering a large panel of ages (19 to 75 years, the later for which obesity and ageing effects might be confused), olfactory dysfunction seems to be more encountered in high BMI than in low ones (Richardson et al., 2004; Patel et al., 2015; Skrandies and Zschieschang, 2015). Simchen and colleagues (2006) made the same observation but, only in subjects younger than 65 years, older ones despite a normal BMI displaying an decreased ability to detect and identify odours (Simchen et al., 2006). In earlier ages, high BMI adolescents show a greater olfactory sensitivity than normal BMI adolescents (Herz et al., 2020) which is not true in children (Obrebowski et al., 2000; Navarrete-Munoz et al., 2020). Among possible explanations to these inconclusive findings, are the characteristics of the odorant used in the threshold assays, which could differentially affect the trigeminal nerve (Obrebowski et al., 2000; Herz et al., 2020) or involvement of reward areas, which are sensitive to BMI (Jacobson et al., 2019). Accordingly, women with high body mass index (BMI) display an increased sensitivity and preference for an energy dense food odour only, suggesting that the nature of the stimulus is determinant (Stafford and Whittle, 2015). Moreover, it seems that, rather than the BMI itself, the endocrine profile of subjects (which is rarely considered) influences odour sensitivity. For example, insulin resistance strongly disserves the relationship between BMI/waist-hip ratio and olfactory sensitivity for food odour in young people (Poessel et al., 2020). In women, the level of fasting plasma circulating 2-arachidonoylglycerol, acting on endocannabinoid receptors, and obesity, interact to decrease olfactory threshold, discrimination and identification score (Pastor et al., 2016). It also seems that the nutritional state modulates olfactory scores since high BMI people display a higher sensitivity to food odours in the satiated versus non-satiated state and a better discrimination ability for food odours, than low BMI ones, whatever their age (Stafford and

Welbeck, 2011). In men, consistent with the latter data, the subcutaneous adiposity is correlated with increased odour sensitivity and, high odour identification scores are associated with high serum leptin levels (Hubert et al., 1980; Karlsson et al., 2002). Thus, the subcutaneous adiposity might participate to the modulation of olfactory performances probably, through the modification of circulating levels of leptin. Altogether, even if individually data are sometimes difficult to conciliate, they almost all indicate that odour detection and discrimination could be altered in obese patients. Recently, a retrospective case-control chart review has confirmed that high BMI is associated with subjective olfactory dysfunction that might by itself contribute to a spiral of increasing food intake and increasing obesity (Patel et al., 2015).

The question remains to know whether these sensory changes originate and/or participate to the development of the pathology. This is why, in the past few years, the causal relationship between obesity and olfactory sensitivity has been especially focused after reversion of the metabolic syndrome. When obesity was reversed by surgery procedures, the observed effects on a possible restoration of olfactory performances, after successful weight loss therapy, are contradictory. Indeed, Richardson and colleagues showed that the negative consequences of morbid obesity on smell identification are not reversed by a gastric bypass surgery and thus, suggested that the olfactory dysfunction may have contributed to the obesity pathology development (Richardson et al., 2012). However, contradictory data showed that threshold detection index scores could be restored following laparoscopic gastric bypass and sleeve gastrectomy surgery in obese subjects (Holinski et al., 2015; Zerrweck et al., 2015; Makaronidis et al., 2016). In the same line, Roux-en-Y gastric bypass patients frequently report olfactory changes and yet more pronounced and immediate shifts have been observed among sleeve gastrectomy recipients (Peng et al., 2019). Sensory restoration could be moreover lower on smell than on appetite or taste, and is often associated with the development of aversion to specific food (Graham et al., 2014; Makaronidis et al., 2016). Besides high level of heterogeneity in the cohort size, obesity status, and olfactory tests, discrepancies as regards the improvement in the olfactory performances might also be related to the fact that these bariatric procedures differently influence nutrient-sensing regulatory mechanisms and hormonal patterns over time (Peterli et al., 2012). However, it seems clear that, postoperatively, patients regularly report some taste/smell changes and signs of food aversions. Unfortunately, to our knowledge, no study has measured the effects of long-term calorie-restricted diets on olfactory performances of former obese people, what has been recently investigated in obese mice models (Thiebaud et al., 2014). In order to solve “the egg and chicken” question linking obesity and olfactory sensitivity, it would be interesting to follow step by step the effect of hypo- or hyper-caloric diets, or surgery, on the olfactory performances in order to clarify the relationship between metabolic imbalance and peripheral sensitivity. Almost all studies compared subjects having evolved in a stable metabolic status for many years, but no one has fully explored the critical time window around the transition from the healthy to the altered physiological status.

15.3.2. In animals

In animal models, most data focusing on the link between obesity and olfaction have been obtained using genetically modified rodent strains displaying gene-targeted deletion for metabolic-related hormones or their receptors, leading to obese status independently of the diet. Such a situation is rarely encountered in human populations, but results on mutants largely allowed pointing out interesting mechanisms involving metabolic hormones and their receptors.

One of the first conclusive studies exploring the link between olfaction and obesity at the peripheral level using transgenic mice has been done in 2006. Using a general olfactory sensitivity test, the authors showed that obese mice lacking leptin signalling (*ob/ob* and *db/db*) performed faster to localize a hidden fatty cookie than their wild-type counterparts (Getchell et al., 2006). Interestingly, in *ob/ob* mice, the experimental leptin supplementation reversed this performance behaviour and induced changes in oscillatory dynamics in their OB indicating a central role for this anorexigenic hormone in their food odour sensitivity (Chelminski et al., 2017). In agreement, olfactory responses to food cues were also found to be increased in leptin receptor-deficient obese Zucker rats compared to their lean counterparts (Aimé et al., 2014; Badonnel et al., 2014). Thanos et al., (2013) more especially showed that fed obese rats showed enhanced nose-poke activities, indifferently for novel or familiar food odour. The same result was observed using a tea-ball test in obese satiated Zucker rats which responded to food odour in the same way as in the fasted state (Badonnel et al., 2014). Moreover, Zucker rats display a better olfactory sensitivity than lean rats in conditioned aversion tests using non-food odours associated to an alteration of OB glucosensing pathways (Aimé et al., 2014). Altogether, these results reinforce the idea that obesity induces modifications in the olfactory system functioning that participate in the observed hyperphagia. However, Tucker et al. (2012) using a gene-targeted-deletion-model of obese/diabetic mouse (the melanocortin receptor null mouse), reported that animals were less efficient in olfactory tests, taking longer time to localize a fatty scented cracker than lean animals; the deficits being mainly attributed to elevated serum leptin and insulin. However, all the experimental models resulting from targeted deletions have several limitations, since important metabolic hormones signalling pathways, mainly leptin, are not functional. Moreover, some perturbations of other metabolic ways associated to the targeted deletion are often observed. Therefore, recent studies have been conducted on diet-induced obesity (DIO) models in order to better fit with the complex surroundings encountered in humans, i.e. overconsumption of palatable food associated or not to a genetic susceptibility (Thiebaud et al., 2014; Lacroix et al., 2015; Lietzau et al., 2020).

In obesogenic environment, Thiebaud et al. (2014) observed learning impairment and decreased discrimination between non-food odours in obesity-prone mice fed with high-fat/high-sugar diet during several months. These olfactory impairments were paired with a marked loss of OSNs and their axonal projections, and a reduction in EOG amplitude responses to non-food odours. In agreement with this study, obese-prone rats made obese by DIO consumption for several months, exhibiting insulin and leptin-resistance and increased food intake during their rest phase, were less efficient than lean ones (fed with normal chow) in food-odour driven olfactory behaviours and task memory (Lacroix et al., 2015). Obese animals were also less sensitive to insulin in an odour-driven test, suggesting that the insulin resistance classically reported in obese subject for functions related to other peripheral tissues could be extended to olfactory processing pathways. Moreover, severe modifications of cell homeostasis at both OM and OB levels were observed in the obese DIO fed rats (Lacroix et al., 2015).

Therefore, the latter studies clearly conclude to a dramatic effect of long-term over-nutrition on olfactory neuronal function that could be related to the known pleiotropic roles of hormones on tissue homeostasis. Consequently, it seems that obesity, depending on the diet, endocrine and phenotypic profiles, might lead to severe modifications of olfactory behaviours, associated to long-lasting structural and functional changes in the first two stages of the olfactory system (Thiebaud et al., 2014; Lacroix et al., 2015; Fardone et al., 2019). As

also shown by Thiebaud et al. (2014), despite the renewal of the OM and bulb neurons, such impairments are not reversed upon diet changes, even after several months of low energy diet, suggesting that central cortical impairment might also be involved. It would be interesting to assess whether such dramatic structural and functional effects are also observed in OM of obese patients and whether the anatomical loss of OSNs could be reversed by bariatric surgery.

15.3.2 Diabetes

Type 1 diabetes (insulin-dependent), often associated to a chronic autoimmune disorder, results in the destruction of the β -cells in the pancreatic islets of Langerhans and affects people at any age (see for a review van Belle et al., 2011). Type 2 diabetes (insulin independent), is often associated with obesity and is acquired at older age, which complicates the identification of causal elements. Regardless of cause, diabetes mellitus (DM: group of metabolic diseases commonly referred to as diabetes) results in high levels of circulating glucose, caused by insufficient insulin functionality. From the aforementioned results highlighting the importance of insulin in the olfactory signal processing (Lacroix et al., 2008; Marks et al., 2009; Fadool et al., 2011; Aimé et al., 2012) and from data supporting that insulin resistance could result in some olfactory dysfunction (Lacroix et al., 2015), it is likely that DM would have deleterious effects on olfactory sensitivity. Indeed, several studies have reported an association between DM and impaired olfactory function: decrease in odour identification (Weinstock et al., 1993; Le Floch et al., 1993; Bramerson et al., 2004) and detection (Patterson et al., 1966; Hubert et al., 1980). However, these data were collected on mixed cohorts of type 1 and 2 DM. The first study discriminating between the DM types reported a decreased olfactory function only in 2 DM patients, compared to 1 DM ones (Naka et al., 2010). This was recently confirmed that non-complicated-type 1 DM patients exhibit normal olfactory function (Altundag et al., 2017).

Also, some of the observed differences seem linked to patient profiles, type 2 DM displaying higher BMI and oldest ages. Moreover, associations of olfactory impairments with other anthropometric and clinical outcomes, such as waist circumference, cholesterol level, hypertension, or fasting glycemic level also recently emerged in type 2 DM patients (Gallo et al., 2020; Catamo et al., 2021). Accordingly, the olfactory deficits only concern patients displaying diabetes-associated pathologies as type 2 DM patients without major complications exhibited normal olfactory function (Naka et al., 2010; Brady et al., 2013). Therefore, olfactory impairments associated to type 2 DM have been proposed as resulting from neuropathy and macrovascular diseases (coronary artery and peripheral vascular diseases), as previously mentioned (Weinstock et al., 1993; Le Floch et al., 1993), even if this observation is not totally corroborated by more recent studies (Gouverni et al., 2014; Sanke et al., 2014). Besides, the decreased performances in odour identification and discrimination suggest an impaired global cognitive processing (including working memory, attention, judgment language function and decision making) as well as a decreased odour threshold score with peripheral neuropathy (Brady et al., 2013; Gouverni et al., 2014; Sanke et al., 2014).

The analysis of literature highlights the difficulties to conclude whether the reduction in olfactory functions in DM patients is due to diabetes pathology and /or to further complications, such as neuropathology, with or without pain, drug intake, duration and severity of the disease or combination of different factors. In any case, obesity seems to worsen DM-induced olfactory disorders (Zhang et al., 2019).

In animals, the nature of the diabetes-inducer diet, either rich in lipids, carbohydrates or both, and the feeding protocols could participate to specific behavioural outcomes. Using two type 2 DM-inducing obesogenic diets, one containing a high proportion of fat (HFD) and one with moderate fat, but high sugar referred as Western diet (WD), Lietzau et al. (2020) showed an earlier impact of WD on odour-related learning and olfactory memory. They suggested that a high sugar content diet could exacerbate glucose intolerance and insulin resistance. Similarly, moderate- or high-fat diet have a differential impact on olfactory-driven behaviours, which suggests a role for adiposity level too (Thiebaud et al., 2014). It is possible that these diets differentially affect the lipid composition of OSN membranes, as shown for omega-3 imbalanced diets (Khoury et al., 2020), with variable electrophysiological consequences on olfactory signalling. More studies, considering all these combined parameters, are necessary to definitely demonstrate that the olfactory dysfunction is modulated from the periphery in DM patients and, if it can be used as a biomarker for neurodegeneration in these patients.

15.3.3 Anorexia

Patients suffering from anorexia nervosa (AN) display an obsessive fear of gaining weight, avoidance of high-energy food and eating disorders associated with decreased pleasure to eat. In response to this severe energy restriction, alterations occur in many endocrines axes including those related to food intake and olfactory function control (Misra and Klibanski, 2014). In a search for clinically AN markers, a number of metabolic, endocrine, and neural biomarkers associated to malnutrition (leptin, NPY, ghrelin...) have been found as being abnormal. Regarding the implication of these biomarkers in olfaction and food intake relationship, it is largely reasonable to speculate that AN patients could have altered olfactory functions. But as for other studies on pathologies related to food-intake deregulations in humans, discrepancies in results on AN effects have been noticed. These are likely attributable to variations of the following criteria: size of the cohorts (often quite low), gender of patients, age (timing of the development of the pathology), feeding state (fasting or not, duration of the starvation) and depressive state (medication). Moreover, the studies mostly lack matched control samples.

First report examining this question resulted in divergent observations, despite the use of the same olfactory score test. Kopala et al. (1995) reported a normal olfactory function, whereas Fedoroff and colleagues (1995) concluded in an impaired ability to identify and detect odours in very low-weight AN-patients (Kopala et al., 1995; Fedoroff et al., 1995). More recent studies built a relative consensus on the following observations: AN patients express i) a lower pleasantness of odours, particularly of food ones in a hungry state (Lombion-Pouthier et al., 2006; Schreder et al., 2008; Soussignan et al., 2011), ii) a decrease of their general olfactory abilities evaluated by computing scores of odour threshold, discrimination and identification (Schreder et al., 2008; Aschenbrenner et al., 2008; Dazzi et al., 2013). However, when examined separately, each of these three scores are difficult to conciliate. Indeed, if odour discrimination seemed reduced in most patients (Schreder et al., 2008; Aschenbrenner et al., 2008; Roessner et al., 2005; Dazzi et al., 2013), some authors did not observe any difference with control subjects (Kopala et al., 1995; Rapps et al., 2010).

Odour identification scores were mostly reported as being reduced (Fedoroff et al., 1995; Schreder et al., 2008; Rapps et al., 2010), except in one study where they were unchanged (Aschenbrenner et al., 2008). The odour sensitivity was reported to be either unchanged (Aschenbrenner et al., 2008; Rapps et al., 2010; Dazzi et al., 2013) or decreased (Roessner et al., 2005) for food odour but, only in hungry conditions (Schreder et al., 2008) or

exclusively in low weight anorexic patients (Fedoroff et al., 1995). Only two studies reported increased odour sensitivity (Lombion-Pouthier et al., 2006; Bentz et al., 2017). Authors suggested that it could account for the over evaluation of odorant intensities and lower score of hedonic valence which were frequently observed in anorexia patients. In the same line, some enhanced olfactory identification performances were reported in AN adolescent, compared to normal matched groups (Schecklmann et al., 2012) or in young women with recent-onset AN and who have just recovered (Bentz et al., 2017). Recent meta-analyses support the idea that AN patients have intact olfactory function compared to health controls in terms of threshold, identification and discrimination, but that the severity of AN could alter olfactory threshold score (Islam et al., 2015; Mai et al., 2020).

Besides the restricting AN, a few studies have evaluated the olfactory function in patients diagnosed for bulimia nervosa and, interestingly, most of them did not find any difference between bulimic and control patients (Kopala et al., 1995; Fedoroff et al., 1995; Aschenbrenner et al., 2008). Only one study has reported an overall decrease of the olfactory function, mainly due to a decreased odour sensitivity and discrimination (Dazzi et al., 2013). Development of appropriate animal models of anorexia/bulimia is difficult, as the aetiology of these multi-faceted eating disorders likely involves complex interaction between genetic, environmental, social, and cultural factors, thus making it impossible to precisely pinpoint the respective roles of anorexia and malnutrition on olfactory function (Mequinion et al., 2015). This is likely why, to date, few models have been developed to investigate olfactory function related to anorexia.

15.3.4 Maternal metabolic status

According to the concept of Developmental Origins of Health and Disease (DoHaD), the metabolic environment during foetal life would influence offspring's health at long-term, with behavioural consequences (Barker, 2007). Among them, alterations of feeding behaviour are reported (Sullivan et al., 2015). As the olfactory system i) develops during embryonic life, ii) is sensitive to the metabolic environment and iii) participates to food intake, the possible impact of the maternal metabolic status on olfactory sensitivity in offspring has been tested. Maternal obesity induced by high fat or high fat/ high sugar diet during pregnancy and lactation has been reported to alter the OM sensitivity, measured by EOG, at weaning and later (Merle et al., 2019; Panchenko et al., 2019). However, offspring born after a high fat/high sugar *in utero* diet exhibits reduced olfactory abilities at weaning despite no alteration of OM functioning, rather suggesting a more central processing alteration (Merle et al., 2019). Whether these effects are linked to events restricted to the *in utero* period or to later modifications of the metabolic profile of the offspring remains to be studied by decoupling the pre- and the post-natal phase in cross-fostering experiments. Indeed, postpartum environment, resulting from nutritional, but also from associated features (maternal-infant bond perturbation, food transition-induced stress) could participate to functional modifications of the olfactory system sensitivity, irrespectively of nutritional considerations. The mother preconceptional status should also be considered, as it has been shown that maternal weight loss could normalize the offspring metabolic phenotypes while, it nevertheless induced an unexpectedly deleterious effect on olfactory performance: reduction in olfactory sensitivity. Furthermore, in fasted male offspring, such reduction was accompanied by an inability to induce olfactory motivation (Panchenko et al., 2019). Noteworthy is that such a programming effect of the maternal metabolic context could participate to the vicious circle of food intake deregulation, with putative intergenerational consequences.

15.4. Conclusion

From this chapter, it is clear that olfaction and food intake are intimately linked at several levels of the olfactory system and that olfactory circuits are sensitive to changes in the organism energy balance. Aberrant metabolism-related hormones production in chronic pathologies as well as acute variations linked to normal food intake cycles, highlight that some olfactory processes are involved to adapt the olfactory sensitivity to the physiological needs. The understanding of the links between olfaction and food intake may serve as a potential strategy to fight, at least partly, against metabolic disorders, and thus may offer therapeutic pathways leading to new preventive diagnostics and curative strategies. The development of auxiliary therapeutic treatments based on intranasal metabolic-related molecules delivery, as performed in rodents models (Marks et al., 2009; Jia and Hegg, 2010; Schulz et al., 2012) and in healthy normosmic humans (Brunner et al., 2013) or in patients suffering from various CNS pathologies (Chapman et al., 2013) could then be considered as promising for upscaling therapeutic treatments of diseases with CNS involvement, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, depression, anxiety, autism spectrum disorders, seizures, drug addiction, or eating disorders.

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