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Review

New insights on food intake control by olfactory processes: The emerging role of the endocannabinoid system

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ABSTRACT

The internal state of the organism is an important modulator of perception and behavior. The link between hunger, olfaction and feeding behavior is one of the clearest examples of these connections. At the neurobiological level, olfactory circuits are the targets of several signals (i.e. hormones and nutrients) involved in energy balance. This indicates that olfactory areas are potential sensors of the internal state of the organism. Thus, the aim of this manuscript is to review the literature showing the interplay between metabolic signals in olfactory circuits and its impact on food intake.

Contents

1. Feeding behavior: general background

The intake, absorption and storage of energy are key issues for living beings. Indeed, the definition of life itself implies the necessity to subtract energy from the external world and to use it for the survival of the individual and of the species. It is, therefore, not surprising that the complexity of the mechanisms regulating these processes is proportionally growing together with the evolutionary scale. Whereas simple plants and animals rely on relatively simple modes to solve this problem, evolved animals elaborated complex strategies to adapt to changing environmental factors. In mammals, the initiation and maintenance of energy intake as well as the regulation of energy expenditure (the so called "energy balance") is co-determined by endostatic (metabolic or "drive") and exostatic (non-metabolic or "incentive") signals that, together, contribute to maintain the energy homeostasis (Berridge et al., 2009; Berthoud, 2006; Karatsoreos et al., 2013). The endostatic factors related to the internal energy state of the individuals is the best understandable regulation of the energy balance and it is common to all species: the body registers an endogenous lack of energy and reacts promoting behaviors and hormonal processes aimed at increasing energy intake, absorption and storage. Hunger, search for food and its

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ingestion are the primary responses to decreases of internal energy, whereas satiety and meal interruptions are the typical responses to excess of energy availability. However, it is common experience in humans and typically observed in other evolved animals that the internal levels of energy are not the sole regulators of food intake and energy storage. If this were the case (i.e. if any individual should eat only in response to endostatic stimuli), the worrying epidemic of obesity would not exist. On the other hand, also gastronomic art and the pleasure of eating palatable food would also be much less developed. Indeed, the second category of stimuli regulating energy intake, but also absorption and storage, are linked to exogenous stimuli linked to the presence and the intrinsic characteristics of food or to cues associated with it, in other words, the salience of the stimuli directly related with sensorial processing. These exostatic stimuli are processed by very complex networks that involve sensorial, cognitive and emotional factors (Berthoud, 2006; Karatsoreos et al., 2013; Kringelbach, 2009). In resume, evolved animals such as mammals ingest and store energy under both, the influence of their internal state (endostatic or drive) and of the presence and/or attractiveness of the food itself (exostatic or incentive), which are regulated by complex circuits. Whereas the evolutionary value of endostatic stimuli is self-explanatory, the existence of exostatic factors is likely due to natural fluctuations in the amount of available energy that can occur during the life of an individual. In "wild" conditions, periods of abundant availability of food are alternated with periods of restricted availability during the life of an individual. It is, therefore, clear that the ability to ingest more food and to accumulate larger stores of energy than what is needed during "abundant" periods provides a clear survival advantage for the periods of "paucity". In this sense, it is important to remark that the main problem of any species is to find *enough* energy to survive and reproduce in "wild" conditions, whereas the actual conditions of excess of energy supplies typical of modern human Western societies is a very new experience in evolutionary terms (Martin and Davidson, 2014). This explains why lifestyle modifications to tackle the obesity epidemic in many parts of the world are so difficult to accomplish. Thus, an important issue is to understand how and where metabolic and nonmetabolic factors interact with each other in order to modulate food intake (Berthoud, 2006, Karatsoreos et al., 2013). As mentioned above, sensorial regulation is a key determinant of feeding behavior. In particular, visual, gustatory and olfactory cues could drive the organisms toward food consumption, or food rejection. From these three sensorial modalities, olfaction is the most mysterious and neglected one (Heymann, 2006; Timothy and Kunwar, 2004), probably because a large part of the olfactory information is processed at the unconscious level in humans (Grammer et al., 2005; Hoover, 2010; Kringelbach, 2009; Li et al., 2007; Stevenson, 2009; Trellakis et al., 2012; Walla et al., 2002; Zucco et al., 2009). However, we cannot imagine the early hunters in the wild without a sharp sense of smell, helping to localize potential predators hidden quietly in the bushes, or other food sources. Nowadays, this is certainly not the case due to the evolution of society. However, the influence of olfaction in the control of behavior and cognitive processes is very important and many studies demonstrate a tight relationship between olfactory perception and behavior (Doty, 1986; Yeomans, 2006). For example, olfactory cues are determinant for partner selection (Fletcher et al., 2009; Johansson and Jones, 2007), parental care (Dias and Ressler, 2014) and, importantly for the scope of this review, feeding behavior (Aime et al., 2007; Rolls, 2005; Stafford and Welbeck, 2011; Yeomans, 2006). The sense of smell is important to evaluate the safety of a potential meal, by triggering mechanisms resulting in approach or avoidance behavior (Nikitin et al., 2008) (Chapuis et al., 2009; Demattè et al., 2014; Zhang et al., 2005). This feature makes olfaction a key determinant in species survival. Accordingly, it has been shown that a malfunctioning of the olfactory system could be causally associated to the occurrence of important diseases, including feeding-related disorders (Oral et al., 2013; Rapps et al., 2010). Thus, a clear identification of the mechanisms involved in olfaction is key in the understanding of animal behavior in physiological and pathological conditions. This work aims at reviewing the most recent advances in the understanding of the neurobiological mechanisms linking olfactory perception to food intake behavior.

2. Olfaction and food intake: the invisible magnet

Imagine yourself walking home after a long day at work, which was even longer because you forgot your lunch in your fridge; yes, you are really hungry. Suddenly, a single smell of cooked meat arouses all your senses; you start to look around to identify the source of that tasty hidden promise, look left, and look right, but nothing is there; you continue walking and the smell becomes stronger and stronger, and just imaging how that beautiful piece of meat looks alike makes you more hungry; your stomach is speaking to you and reminds you how good was that barbeque with all your family together 5 years ago; a nice memory that makes you happy for a moment. But no time for nostalgia, the odor keeps hunting you, and you keep hunting the odor. Following your nose you turn right in the next block and you finally found the source of that smell, but also a surprise; the place is not what you imagined, it is not an Argentinian restaurant, it is not a barbeque in someone's place; in fact it is just one of the big chains of burger shops that you swore would never taste, due to its doubtful origin and nutritional content. You are shocked, but your stomach is not, and there is still 40 minutes walk before arriving home. Nothing else matters now, you entered the shop asking for the double-triple mega burger that tastes as heaven on that particular day. Everybody, in a more or less dramatic way, has experienced something similar, exemplifying how powerful is the relationship between smell and food, and how the food scent can influence our emotional and cognitive life depending of the internal state of the organism.

During the last 50 years a great effort has been done in identifying the different circuits (centrally and peripheral) involved in feeding regulation (for an extensive review see Coll et al., 2007; Morton et al., 2006; Schwartz et al., 2000) with an important emphasis in the characterization of brain areas responsible for the homeostatic (i.e. hypothalamus and brain stem) and hedonic (i.e. reward system) regulation of food intake (Lutter and Nestler, 2009; Saper et al., 2002) and their continuous cross talk with the hormonal and nutritional *milieu* (Coll et al., 2007; Lutter and Nestler, 2009; Obici and Rossetti, 2003; Stanley et al., 2005; Volkow et al., 2011). However, although it is commonly known that much of the urge to eat is driven by our sensors, including olfaction (Fantino, 1984; Rolls, 2007a, 2007b; Yeomans, 2006), the identification of the neural mechanisms involved in this regulation has been less studied.

Odors are processed in the brain through complex mechanisms that are rather similar in different animal species (Fig. 1). In short, in mammals, everything starts with a sniff, and then the odors reach the main olfactory epithelium (MOE) in the olfactory mucosa (OM) where olfactory sensory neurons (OSN) transmit the information to the glomerular area of the main olfactory bulb (MOB), forming the first relay of olfactory information (bottom-up processing). From there, the principal cells of the MOB, the so-called mitral cells (MC) send the information to the rest of the brain, translating olfactory signals into cognition and behavior. The inputs and outputs of olfactory information is tightly regulated by a feedback control of the MOB, named the corticofugal circuit, formed by fibers coming from higher brain regions targeting granular cells (GC) and MC, and ultimately shaping the olfactory response (Ache and Young, 2005; Giessel and Datta, 2014; Luna and Morozov, 2012; Shepherd, 1972; Strowbridge, 2009; Wachowiak, 2011). In particular, the glutamatergic corticofugal fibers coming from the anterior

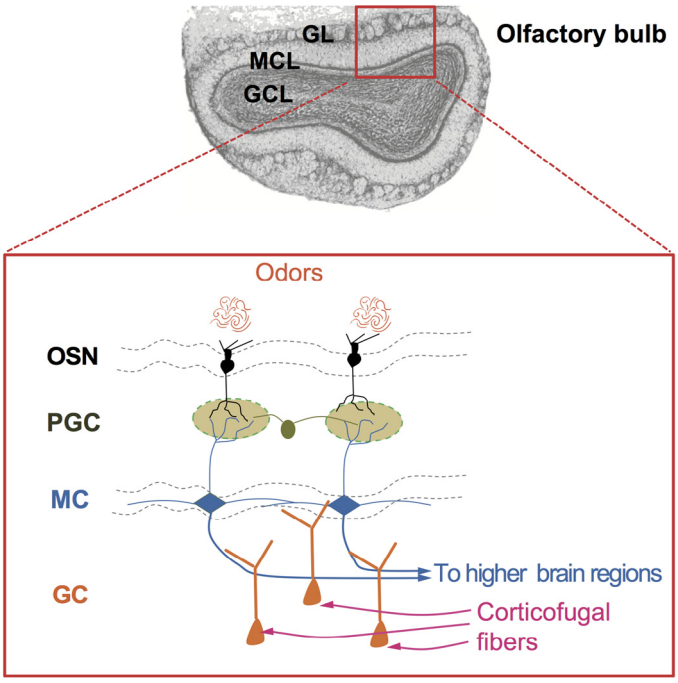

Fig. 1. Olfactory microcircuitry. Odor molecules arrive to the main olfactory epithelium where olfactory sensory neurons (OSN) transmit the olfactory information to the principal cells of the main olfactory bulb (MOB), the so-called mitral cells (MC), which in turn, transmit the information to the rest of the brain. There are at least two sources of modulation of olfactory information in the MOB. The first one by the periglomerular cells (PGC) localized in the glomerular region and modulating the synapses between OSN and MC; and the second one by inhibitory granular cells (GC), the main target of the corticofugal fibers carrying information from higher brain regions. The top panel is a coronal section of the mouse MOB showing the main cellular layers. GCL, granular cell layer; GL, glomerular layer; MCL, mitral cell layer.

olfactory cortex (AOC, formed by the anterior olfactory nucleus and anterior piriform cortex) form the main top-down control of olfactory information. The AOC stimulation leads to an activation of GABAergic GC resulting in an inhibition of MC and consequently, a reduced response to odorants and potentially affecting olfactory processes such as olfactory habituation and olfactory learning (Gire et al., 2013; Markopoulos et al., 2012; Tong et al., 2014).

As well as other brain areas classically involved in the control of food intake (i.e. hypothalamus), olfactory circuits are sensitive to the changes of the energy balance of the organism (Apelbaum and Chaput, 2003; Badonnel et al., 2012; Palouzier-Paulignan et al., 2012). Particularly, food deprivation is able to change the activity of the principal cells of the MOB, after exposure to different kinds of food odors, being more active when rats are exposed to the familiar diet and inhibited when the rats are satiated (Apelbaum and Chaput, 2003; Pager, 1974a; Pager et al., 1972). Interestingly, such responses are blocked after selective lesions of the centrifugal fibers (Pager, 1974b). Other lesion studies (Meguid et al., 1993; Miro et al., 1980) showed that olfactory bulbectomy in rodents [a surgical removal of the MOB commonly used as a model of depressive-like behavior (Song and Leonard, 2005)] is able to modify the total amount of food intake and the feeding pattern (meal frequency) as well as the sniffing exploratory behavior. However, such responses could vary depending of the internal state of the organism as well as the presence or absence of several environmental factors (Meguid et al., 1993; Miro et al., 1980). More recently, by using the same experimental approach, Primeaux et al. (2007) showed that olfactory bulb removal produces hyperphagia only in rats that are genetically predisposed to obesity but not in obesity protected rats (Primeaux et al., 2007). These data suggest that the integrity of the MOB is key in feeding regulation and that metabolic related signals could target olfactory circuits in order to modulate food intake. Furthermore, MOB responses to food odors depend on the inputs coming from higher brain regions. For example, classical anatomical and electrophysiological experiments suggested the existence of an olfactory–hypothalamic axis in the control of food intake (Gascuel et al., 2012; Price et al., 1991; Velozo and Almli, 1992). These studies have shown that electrical stimulation of the MOB or the olfactory cortex elicits a response in the lateral hypothalamic region, an area classically known as an important feeding-promoting center (Anand and Brobeck, 1951). However, the functional significance of such connection is not yet clarified. Another important issue recently studied, is how satiety state could impact olfactory circuits physiology. In particular, the group of Masahiro Yamaguchi in Japan has shown that during the postprandial period (the time window after eating characterized by several behaviors like grooming, resting and sleeping) there is an elimination of new-born cells in the granular cell layer of the MOB (Yamaguchi et al., 2013; Yokoyama et al., 2011). Interestingly, the same group demonstrated that the teaching signal of this process is coming from the corticofugal fibers from the olfactory cortex (Komano-Inoue et al., 2014). This suggests that satiety (i.e. hormones and peptides) signals could have a direct impact in the reorganization of olfactory circuits, and consequently in olfactory based behaviors.

3. Hormonal and peptidergic influences on olfaction

The sensation of hunger is driven by the interplay of several physiological factors and hormonal and peptidergic signals play a key role among them (Stanley et al., 2005). These signals could be divided in orexigenic (appetite stimulating) and anorexigenic (appetite suppressant) and their production and site of action are located in the periphery (e.g. gastrointestinal tract, adipose tissue and others) and/or in the central nervous system (e.g. hypothalamus, reward circuits) after changes in the energy metabolism. For instance, ghrelin, an appetite-stimulating hormone mainly produced by gastrointestinal cells during negative energy balance conditions (Date et al., 2000; Nakazato et al., 2001; Pradhan et al., 2013; Tschop et al., 2000), exerts its effects targeting hypothalamic nuclei, and also brain areas involved in food reward (Abizaid et al., 2006; Egecioglu et al., 2010). Interestingly, in a recent study conducted by the team of Matthias Tschop, it is shown that olfactory circuits and olfactory processes are under ghrelin influence in humans and rodents (Tong et al., 2011). Ghrelin increases exploratory sniffing and enhances odor detection in both organisms, potentially by acting in the olfactory cortex and the glomerular area (Tong et al., 2011). Thus, ghrelin orexigenic functions could be explained at least in part by the hormonal action in olfactory areas, enhancing the salience of the food by boosting sensory performance. This has been also hypothesized for other appetite-stimulating peptides, such as orexins and neuropeptide Y (NPY). ORX-containing cells are exclusively expressed in the lateral hypothalamic area, one of the main “feeding centers” in the brain (Morton et al., 2006; Grimaldi et al., 2014), and project to different brain areas, including the MOB (Caillol et al., 2003; Gascuel et al., 2012; Peyron et al., 1998). In the MOB, orexin-expressing neurons modulate mitral cell excitability *via* action on GABAergic cells present in the granular and glomerular layer (Apelbaum et al., 2005; Hardy et al., 2005; Shibata et al., 2008). Additionally, orexin immunoreactivity and its receptors have been identified in other regions of the olfactory circuits such as the main olfactory epithelium (Gorojankina et al., 2007), but no functional studies have been done yet. Furthermore, orexin administration in satiated animals induces an increase of MOB reactivity to food odors, as measured by c-Fos expression in different layers of the MOB, mimicking fasting conditions (Prud’homme et al., 2009). Another parameter that is modified after orexin administration is the olfactory sensitivity. Using

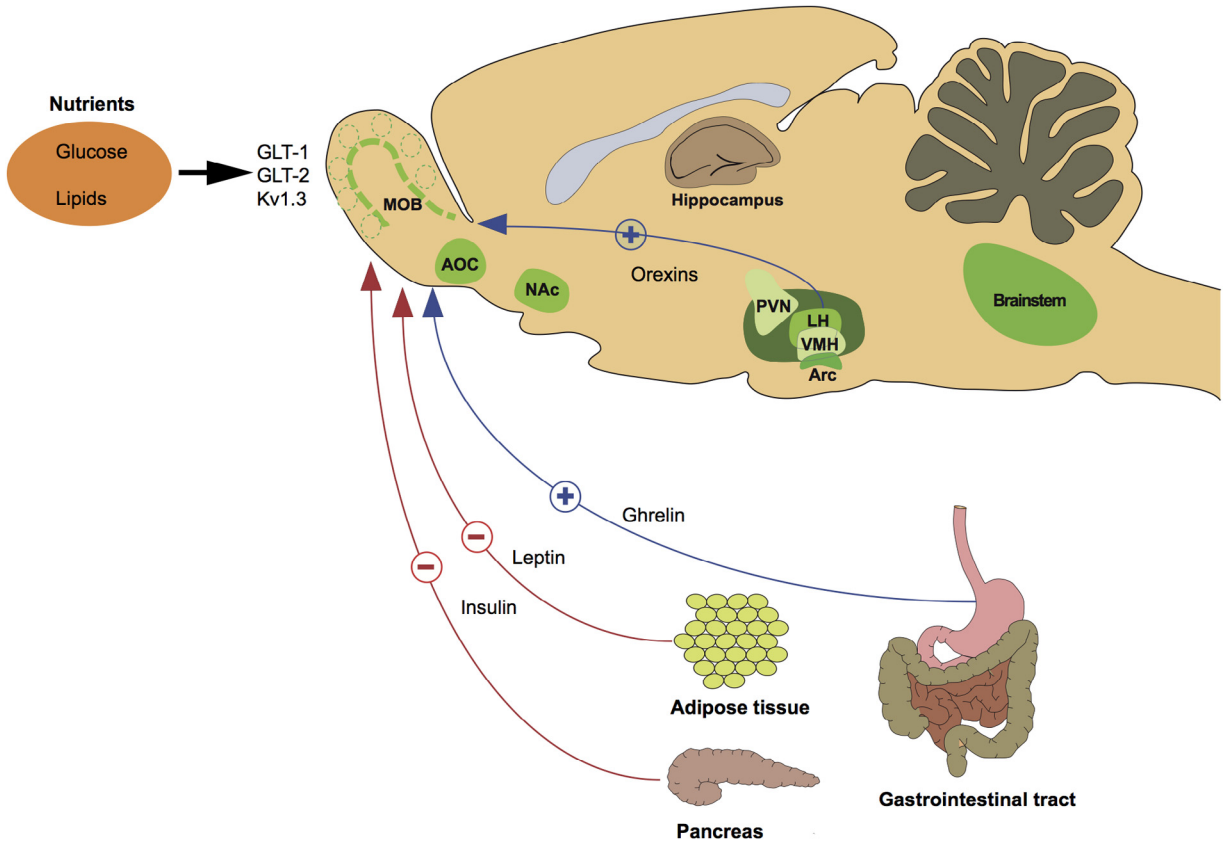

Fig. 2. Hormonal- and nutrient-dependent modulation of olfactory circuits. Orexigenic molecules produced peripherally and centrally, such as ghrelin and orexins respectively, enhance olfactory sensitivity, while anorectic signals such as leptin and insulin disrupts odor perception. Likewise, glucose and lipid metabolism could be sensed directly by olfactory circuits throughout several mechanisms (i.e. glucose transporters and potassium channels), resulting in modifications in olfactory processes. AOC, anterior olfactory cortex; Arc. Arcuate nucleus; GLT-1, glucose transporter 1; GLT-2, glucose transporter 2; LH, lateral hypothalamus; Kv1.3, voltage-gated potassium channel 1.3; MOB, main olfactory bulb; PVN, paraventricular hypothalamus; VMH, ventromedial hypothalamus.

a conditioned odor aversion paradigm, Julliard et al. (2007) showed that the animals that received orexin consumed less odorized water (previously paired with gastric malaise) than vehicle-treated mice, suggesting a sharpened olfactory sensitivity (Julliard et al., 2007). NPY neurons are present in the arcuate nucleus of the hypothalamus, adjacent to third ventricle, where they receive important information of the nutritional status of the organism coming from the periphery (Morton et al., 2006). In olfactory circuits, NPY could act in the OM (Doyle et al., 2008), depending of the energetic balance. In fact, NPY agonists increase the activity of OSN in the OM when stimulated by different odorants after fasting conditions, as compared with satiated animals. This is also accompanied with an up regulation of NPY receptors in OM.

Thus, there is abundant evidence that orexigenic factors and fasting conditions enhance olfactory performance. Conversely, satiety and hypophagic molecules induce a decrease in olfactory sensitivity. Two of the main hormones involved in satiety processes are leptin and insulin (Coll et al., 2007; Morton et al., 2006). They both are blood-circulating peptide hormones. Leptin is produced by adipocytes and it is one of the main responsible of the control of body lipid homeostasis; on the other hand, insulin is produced by pancreatic cells, participating in glucose sensing and metabolism (Stanley et al., 2005). Importantly, both hormones and their receptors are also locally expressed in olfactory circuits, mainly in the OM and MC, and are positively regulated after periods of fasting (Aime et al., 2012; Badonnel et al., 2009; Baly et al., 2007; Banks et al., 1999; Kuczewski et al., 2014; Lacroix et al., 2008; Tucker et al., 2010). Electrophysiological recordings of OSN and MC have revealed that leptin and insulin increase the activity of those cells in basal conditions (Fadool et al., 2011; Kuczewski et al., 2014; Savigner et al., 2009). However, in the presence of odorants, such hormones produce the contrary effect, an inhibition of the response (Savigner et al., 2009), which could be linked to the behavioral effects produced by these satiety signals under different nutritional status. For instance, it has been shown that mice carrying leptin deficit signaling (*ob/ob,* leptin deficient mice; and *db/db,* leptin receptor knock out mice) subjected to caloric restriction present an enhancement in olfactory sensitivity in the buried food paradigm; they are faster in finding the buried food, and this effect is reversed by leptin administration (Getchell et al., 2006). This treatment is also able to decrease the sniffing time of food odors in fasted mice (Prud'homme et al., 2009). In the case of insulin, Aime et al. (2012) showed that insulin levels in the MOB are higher in satiated animals as compared with fasted ones. Furthermore, central administration of insulin decreases olfactory detection (Aime et al., 2012), mimicking a satiety state.

Altogether, these data show that the nutritional status and its hormonal-peptidergic components modulate olfactory circuits, consequently modifying olfactory behaviors related with food consumption (Fig. 2**)**. Other feeding-related factors, such as sympathetic and parasympathetic activity (Messina et al., 2013) could also participate in olfactory processes (Hall, 2011). Indeed, Nagai et al., (2014) found a reduction in food intake after presentation of grapefruit scent. This was associated with an increase of sympathetic nerves activity innervating the white and brown adipose tissue (Nagai et al., 2014). This suggests that the hypophagic effects are mediated by an autonomic-dependent increase of peripheral anorectic hormones (i.e. leptin).

4. Olfactory circuits are sensors of glucose and lipid metabolism

Beyond the hormonal components, olfactory circuits are able to sense the internal state of the organism using other metabolic signals. Glucose and lipids are part of the essential energy chain necessary for the functioning of brain cells (i.e. neurons and astrocytes) (Dwyer, 2002). Thus, changes in the levels of these two signals can result in modifications of several physiological processes, including olfaction and its impact on feeding behavior. Particularly, olfactory structures (among others) are sensitive to peripheral glucose levels (Delaere et al., 2013). The presence of glucose transporters and associated proteins has been described in detail in the different compartments of olfactory circuits. The glucose transporters 1 and 2 (GLUT-1 and GLUT-2) are expressed in the MOB and OM (Hussar et al., 2002) (Hichami et al., 2007; Leloup et al., 1994), and their expression is modified depending of the nutritional state of the organism resulting in modulation of olfactory behaviors (Hichami et al., 2007). However, a detailed mapping of expression in the different layers and subregions of olfactory areas are yet to come. Recently, the group of Debra Fadool in Florida described the participation of a voltage-gated potassium channel, the Kv1.3 as a key component in the glucose and lipid sensing-capabilities of olfactory cells (Tucker et al., 2010). Interestingly, the same group previously showed that null mice mutants lacking Kv1.3 (Kv1.3-KO) are "super smeller" and carry structural modifications in olfactory structures (Fadool et al., 2004). Regarding energy metabolism, Kv1.3-KO mice are insensitive to the insulin-dependent modulation of MC activity, resistant to obesity and present elevated glucose in fasting conditions (Fadool et al., 2011; Thiebaud et al., 2014; Tucker et al., 2012a), suggesting that Kv1.3 channels are necessary for insulin (and potentially glucose) signaling in olfactory circuits. Indeed, these potassium channels in MC are directly sensitive to metabolically active glucose, whose increase produces an inhibition of MC frequency activity, which in turn modifies the communication between olfactory circuits and higher brain regions (Tucker et al., 2013).

5. Involvement of olfaction in metabolic disorders

As changes in energy metabolism, as well as aberrant hormonal production have been associated with several metabolic disorders such as obesity and diabetes, it is possible that olfactory circuits are modified in these pathologies. Different animal models of obesity have been proven to carry also modifications in olfactory behaviors related with feeding (Badonnel et al., 2014; Tucker et al., 2012b). In a very elegant study, Thiebaud et al., (2014) demonstrated the structural and functional consequences of a chronic energy imbalance in olfactory circuits (Thiebaud et al., 2014). Specifically, diet-induced obesity and high-fat diet produces a loss of around 50% of OSN, resulting in impairment of olfactory discrimination and olfactory learning (Thiebaud et al., 2014). These studies suggest that olfactory modifications at the level of circuits and behavior are produced by a metabolic disorder. However, it is still to be demonstrated if such changes contribute to the development of the disease. The better clarification of this point will help for the potential treatment and diagnostics of metabolic disorders.

6. The endocannabinoid system: the missing link

The endocannabinoid system (ECS) is formed by the cannabinoid receptors type-1 (CB1) and type-2 (CB2), the endogenous ligands of these receptors, the so-called endocannabinoids, and the enzymes participating in their formation and degradation (Piomelli, 2003). This system is widely expressed in the brain and it is necessary for several physiological processes, ranging from the regulation of cellular energy metabolism to the modulation of complex cognitive functions (Piomelli, 2003), (Di Marzo, 2008). Accordingly, malfunctioning of the ECS has been strongly linked to pathological conditions, such as obesity and mood disorders (Matias et al., 2012; Micale et al., 2013). It is widely known that the ECS is an essential regulator of energy homeostasis (Pagotto et al., 2006) and particularly of exostatic factors involved in feeding behavior. For example, CB1 activation is strongly linked with the intake of palatable and fat food (DiPatrizio and Simansky, 2008; Higgs et al., 2003; Simiand et al., 1998). However, the underlying mechanisms are far from being fully understood. A previous study from our laboratory showed that the ECS bimodally controls stimulated food intake (Bellocchio et al., 2010). Thus, whereas CB1 activation in GABAergic neurons inhibits food intake, inhibition of glutamatergic transmission by CB1 receptors activity produces the opposite phenotype, namely hyperphagia (Bellocchio et al., 2010). The ECS is a common target and modulator of several metabolic signals, such as ghrelin and leptin (Bermudez-Silva et al., 2012; Di Marzo et al., 2001; Kola et al., 2008), as well as glucose and lipids (Bermudez-Silva et al., 2012; Matias et al., 2008; Nogueiras et al., 2009). This suggests that the ECS in olfactory circuits could be a potential link between energy sensing cues, olfactory processes and food intake. Accordingly, several studies have shown a cannabinoid modulation of olfactory activity (Breunig et al., 2010a, 2010b; Wang et al., 2012).

Recently, we demonstrated that specific olfactory circuits are the target of (endo)cannabinoid signaling to increase odor sensitivity and promote food intake (Fig. 3) (Soria-Gomez et al., 2014); using genetic, pharmacological, behavioral and *in vivo* optogenetic electrophysiological approaches, we could show that hunger induces CB1 receptor activation in olfactory circuits, thereby determining olfactory performance and the amount of food ingested during refeeding. The results are consistent with a mechanism in which CB1 receptors directly modulate glutamatergic cortical feedback projections originating from the AOC, and targeting a population of olfactory bulb GABAergic interneurons (granule cells). In our model, the levels of endocannabinoids increase in the MOB upon fasting, thus activating CB1 receptors on olfactory cortex axon terminals, leading to a reduction of glutamatergic transmission onto granule cells. In turn, by reducing the excitation of granule cell, activation of CB1 receptors induces a disinhibition of the olfactory bulb output neurons (mitral cell), eventually increasing odor detection and food intake. Thus, CB1 receptor-dependent control of cortical feedback projections in olfactory circuits couples internal states (*e.g.* hunger) to perception (*e.g.* olfaction), to eventually modulate behavior (*e.g.* food intake).

7. General conclusion

Olfaction and food intake are tightly linked by common molecular mechanisms. This particular relationship shows how important are sensory processes in the guidance of behavior, and the key role played by internal states of the organism in fine-tuning this link. The better understanding of the link between olfaction and food intake will hopefully serve as a potential strategy to fight the devastating consequences of metabolic disorders. Thus, the challenge for the future is in the identification of how the common molecular mechanisms interact with each other in the modulation of feeding behavior and olfactory processes.

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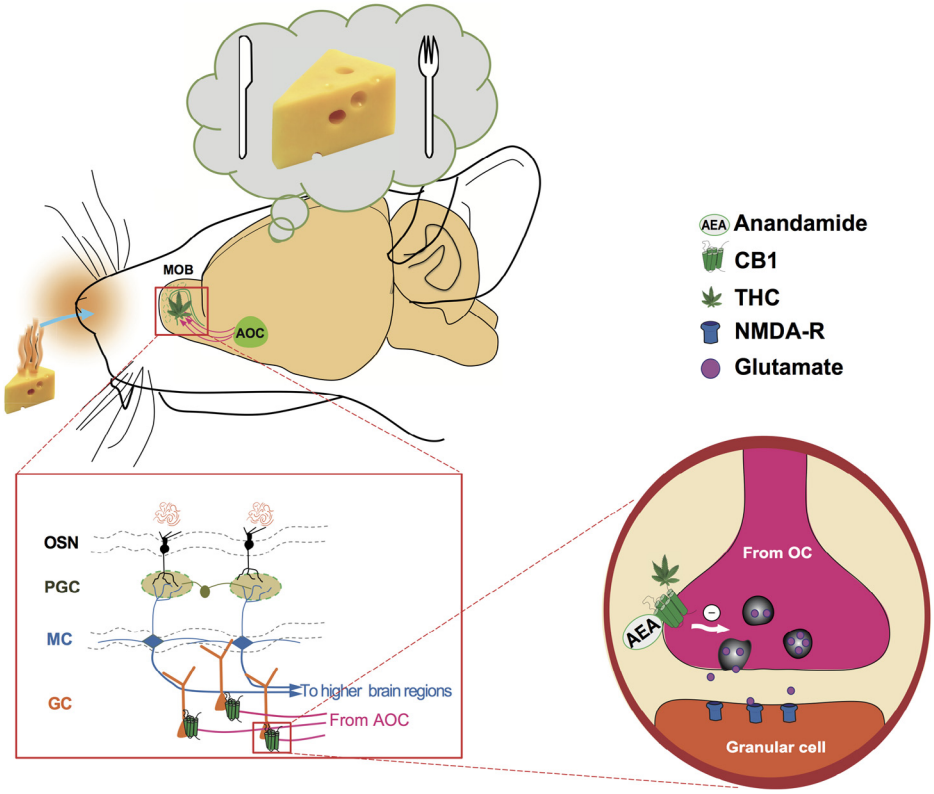

Fig. 3. The endocannabinoid system controls food intake via olfactory processes. Cannabinoid stimulation in the corticofugal system stimulates olfactory perception and food intake. Presynaptic CB1 receptors are the target of exogenous (i.e. THC) and endogenous cannabinoids (i.e. anandamide) in olfactory circuits. Particularly, CB1 stimulation in the granular cell layer of the main olfactory bulb produces an inhibition of glutamatergic fibers coming from the anterior olfactory cortex (AOC) resulting in a decrease of inhibitory granular cell activity and a concomitant stimulation of mitral cells (MC).

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