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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