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Taste and odor recognition memory: the emotional flavor of life

Abstract: In recent years, our knowledge of the neurobiology of taste and smell has greatly increased; by using several learning models, we now have a better understanding of the behavioral and neurochemical basis of memory recognition. Studies have provided new evidence of some processes that depend on prior experience with the specific combination of sensory stimuli. This review contains recent research related to taste and odor recognition memory, and the goal is to highlight the role of two prominent brain structures, the insular cortex and the amygdala. These structures have an important function during learning and memory and have been associated with the differences in learning induced by the diverse degrees of emotion during taste/odor memory formation, either aversive or appetitive or when taste and odor are combined and/or potentiated. Therefore, this review includes information about certain neurochemical transmitters and their interactions during appetitive or aversive taste memory formation, taste-potentiated odor aversion memory, and conditioned odor aversion, which might be able to maintain the complex processes necessary for flavor recognition memory.

Keywords: gustatory; inter-structural communication; intracellular signaling; learning; memory interaction; memory model olfaction; recognition memory.

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Introduction

Throughout our lives, although we are not always aware of them, our senses of taste and olfaction provide a broad range of daily sensations. Certainly, most animal species rely on their ability to detect and respond in an adaptive manner to chemical signals for their primary representations of the sensory world. This basic function underlies the recognition of the flavor contained in the food which, when ingested, activates specific chemosensory organs and systems.

In recent years, our knowledge of the neurobiology of taste and smell has greatly increased; in particular, by using several learning models, we now have a better understanding of the behavioral and neurochemical bases of taste and odor memory recognition. Several studies have provided new evidence of some processes that depend on prior experience with the specific combination of sensory stimuli; however, even though flavor-taste and flavor-nutrient associations can be dissociated and currently are widely studied, relatively few studies have specifically focused on how the brain structures are involved when flavor is integrated during memory formation. In this review, recent research related to taste and odor recognition is presented, along with evidence about certain brain structures, neurochemical transmitters and their interactions during taste memory formation, taste potentiated odor aversion memory (TPOA), and conditioned odor aversion (COA). The purpose of this review is to highlight the role of two prominent brain structures, the insular cortex (IC) and the amygdala, that have an important function during learning and memory, and have been associated with the learning differences induced by the different degrees of emotion involved during taste/odor learning, aversive or appetitive and when taste and odor are combined and/or potentiated. First, I present a detailed description of the models used most frequently over the past several decades and then evidence from studies of the interaction between taste or odor, as well as models which allow the combined effects of both stimuli to be studied; the intention is to ascertain the functional differences between the IC and the amygdala. These structures are modulated by the interaction with other areas of the brain and by different neurochemical activity, depending on the stage of formation of the taste memory. The information covered in this review highlights the complexity of the processes activated when foods are ingested and are recognized as a particular flavor. It is clear that during ingestion of most foods, the gustatory, somatosensory and olfactory systems are simultaneously activated – the latter via a retronasal route. One complex example is fat, which after being degraded by lipases to produce free fatty acids, activates receptors on taste cells (Sclafani

et al., 2007), whereas information about texture and viscosity is conveyed by the somatosensory system (Kadohisa et al., 2005). In addition, depending on the temperature and chain length of the fatty acid, it can activate the olfactory system via the retronasal route (Small et al., 2005). Thus, each chemical present in the food may activate multiple sensory systems (Simon et al., 2006; Roper, 2007; de Araujo and Simon, 2009), and this activation could be different if the concentration of the substance varies. Notable examples are artificial sweeteners, which induce the sensation of sweetness at relatively low concentrations but of bitterness and 'metallic taste' at higher concentrations. In summary, given that a multitude of sensorial experiences can be evoked once the foods reach the mouth, a complex set of experiences must be also learned and retrieved. This review will also summarize the extensive evidence about taste and odor pathways and some of their inputs in the amygdala and IC, brain areas that could coordinate part of the neural activity necessary for flavor memory.

Flavor recognition memory

Information derived from multiple sensory afferent systems (e.g., gustatory, olfactory, somatosensory), the senses of taste and olfaction serve the essential function of distinguishing nutrient-rich food sources from toxins. Additionally, chemical structures can elicit responses, such as odor or taste stimulus signals. Therefore, taste and smell are used to identify the chemical composition of what is to be ingested. However, taste recognition for modern and wealthy humans is primarily used to enhance the hedonistic enjoyment of food, evoking the sweet and bitter context of food experiences. In fact, during consumption of complex human foods, several of the food compounds are sensed by the nose because they are particles that are released and dispersed in the air. It has been estimated that approximately 80%–90% of what is perceived as food 'taste', is actually due to sense of smell (Breer, 2008). Nevertheless, food flavor is perceived as an overall, unitary experience (Small and Prescott, 2005).

The sense of taste in humans involves the detection of five taste qualities: bitter, sweet, salty, sour and umami (Scott, 2005). Because the chemical structures that give rise to these taste qualities are diverse, taste cells use numerous mechanisms to detect them. Furthermore, taste includes both the recognition and memory of a taste as well as its characteristics, such as hedonic value, degree of familiarity and the nutritive or toxic properties associated with that taste. In terms of evolutionary adaptation, taste memory is necessary for the proper identification of available nutritive foods and, of course, it is essential for the ability to detect chemical cues that distinguish the palatable from the unpalatable and others that elicit taste acceptance or avoidance behaviors.

Olfaction is the chemosensory modality mainly dedicated to detecting low concentrations of airborne, volatile chemical substances (Ache and Young, 2005). Odor signals themselves are often very complex and may serve to convey diverse and complex messages. Consequently, olfaction and odor memories are used in many behaviors, such as mate selection and kin recognition, or to detect food sources and avoid potentially harmful compounds. For example, environmental odors help animals locate desirable items (food, water, nesting sites, etc.) and also avoid danger (fire, etc.). It is clear that odor signals serve to integrate a diverse array of information during complex behavior tasks, such as food flavor memory recognition. Single chemical compounds can elicit physiological and behavioral responses, but a complete biological response often requires stimulation with complex, multicomponent mixtures of chemicals (Ache and Young, 2005). The odor and taste signature of a particular food is not necessarily static and may include information shaped by dynamic processes included in learning and memory.

Furthermore, it is important to mention that although most studies of taste or odor memory have used chemicals, e.g., saccharine, or smells, e.g., amyl acetate, which are perceived mainly by the gustatory system or the olfactory system, respectively; the substances still activate to some degree these systems. Accordingly, it is clear that the perception of each of these compounds, at different levels of both smell and taste, involves parallel integration when the studies are performed *in vivo* animal models. Although there is evidence that allows us to minimize the olfactory component of a mainly gustatory substance or to minimize the gustatory component of a mainly olfactory substance, we should not neglect the multi-sensorial integration when new doses or substances are used or the procedures in behavioral models are changed.

Below is a description of the most important models to study different processes and structures involved in the formation of taste or odor, together with models that allow us to see the interaction of these two stimuli to potentiate the aversive association and, consequently, the emotional experience during flavor recognition.

Taste recognition memory: 'gustatory' models

Taste recognition memory subserves processes of vital importance for living organisms, as it includes the ability to associate taste-related properties with the consequences of food ingestion. This memory allows conscious awareness that the food is familiar and simultaneously enables comparison of diverse features related to consumption, such as its chemosensory (modality, intensity), orosensory (texture, temperature, pungency) and rewarding properties (Carleton et al., 2010). It is clear that taste memory initially requires activation of the gustatory system, which, together with several other systems, is involved in codifying the consumption experience. Although olfaction and vision also contribute to food detection and codification, the gustatory system acts as a final control checkpoint for food acceptance or rejection (Scott, 2005; Yamamoto, 2006). In this regard, the increasing complexity of the neural gustatory pathway has been demonstrated by evidence that cortical areas also contain information about the pleasing nature or hedonic value of tastants (Carleton et al., 2010).

Appetitive taste memory models

In general, the consumption of a new taste, when not followed by intoxication symptoms or a hedonic response, leads to the formation of an incidental taste memory. The development of appetitive taste memory allows for an increase in the range of available food that might be very useful when the main source of nutrients is scarce or unavailable. Hence, several tastes, including sweet, umami and fat, can easily induce an appetitive response (observed as an increase in or preference for the consumption of such tastes), which could be interpreted as appetitive taste memory (Bermúdez-Rattoni, 2004). Accordingly, incidental taste memory, measured by appetitive responses, is one of several ways to study non-aversive or very low emotional memory formation. Thus, for purposes of research, different models are available to explore appetitive taste memory; for example, appetitive response, habituation, choice test preference and attenuation of neophobia, among others. The simplest of these models, the appetitive response, can be evaluated by registering the increase of consumption after several presentations of a particular taste, and then comparing the differences between novel and familiar consumption (Reilly et al., 1993). This simple model has close similarities with the attenuation of neophobia, one of the models most commonly used to study taste memory. Appetitive response and attenuation of neophobia are based on the evolutionary 'fact of fear response' for novel stimuli, which is usually observed during the first encounter with a novel taste, odor or flavor. Usually, when food with a novel taste- and/or odor-relevant or salient component is ingested in significantly lower amounts, but after several presentations, this food becomes familiar-safe, and its consumption increases; this is interpreted as attenuation of neophobia and also as appetitive memory for that food (Domjan, 1976; Gutiérrez et al., 2003a,b). Clearly, the attenuation of neophobia model requires that a novel stimulus induces a significant decrease of consumption during the first presentation, a requirement that is usually achieved using a very salient stimulus, such as highly concentrated saccharine or sucrose (Domjan, 1976; Domjan and Best, 1977; Gutiérrez et al., 2003a,b). In contrast, during the appetitive response, the significant increase in consumption is only observed after the first encounter (Touzani et al., 2010a,b). Furthermore, appetitive memory can easily be measured as choice preference between two tastes or flavors (Bures et al., 1998). The best known examples are preferences for foods that counteract a dietary deficiency, i.e., thiamine (Rodgers, 1967), salt (Schulkin, 1982; Sakai et al., 1987), or contain a hedonic value, like a sweet flavor such as sucrose (Reilly and Pritchard, 1996a,b; Sclafani, 2004) or saccharine (Sclafani and Clare, 2004; Núñez-Jaramillo et al., 2010). Preference for a particular taste can be demonstrated in a two- or multiple-bottle test during the first and subsequent taste presentations (Ackroff and Sclafani, 1991; Reilly et al., 1993; Sclafani, 2004; Touzani et al., 2010a,b).

Essentially, Rozin and Kalat (1971) proposed that taste preference learning and conditioned taste aversion (CTA) are extremes of a continuum (Rozin and Kalat, 1971). Furthermore, taste memory formation is determined by innate, unlearned reaction behaviors to particular (novel) tastes and by conditioned changes in taste learning produced by post-ingestion nutrient feedback. These conditioned changes increase the incentive salience of the taste, and at times also increase the hedonic value, reflected as a preference and increase in consumption (familiar-safe). Otherwise, aversive circumstances during taste learning, produced by post-ingestion feedback, can elicit a dramatic decrease of taste consumption, as observed in CTA. Appetitive models provide the possibility of separately studying the different processes activated, depending on the consequences of ingesting a taste, and are providing additional information about the various molecular and

cellular processes necessary for complex learning, such as flavor memory.

Conditioned taste aversion

Conditioned taste aversion is an exceptionally important learning process for all animal species, given that it allows for food recognition and prevents sickness, even death, due to repeated toxic food consumption (Garcia et al., 1974). Consequently, CTA has been widely used to study the neurobiology of learning. During CTA, animals learn to avoid a novel food if its initial ingestion is followed by poisoning; this conditioning occurs readily after a single taste, illness pairing, even when there is a delay of several hours between taste consumption and digestive illness (Garcia et al., 1985; Riley and Tuck, 1985; Schafe et al., 1995). This feature of CTA was initially received with considerable scepticism (Garcia et al., 1974), but there is currently a vast body of evidence indicating that CTA is a prototype of long-delay learning executed by mechanisms that do not require close temporal contiguity between taste and visceral stimuli (Chambers, 1990; Schafe et al., 1995). During CTA, a new taste is already stored in short-term memory as a central representation when a delayed visceral malaise emerges and lasts for several hours (Rozin, 1969; Revusky, 1970; Bures et al., 1998). Actually, taste recognition involves processes that go beyond the period of perception during consumption; evidence shows that these processes may involve independent neuronal substrates. For example, induction of deep anesthesia, using pentobarbital after novel taste presentation and maintaining it for several hours after the administration of the malaise-inducing agent, does not block the formation of CTA (Buresova and Bures, 1977).

CTA is easily demonstrated and quantified in the laboratory by administering a novel gustatory stimulus to rats, followed 1–4 h later by oral or intraperitoneal (i.p.) injection of a pharmacologic agent that elicits a transient malaise stimulus; with increasing time between taste and visceral malaise, the aversion learning gradually decreases (Gutiérrez et al., 2003a,b). Saccharin solution is one of the most commonly used taste stimuli, and it is mainly associated with gustatory activation as anosmic animals are still able to develop conditioned saccharin aversion; the malaise agent may be radiation (Smith et al., 1964), centrifugal spins (Hutchison, 1973) and even various venoms (Islam, 1978), but usually an i.p. injection of lithium chloride (LiCl) is used (Bures et al., 1998).

Taste aversion learning, as a model, is a robust task that for several years has been the focus of intensive behavioral research (Domjan, 1980; Garcia et al., 1989; Chambers, 1990; Bures et al., 1998; Bermúdez-Rattoni et al., 2004; Yamamoto, 2008; Davis and Riley, 2010; Núñez-Jaramillo et al., 2010; Gal-Ben-Ari and Rosenblum, 2011). The obvious advantages of this task are its well-described pathways for the gustatory and visceral stimulus and the wealth of available anatomical and pharmacological data implying the involvement in CTA of several brain structures (e.g., parabrachial nucleus, amygdala, IC) (Núñez-Jaramillo et al., 2010), neurotransmitters and their receptors (e.g., cholinergic system, glutamate receptors) (Berman et al., 2000; Miranda et al., 2003a,b; Bermúdez-Rattoni et al., 2004; Jimenez and Tapia, 2004), and cellular processes (e.g., expression of immediate early genes, kinase signaling pathway, c-AMP response element-binding (CREB) phosphorylation, protein tyrosine phosphorylation, protein synthesis) (Shema et al., 2007; Yamamoto, 2008; Gal-Ben-Ari and Rosenblum, 2011; Shema et al., 2011). CTA is also a very convenient model for studying, relatively, during separate time intervals, the different stages of memory formation and retrieval. For example, either the taste presentation or visceral stimulation can be manipulated in several ways, evaluating acquisition and/or CTA memory consolidation, because time intervals between taste and gastric malaise can be short or extended even for hours, and aversion will still be reliably induced after a single stimuli pairing (Miranda et al., 2008a,b; Miranda et al., 2011). Additionally, during CTA training, taste can be delivered to the subjects by different methods, either by means of a single bottle containing the taste solution, multiple bottles containing several tastes or by intra-oral taste infusion through a cannula connected to a pump, which delivers the taste at a constant rate (Fouquet et al., 2001; Yamamoto et al., 2002). However, when results are interpreted and compared, it is important to consider the type of administration and consumption (e.g., voluntary vs. controlled), because both the release of neurotransmitters and cellular activity can significantly change depending on the method used.

Unlike visual and auditory learning that occurs when externally applied signals are followed by punishment, CTA is a conditioning to the homeostatic effects of food; this conditioning normally occurs in a single trial and rarely requires overtraining. Therefore, the mechanisms of memory formation of food effects may be fundamentally different from those involved in other memories of specific time-space contingencies (Garcia et al., 1974).

New learning and re-learning taste models: extinction and latent inhibition

When a taste aversion memory has already been formed, new learning can be evaluated with successive presentations of the same taste but without the subsequent gastric malaise. The aversion extinction induced by this new taste association (now without painful consequences) leads to the re-acceptance of the taste and can be evaluated by the increase in consumption. Extinction is considered complete when the taste consumption or behavior is similar to that of the animals for which the taste is novel or appetitive (Barad, 2005). As already mentioned, after novel taste consumption, a long-term memory is developed, and this taste becomes recognized as familiar-aversive or familiar-incidental/appetitive, depending on its gastrointestinal effects (Núñez-Jaramillo et al., 2010; Yamamoto and Ueji, 2011). Using CTA extinction, it is possible to evaluate the strength of the first novel taste association as well as the mechanisms involved in a new learning type from the same stimulus, and taste re-learning after several presentations during the extinction curve (Berman and Dudai, 2001).

Another particular experimental model employed to study new learning of the same stimulus is latent inhibition of CTA, where subjects are unable to acquire a robust taste aversion if a previously established, appetitive/incidental memory for that taste was already formed (Rosenblum et al., 1993; Naor and Dudai, 1996; Miranda et al., 2003a,b). Latent inhibition also can be used with several types of stimulus to study attention, learning and memory processes (Lubow, 1989; Bouton, 1993) and is defined as the retarded performance of a learning task in which the conditioned stimulus (CS) was previously irrelevant as compared to a group for which the CS is new (Lubow, 1989). The latent inhibition for aversive taste memory (i.e., CTA) is achieved with a pre-exposure to the taste, without adverse consequences, days or weeks before CTA acquisition. As taste memory has been already formed during pre-exposure, the aversive taste memory strength, measured as a decrease in consumption, will be lower than a regular CTA induced without pre-exposure to the taste (Revusky and Bedarf, 1967; Berman et al., 2000).

Evidence suggests that appetitive and aversive taste memories are acquired by different neuronal mechanisms that, probably, share similar processes during early stages of neural taste representation (Buresova, 1980). Extinction and latent inhibition are two models that allow for the study of the mechanisms involved after aversive or appetitive taste memory representations, respectively, have already been formed and are then learned in new association conditions. The appetitive and aversive taste memory models are the ones most commonly used to understand the neurobiology of gustatory learning. However, several results have been obtained with tastes that also have an odor component. Although it is clear that anosmic animals develop CTA, which is why it is considered primarily a gustatory model, in models using saccharine, sucrose or other sugars, the olfactory component continues to be present and forms part of the integral perception of the flavor. For this reason, there are useful models that also use the same substances as well as robust odors to study the integration of taste and odor components, including taste-potentiated odor aversion (Rusiniak et al., 1982; Trost and Batsell, 2004; Inui et al., 2006; Batson et al., 2008; Dardou et al., 2008) and COA (Chapuis et al., 2007). Furthermore, in real life, food aversion is a complex associative behavior that transcends broad species differences. Food aversion is the long-term retention of experience gained from a single association between ingestion and subsequent illness that is enhanced through co-association with odor cues (Capaldi et al., 2004). Given the above, it has been postulated that preference- or aversive-flavor learning involves multiple learning processes, although it is usually interpreted as a form of classical conditioning in which a particular flavor (the CS) is associated with the oral and/or post-oral properties of nutrients (the unconditioned stimulus, US) (Garcia et al., 1974; Sclafani, 2004).

Taste/odor recognition memory models

Olfactory and gustatory cues are known to play a major role in food. For example, it is possible to acquire a strong taste aversion (e.g., CTA), even if the taste and gastric malaise are separated by an interval of several hours (Palmerino et al., 1980); however, subjects acquire little aversion to an odor stimulus presented next to drinking water (i.e., external odor). Only if odor and taste are presented as combined stimuli and subsequently paired with delayed malaise do we observe a significant odor aversion memory. Pioneering studies indicated that the olfactory system, which primarily projects to the limbic system, does not play a primary role in adjusting food incentives. Rather, it plays a secondary role in the activation of feeding, as do other external sensory systems (Kiefer et al., 1982).

Nonetheless, it is clear that, taken together, afferent signals from the olfactory system, gustatory system

and gastrointestinal tract are essential for the control of visceral functions, such as oral and gut secretions and of several digestive, endocrine, thermogenic, cardiovascular and renal responses via autonomic reflexes (Kitamura et al., 2010), complex processes that are beyond the scope of this review.

Taste-potentiated odor aversion

Odor and taste learning allow for recognition and discrimination between dangerous and safe foods; therefore, odor or taste stimuli can acquire biological significance after having been paired with visceral malaise by inducing an aversion to these stimuli that protects against poisoning (Bernstein, 1999). For example, if the animal tries the taste prior to illness, it will markedly decrease its consumption of that taste. However, if the animal is in contact with the odor prior to illness, its consumption in the presence of that odor cue is not decreased to the same extent as in the presence of the taste cue. Surprisingly, the experience of taste plus odor combined prior to illness induces a quite different response. Specifically, if the animal later encounters the odor, its consumption in the presence of this cue is significantly less than if it had only experienced the odor alone with illness. The increase in the strength of the odor aversion following 'taste plus odor compound conditioning' has been termed taste-mediated odor potentiation (Rusiniak et al., 1979). Therefore, if external odor is presented alone, it does not induce aversion; only odor together with taste can achieve a mediated potentiation, which increases the associative strength with the visceral malaise and induces a subsequent avoidance of flavor consumption based exclusively on its olfactory characteristics (Bernstein, 1999). Thus, TPOA is a particular learning task in which the simultaneous presentation of an odor and a taste cue is followed by a delayed visceral illness; a stronger odor aversion can be obtained compared to odor-conditioning alone (Palmerino et al., 1980; Rusiniak et al., 1982; Westbrook et al., 1983). TPOA is also a remarkable kind of learning, as generally, when a weak stimulus is conditioned with a stronger one, the weak stimulus is expected to be overshadowed (Durlach and Rescorla, 1980).

The mechanism of taste-mediated odor potentiation has been of theoretical interest because it is not anticipated by most formal models of associative learning. Given that the presence of a taste stimulus at the time of conditioning by strong odor components potentiates rather than overshadows the resulting odor aversions, and the fact that continued aversion to the taste is necessary to potentiate the odor aversion, an alternative hypothesis has been proposed attributing potentiation to the combined effects of within-compound odor-taste associations and odor-unconditioned stimulus associations (Durlach and Rescorla, 1980). This theoretical model of potentiation, which has acquired good empirical support, proposes that the potentiation effect can be explained through the formation of three associations: odor-illness, taste-illness and taste-odor within-compound association. Following taste plus odor compound conditioning, subsequent odor testing can elicit the US representation both directly via the odor-illness association and indirectly through the odor-taste-illness association. As a result of the summation of the direct and indirect pathways, the conditioned response to the odor will be significantly stronger after compound conditioning, compared to the conditioned response produced by odor-alone conditioning.

Other results regarding the study of within-compound association accounts of potentiation suggest that the perceptual representations of specific taste plus odor compounds are different, showing that odors that are similarly aversive-conditioned are differentially potentiated by the same taste (Trost and Batsell, 2004). Furthermore, the within-compound association theory has been proposed to account for synergistic conditioning in flavor aversion learning, which suggests that taste plus odor association is symmetrical because post-conditioning inflation of one element of the compound is increased in response to the second element (Batsell et al., 2003).

As with CTA, TPOA can be implemented after several days of habituation to a water-deprivation schedule followed by acquisition (conditioning day), which consists of simultaneous presentation of an odorized filter paper with a particular odor (e.g., amyl acetate, vanilla) and an oral solution, generally presented in a special chamber different from the home cage. Several minutes later, the animals received an i.p. administration of visceral malaise agent (e.g., LiCl) (Palmerino et al., 1980; Ferry et al., 1995). One or several days later, the TPOA memory can be assessed by again presenting the odor and water only (without taste) in the same experimental cage to evaluate avoided context-illness association (Ferry et al., 1995; Dardou et al., 2007).

TPOA is a robust behavior that is rapidly learned in one trial, which reflects an important adaptive feature regarding diet selection and, consequently, animal survival. As a result, it is an attractive model for studying the interactions between the processing of different stimuli as well as between learning and memory processes involved

in multiple stimulus associations. Studies using lesions, pharmacological injections or mapping of immediate early genes have examined the brain areas and circuits involved in TPOA learning (Kiefer et al., 1982; Ferry et al., 1995; Dardou et al., 2007). Also, TPOA has recently been used as a behavioral model for studying memory retrieval at recent and remote time points after acquisition (Shionoya and Datiche, 2009). Despite the current advances, further studies are necessary to better understand the mechanisms underlying TPOA.

Conditioned odor aversion

It has long been known that external odor alone, when paired with gastric malaise, is unable to induce a significant conditioned odor aversion, unlike taste, which is considered to be the critical stimulus for flavor aversion. In contrast to the well-known CTA paradigm, COA can be obtained only if the interval separating odor presentation from illness is very short (Palmerino et al., 1980; Garcia et al., 1985). However, there is now evidence demonstrating that, when paired with visceral malaise, oral consumption of odor mixed with water (instead of odor presented close to water) is as effective at inducing conditioned aversion as taste (Slotnick et al., 1997; Chapuis et al., 2007). With this evidence, the importance of odor ingestion in COA has greatly challenged the previous assumption that in food memory formation, particularly for aversions, odors have a secondary role compared to taste. Historically, the main role was assigned to taste when it was discovered that CTA could resist a CS-US delay of several hours (Palmerino et al., 1980), whereas conditioned aversion for external odor only tolerated a very short delay between stimuli (around 15 min) (Hankins et al., 1973). This idea was further supported by the TPOA experimental model, where taste and odor are presented simultaneously and enable an odor aversion even with long CS-US delays (e.g., 2 h) (Rusiniak et al., 1979; Palmerino et al., 1980). After this, most evidence related to food aversions used CTA and TPOA, assuming that odor had a minor or non-significant role in flavor-aversive associations (Chapuis et al., 2007). Although it had already been demonstrated that the odor mixed in a water solution was a more effective cue for illness than the same odor located separately from the solution, it was not investigated for CS-US delays longer than 30 min (Rusiniak et al., 1982). Only later did Slotnick et al. (1997) demonstrate that when an odor (e.g., isoamyl acetate) is ingested in water at a concentration that does not confer any gustatory sensation to the solution, the olfactory-only stimulus acquires a strong aversive value even with CS-US delays similar to those regularly used for CTA (Slotnick et al., 1997). As a result, as the evidence that odor ingestion was crucial for COA acquisition, COA is recognized as a robust and long-lasting learned association that leads to the avoidance of ingesting an odorized-tasteless solution. Altogether these findings have revealed the importance of these olfactory routes in the different perceptual qualities during food recognition (Rozin, 1982; Sun and Halpern, 2005). In the COA model, ingested odor induces both orthonasal and retronasal stimulations, which have the same properties as taste when associated with a visceral malaise: COA requires a single trial, resists an inter-stimulus delay of several hours and can be recalled several weeks after acquisition (Chapuis et al., 2007). Moreover, COA seems to be stronger than CTA, especially during remote memory tests (Desgranges et al., 2009).

Recently, COA has been assessed under experimental conditions more similar to those used in the CTA protocol; i.e., in the home cage with free access to bottles during conditioning and testing (Miranda et al., 2007; Desgranges et al., 2008), instead of the original experimental framework for COA studies that used an experimental chamber outside the home cage (Slotnick et al., 1977; Chapuis et al., 2007). With this new arrangement, the results can be compared with those of the CTA test as many of the variables are similar, which should improve interpretation (Chapuis et al., 2009). Generally speaking, COA is achieved after several days of habituation to a water-deprivation schedule in the home-cage; during the conditioning phase an odorant dissolved in water is presented (e.g., amyl acetate diluted in water) (Slotnick et al., 1997). After several minutes, an irritant agent (e.g., LiCl) is i.p. administered. One or several days later, odor aversion is assessed by again presenting the odorized-tasteless solution. The reduction of consumption during the test is used as a measure of odor memory (Miranda et al., 2007).

Once more, the COA evidence demonstrates the important fact that when odor has post-ingestive consequences, the memory strength depends mainly on how the stimulus is presented. (In other words, a completely different memory occurs after a different method of odor presentation.) Also, it highlights the importance of seeking experimental models that can help unlock the complexity of the multi-sensorial perception that the brain faces every day in the natural world, where the connection among perception, learning and retrieval are considered to be continuous.

Flavor integration: main areas for odor-taste associations

As mentioned previously, flavor integration may require the development of convergent odor and taste neuronal activation by allowing the memory representation of such association; this activation involves the central gustatory and olfactory pathway, which includes the the basolateral amygdala (BLA) and the IC, two major areas for odor-taste associations.

Gustatory pathways

The central gustatory pathway is currently well documented for several species (Rolls, 1989; Travers and Norgren, 1995; Carleton et al., 2010). In a general description, receptor cells in the taste buds, innervated by the facial, glossopharyngeal and vagus nerves, are activated and then transmit taste information to the rostral part of the nucleus of the solitary tract (NTS) (Yamamoto, 2006), which is the first central synaptic relay for gustatory information and the major interface between visceral sensory afferents and the central nervous system (Hamilton and Norgren, 1984). Accordingly, the majority of vagal afferents project to the NTS, and these projections influence many homeostatic functions, including the cardiovascular reflex, food intake, stress and cognitive processes (Ciriello, 1983; Altschuler, 1989; Andresen and Kunze, 1994; Clark et al., 1995). Gustatory information is carried by projections of nerves VII, IX and X, which have been well described (Hamilton and Norgren, 1984); also, significant progress has been made in mapping taste-responsive regions in the solitary tract nucleus (Hayama et al., 1985; Travers and Norgren, 1995). The parabrachial nucleus (PBN) is the second relay station in both the taste and visceral sensory pathways coming from the NTS (Yamamoto et al., 1994; Sakai and Yamamoto, 1999; Smith and St John, 1999). Axons of neurons of the gustatory area in the rostral part of the NTS project to the medial sub-nuclei of the PBN, whereas the general visceral area of the caudal NTS sends projections mainly to the lateral sub-nuclei of the PBN (Yamamoto et al., 1994; Reilly, 1999). The PBN has efferents toward the central (CeA) and BLA, lateral hypothalamus and bed nucleus of the stria terminalis (Fulwiler and Saper, 1984; Karimnamazi and Travers, 1998). The core of these structures and projections constitutes the gustatory area in the IC, which has reciprocal connections with the PBN (Reilly, 1999; Yamamoto, 2006) and efferents toward the NTS (Schafe and Bernstein, 1996) and the nucleus accumbens (NAcc) (Wright and Groenewegen, 1996), as well as bidirectional connections with the amygdala (Yamamoto, 2006) and medial prefrontal cortex (Vertes, 2006; Hoover and Vertes, 2007).

A significant number of studies demonstrate that the IC subserves the processing, encoding and storage of taste information and, therefore, is the crucial structure for taste-memory integration (Bermúdez-Rattoni, 2004; Núñez-Jaramillo et al., 2010). This cortex processes multiple taste properties (Rolls et al., 2003a,b; Verhagen et al., 2004), including sensory and hedonic responses (Yamamoto et al., 1989), visceral and nociceptive responses (Yamamoto, 2006; Kobayashi, 2011), novelty processing (Miranda et al., 2000; Bahar et al., 2004), ingestion and motivation (Yamamoto et al., 1988) and temporal responses (Katz et al., 2001). An understanding of the detailed gustatory interactions between the several structures connected with the NTS, PBN and amygdala, as well as with the IC, requires additional sophisticated research to integrate the diverse features related to the consumption and multimodal integration involved during flavor recognition.

Olfactory pathway

The central olfactory pathway is activated when an odorant stimulates the primary olfactory neurons that are the starting point of olfactory transduction. The glomerulus of the olfactory bulb is the only relay between the peripheral and central olfactory systems (Meisami et al., 1998). The axons of the olfactory bulb mitral cells successively cross the olfactory peduncle and olfactory tract before projecting onto the primary olfactory cortex; the mitral cell axons terminate in the superficial layer of the piriform cortex, synapsing with pyramidal cell dendrites to form an excitatory and/or inhibitory set of connections. The secondary olfactory cortex receives fibers from the primary olfactory areas, and it is situated mainly in the insula and entorhinal cortex, the input areas of the hippocampus attached to the parahippocampal cortex. The information processed in the piriform cortex then projects to various brain regions: the orbitofrontal cortex, amygdala, hypothalamus, insula, entorhinal cortex and hippocampus (Meisami et al., 1998). The olfactory cortex includes the forebrain areas receiving the direct olfactory bulb (mitral/tufted cell) input; interestingly, all regions of the olfactory cortex send projections back to the olfactory bulb. There are also strong commissural projections between the bilateral olfactory cortical subregions via the anterior commissure: olfactory sensory neurons in particular project exclusively to the ipsilateral olfactory

bulb, and cortical neurons have access to bilateral input (Wilson, 1997; Kikuta et al., 2008). In rodents, the olfactory cortex consists of the majority of the ventrolateral brain that is ventral to the rhinal fissure, including the anterior olfactory nucleus, tenia tecta, olfactory tubercle, cortical nuclei of the amygdala, anterior and posterior piriform cortex and lateral entorhinal cortex. In general, these same regions can also be identified in the human brain (Wilson and Sullivan, 2011).

Direct, reciprocal connections have been described between all or parts of the olfactory cortex and the orbitofrontal cortex (Illig, 2005), amygdala (Majak et al., 2004) and perirhinal areas, such as the entorhinal cortex (Haberly and Price, 1978; Haberly, 2001; Kerr et al., 2007). These diverse connections indicate the information complexity available to the olfactory cortex, including valence, reward, context, hedonic value and expectation. For example, neurons in the piriform cortex of rats performing an odor-discrimination task show changes in activity in response to several components of the task in addition to odor sampling, including approaching the odor port prior to odor onset and access to the water-reward port (Schoenbaum and Eichenbaum, 1995; Zinyuk et al., 2001).

The olfactory cortex is highly modulated by the noradrenergic activity of the locus coeruleus; for example, it has been demonstrated that activation of the locus coeruleus enhances odor-evoked responses (Bouret and Sara, 2002). Also, this cortex is modulated by serotonergic activity mediated by the raphe nucleus (Shipley and Ennis, 1996) and by cholinergic activity from the nucleus of the horizontal limb of the diagonal band. Disruption of normal cholinergic activity within the piriform cortex impairs odor memory and discrimination between similar odors (Ravel et al., 1992; De Rosa and Hasselmo, 2000; Linster et al., 2001; Saar et al., 2001; Fletcher and Wilson, 2002; Wilson and Sullivan, 2011). Furthermore, associative odor learning modifies odor-evoked changes in the piriform cortex; for example, odor learning changes the synaptic strength of projections from both the olfactory bulb and the orbitofrontal cortex to the piriform cortex (Cohen et al., 2008). As already mentioned, the major interaction between the olfactory cortex and other structures may be involved not only in associating odors with context or outcome, but also in helping to modify sensory perception and emotional association of the learned odor (Kadohisa and Wilson, 2006; Chen et al., 2011; Chapuis and Wilson, 2012).

Functional human studies have shown that odor intensity involves activity of the piriform cortex (Rolls et al., 2003a,b) and amygdala (Anderson et al., 2003), whereas the orbitofrontal cortex is required during odor identification and olfactory memory (Zald and Pardo, 1997; Zald et al., 2002; Soudry et al., 2011). Other studies found that amygdala activation is associated with odor intensity but not valence, whereas orbitofrontal cortex activation is related to valence and is independent of intensity (Anderson et al., 2003), also indicating that the amygdala seems to be a strategic brain area where olfactory and neuroendocrine stimuli are integrated, modulating feeding behavior (King, 2006).

Amygdala involvement during odor/taste memory recognition

In the course of investigating the neurobiological substrate involved in taste and odor memory, studies have shown that the amygdala plays a prominent role during taste memory. In general, evidence indicates that the amygdala is more involved in the processing of the visceral stimulus than of the taste stimulus (Roldan and Bures, 1994; Miranda et al., 2002), as amygdala inactivation before or after visceral illness impairs CTA memory formation (Roldan and Bures, 1994). However, an increase in c-Fos expression after novel saccharin consumption was only seen in the amygdala when a highly neophobic taste (0.5% saccahrin) was used (Montag-Sallaz et al., 1999; Koh et al., 2003), as well as in the CeA after CTA retrieval in an over-training conditioning protocol, which also increases the level of taste aversion (Navarro et al., 2000). An increase in c-Fos expression after visceral malaise/stimulation has also been observed in the basal and lateral amygdala (Ferreira et al., 2006). Interestingly, the expression of c-Fos in the amygdala can be modulated by the intensity of illness (Ferreira et al., 2006), emphasizing the importance of the amygdala in processing the visceral stimulus during CTA learning. Furthermore, CTA extinction also changes c-Fos activity in the amygdala; for example, at the beginning of the extinction procedure c-Fos activity increases slightly in the BLA, and then decreases rapidly as the aversion is extinguished. In the CeA, extinction does not seem to affect c-Fos activity (Navarro et al., 2000; Mickley et al., 2004). Recently, using cellular compartmental analysis of temporal gene transcription by fluorescence *in situ* hybridization (catFISH), populations of neurons have been detected that respond to both the CS and US during CTA. Individual BLA neurons in particular responded to both the taste and visceral stimulation during training. This coincident activation was decreased when stimuli were not able to induce learning (e.g., latent inhibition) (Barot et al., 2008).

The BLA has a central modulating role during CTA, proving once more that the BLA is critical for regulating

the consolidation of lasting memories of significant experiences (McGaugh et al., 2002). Moreover, there is extensive evidence that lesions or inactivation of β-adrenoreceptors in the BLA block the taste memory-enhancing effect of drugs infused into other brain regions (Miranda and McGaugh, 2004). Electrophysiological studies have demonstrated that BLA neurons respond differentially to taste stimulus during acquisition and conditioned taste retrieval (Yasoshima et al., 1995), which suggests that the BLA is also involved in the retrieval process. The BLA in the rat receives gustatory and visceral information via cortical and subcortical pathways, including heavy projections from the primary gustatory and the primary visceral cortices of the IC. Results indicate that the potentiation of the amygdala-cortical projection is a possible mechanism for memory-related functions performed by the IC (Escobar and Bermudez-Rattoni, 2000) and that important amygdalo-cortical interaction during taste memory formation is crucial for development of aversive/emotional consolidation (Miranda, 2002; Miranda and McGaugh, 2004; Ferreira, et al., 2005).

Recent evidence using catFISH to visualize odor-taste convergence onto single neurons in the BLA and in the IC during conditioned odor preference has demonstrated that flavor learning induced an increase in cell activation by both taste and odor stimulations in the BLA, but not in the IC, and suggested that odor-taste convergence in individual BLA neurons can be activated by both odor and taste only after the association. Accordingly, the development of convergent activation in amygdala neurons after odor-taste associative learning may provide a cellular basis for flavor memory (Desgranges et al., 2010).

Moreover, the amygdala has a role in incidental taste memory formation, as blocking the NMDA receptor in the amygdala impairs attenuation of neophobia (Figueroa-Guzman and Reilly, 2008), and β-adrenergic antagonist infusion in the BLA impairs incidental taste memory formation (Miranda et al., 2008a,b). These results suggest that glutamatergic activity participates in the later stages of acquisition as well as in aversive taste memory consolidation and that glutamate has the function of signaling, at least partly, the visceral input that will eventually converge with the taste signal during consolidation of aversive taste memory.

The BLA is abundantly interconnected with the orbitofrontal cortex (McDonald, 1998), which is known to be involved in olfactory memory (Schoenbaum and Eichenbaum, 1995) and in the processing of odor cues linked to food intake (Rolls et al., 2005). The BLA could participate in modulating specific sensory memory representations in the cerebral cortex of several modalities (Chavez et al., 2009). For example, it has been demonstrated that the amygdala plays a critical role in the acquisition of TPOA (Bermudez-Rattoni et al., 1983; Hatfield et al., 1992; Ferry et al., 1995); other results suggest that NMDA receptors of the BLA are involved in the formation of 'potentiation by taste of the olfactory' memory (Ferry and Di Scala, 2000). Later, it was shown that the same BLA lesion that disrupted TPOA acquisition did not affect its retrieval (Ferry et al., 1995). However, a more recent study using immunocytochemical detection of c-Fos suggests that the BLA might be involved in TPOA retrieval (Dardou et al., 2007); also, it was demonstrated that the BLA is necessary for odor retrieval regardless of whether the aversion was acquired recently or a month ago, in contrast to the fact that BLA inactivation is not essential for taste memory retrieval (Shionoya and Datiche, 2009). This suggests that after taste potentiates odor conditioning, the stimuli, taste and odor are differentially processed by the amygdala and that retrieval of taste or odor memory might also depend on other brain areas.

Compared with CTA, much less is known about the neural bases of COA; however, pharmacological studies have demonstrated the crucial role of the BLA in COA (Ferry et al., 1996; Slotnick et al., 1997; Desgranges et al., 2008; Sevelinges et al., 2009). Previous results showed that the depletion of the catecholaminergic system in the amygdala impaired the taste-potentiated COA (Fernandez-Ruiz et al., 1993). Additionally, it is known that intra-BLA infusion of a γ-aminobutyric acid (GABA) agonist immediately before or after odor presentation during the conditioning prevents taste-potentiated COA (Ferry et al., 1995), whereas post-odor infusion of a GABAergic antagonist rendered COA tolerant to extended stimulus delay (Ferry and Di Scala, 1997). Recently, it was found that the β-adrenergic system in the BLA is involved in the initiation, but not in the maintenance, of the odor memory trace during COA acquisition (Miranda et al., 2007).

The amygdala function during taste and/or odor memory formation as well as odor retrieval may be explained by the fact that the amygdala receives both odor and visceral inputs (Saper and Loewy, 1980; Azuma et al., 1984; Inui et al., 2006). It has been postulated that '...a subset of amygdaloid neurons receives the convergent inputs from the taste and olfactory systems, and the taste inputs enhance the responsiveness to the odor inputs. This potentiated or long-lasting odor response may be associated with the visceral inputs leading to the formation of odor aversion' (Inui et al., 2006).

The connections and interactions between the anatomical substrates implicated in taste are complex. There is extensive evidence implicating the amygdala

in motivation- and reward-related learning (Baxter and Murray, 2002; Cardinal et al., 2002). Furthermore, the amygdala has a particularly important function in flavor preference learning induced by both the sweet taste and the post-oral reinforcing properties of nutrients (Gilbert et al., 2003; Touzani and Sclafani, 2005). Further experiments are needed to examine the role of cortical regions richly connected with the amygdala in the complex interactions of odor and taste experiences during food recognition.

Insular cortex involvement during odor/taste recognition memory

The IC is a structure crucial for taste memory (Bures et al., 1998; Bermudez-Rattoni, 2004; Bermúdez-Rattoni et al., 2004); temporary inactivation of the IC, as well as irreversible lesions, either electrolytic or excitotoxic, affect acquisition (Braun, 1990; Bermudez-Rattoni and McGaugh, 1991; Nerad et al., 1996) and retrieval of CTA (Ormsby et al., 1998; Cubero et al., 1999; Berman et al., 2000; Desgranges et al., 2009). Novel taste consumption induces a greater increase of c-Fos expression in the IC than that induced by a familiar taste (Koh et al., 2003). Accordingly, CTA also induces a significant increase of c-Fos expression in the IC (Koh and Bernstein, 2005). However, reducing the LiCl concentration produces a weaker CTA, but does not influence the level of c-Fos expression in the IC (Ferreira et al., 2006).

The cholinergic and glutamatergic systems have been studied the most; both are important in taste memory formation, and their role in many other types of learning and memory has been well established (Aigner, 1995; Castellano et al., 2001; Kilgard, 2003; Miranda et al., 2003a,b; Pepeu and Giovannini, 2004). For example, increased ACh release has been observed in the IC during consumption of a novel taste, and it correlates strongly with the novelty of the stimulus (Miranda et al., 2000). Moreover, blockade of muscarinic ACh receptors (mAChR) in the IC before novel taste consumption disrupts both CTA acquisition and the attenuation of neophobia (Naor and Dudai, 1996; Berman et al., 2000; Gutiérrez et al., 2003a,b). Furthermore, many intracellular mechanisms unleashed by novel taste consumption appear to involve cholinergic activity (Rosenblum et al., 1997; Berman et al., 2000; Núñez-Jaramillo et al., 2008).

Glutamatergic activity occurs during early stages of taste memory formation; for example, an NMDA receptor blockade in the IC impairs CTA but does not affect attenuation of neophobia (Gutiérrez et al., 2003a,b), indicating that NMDA receptors participate during the association and consolidation phases of aversive taste memory. In contrast, non-competitive antagonists of NMDA receptors do impair the attenuation of neophobia (Figueroa-Guzmán et al., 2006). Other neurotransmitters in the IC are also involved during learning and memory; one example is the discovery that activation of the endocannabinoid receptor CB1 in the IC impairs CTA, but it has no effect on memory extinction (Kobilo et al., 2007). Additionally, the activity of GABA receptors in the IC during taste demonstrated (Berman et al., 2000); noradrenergic activity learning in the IC has been explored as well, demonstrating that blockade of β-adrenergic receptors impairs CTA (Berman et al., 2000) or has no effect (Miranda et al., 2008a,b). β-Adrenergic receptors in the IC are also needed during appetitive taste learning (Miranda et al., 2008a,b) and during the induction of latent inhibition for CTA memory formation (Berman et al., 2000). Unfortunately, no detailed studies of the neurochemistry associated with odor tasks have been reported; thus, it is not yet known whether these neurotransmission systems participate in a similar fashion during the CAO and/or TPOA.

Considerable evidence has demonstrated plastic changes in the IC are associated with the encoding and integration of taste stimuli. For example, taste map plasticity and hedonic value representations during CTA learning and extinction have been examined (Grinvald et al., 1999), demonstrating that the taste maps rearrange depending on the hedonic value of the taste, both during CTA acquisition and extinction. These results suggest that the IC is important for the intensity and modality of encoding during memory formation, as well for processing hedonic value (Accolla and Carleton, 2008). It would be interesting to establish models to evaluate the hedonic, emotional or social part of the olfactory component, similar to what is currently known from previous gustatory evidence.

Regarding taste/odor association, although a number of investigators have examined the effects of lesions of several brain regions during acquisition and retention of TPOA (Roldán et al., 1974; Lasiter et al., 1985a,b; Bermúdez-Rattoni et al., 1986; Fernandez-Ruiz et al., 1993; Ferry et al., 1995; Hatfield and Gallagher, 1995), the results have been inconsistent. For example, it was reported that lesions of the IC disrupted CTA acquisition without affecting TPOA learning (Fernandez-Ruiz et al., 1993). However, evidence showed that IC lesions disrupted acquisition of both CTA and TPOA (Lasiter et al., 1985a,b). The most likely reason for this discrepancy is the apparent difference in experimental procedures. Despite the contradictory evidence, the IC is a very likely site for the integration of odor and visceral stimulus, in view of the fact that the

IC receives both olfactory and visceral inputs, in addition to gustatory information (Sewards and Sewards, 2001). It is known that permanent IC lesions did not affect COA (Kiefer et al., 1982; Lasiter et al., 1985a,b; Roman et al., 2006); furthermore, transient inactivation of the IC during acquisition spared COA, but greatly impaired CTA. Similarly, blockade of protein synthesis in the IC did not affect COA but prevented CTA consolidation, and IC inactivation impaired the retrieval of both recent and remote CTA memory (Desgranges et al., 2009). These results suggest that the IC is not involved during aversive odor memory, whereas it is essential for acquisition, consolidation and retrieval of aversive taste memory. Interestingly, there is also evidence that IC lesions have no effect on either taste or flavor preference learning (Touzani and Sclafani, 2007), which suggests that the IC is differentially involved during aversive or appetitive taste associations but has no significant role during aversive (e.g., COA) or conditioned odor preference.

Taste system and the reward and feeding systems

Learning taste information is a prolonged process that follows acquisition; it starts with an internal, gustatory representation and continues with internal and visceral processing for several hours (Bures et al., 1998). In this regard, taste memory contributes to the development of preferences for several caloric- or fat-rich flavors, due not only to the absence of noxious or toxic consequences, but also to metabolic feedback (Sclafani and Mann, 1987; Ackerman et al., 1992; Sclafani and Ackroff, 2004). The evidence thus far indicates that during taste memory formation, there are principal structures, like the IC, amygdala and prefrontal cortex that could be integrating the complexity of taste processing; however, much remains to be done to understand their specific roles and interactions. Using aversive and appetitive models we are obtaining additional knowledge about how each of these structures participates in the formation of flavor memory. Accordingly, the behavioral parallelism and the convergence of anatomical structures involved during taste recognition memory and food consumption regulation indicate an important interaction between the taste system and the reward and feeding systems. In particular, it has been suggested that the amygdala, the prefrontal cortex and the IC are among the main candidates for the interfaces between these systems (Yamamoto, 2006). As the prefrontal cortex is interconnected with the subcortical feeding and reward areas, such as the amygdala (Perez-Jaranay and Vives, 1991), ventral tegmental area (Divac et al., 1978) and the nucleus accumbens (Brog et al., 1993), this cortical area could be an important node of interaction with the IC, which also has significant projections to the prefontal cortex (Saper, 1982). Furthermore, neurons in the dorsomedial prefrontal cortex respond to gustatory stimuli (Karádi et al., 2005) and lesions or pharmacological manipulations of the prefrontal cortex induce feeding disturbances (Kolb and Nonneman, 1975) or impair taste memory formation (Hernadi et al., 2000; Mickley et al., 2005; Akirav et al., 2006; Reyes-López et al., 2010); these facts strongly suggest that the prefrontal cortex also plays an important role in more complex behaviors, such as flavor recognition and learning the emotional consequences of food consumption.

The modulation of the reward value of a food taste by motivational state, e.g., hunger, is one important way in which consumption behavior is controlled (Rolls, 1999; Higgs, 2005; Rolls et al., 2005). However, after taste learning, modulation of the emotional value of a particular taste stimulus is one of the most important factors that regulates further consumption (Garcia et al., 1989). So far, the amygdala and related circuits constitute the main anatomical intersection for translating stimulus perceptions and conditioned associations into focused appetitive and aversive motivation, as has also been seen in other kinds of learning (Everitt et al., 2003; Gabriel et al., 2003; Ambroggi et al., 2008; Ishikawa et al., 2008; Mahler and Berridge, 2012).

Final remarks

The sensorial integration induced by eating requires the parallel recognition of all the characteristics contained in the food when it reaches the mouth, but also includes the context; e.g., where and how the food is eaten. The specific, highly efficient perception of these basic gustatory modalities is achieved when their characteristic molecules are detected, which induces an ulterior selection through their involvement in the acquisition of learned aversions (Bernstein, 1999). In the real world, odors are rarely experienced as single compounds; mainly they are complex mixtures and may contain many of the same components in different ratios (Ache and Young, 2005). In this regard, perception, integration and recognition memory of flavor integrate models for studying cross-modal sensory interactions, and have started to provide an understanding of the integrated activity of sensory systems that generate

such unitary perceptions (Small and Prescott, 2005). Recently, psychophysical, neuroimaging and neurophysiological research of several mechanisms by which odor and taste signals are processed revealed some similar functions despite separate anatomic activities (Scott and Plata-Salaman, 1999; Small et al., 1999; Savic et al., 2000). Thus, flavor perception in mammals depends upon neural processes occurring in similar chemosensory regions of the brain, including the anterior insula, frontal operculum, orbitofrontal cortex and anterior cingulate cortex (Small and Prescott, 2005). Odor-dependent associative learning appears to involve changes in the first olfactory relay in diverse species (Coopersmith et al., 1986), and taste and odor are processed simultaneously during flavor recognition memory, in structures that are similar among mammals. However, these stimuli are also functionally distinct among species and show different properties related to ingestive behavior (Inui et al., 2006). An interesting review covered this information and proposed a model of flavor processing that depends on prior experience with the particular combination of sensory inputs, temporal and spatial concurrence and attentional allocation (Small and Prescott, 2005).

It is clear that there are striking similarities between species in the organization of the olfactory and taste pathways, but there are also significant differences in the processing of these stimuli. CTA, COA and TPOA are very useful models to investigate two sensorial memories that interact during food recognition. Insight into the mechanisms of taste and olfaction recognition memory has come from a diverse array of methods and approximations, employed mainly in animal models, each with its own advantages and disadvantages for study.

Current knowledge indicates that the route to perceive and recognize a taste begins with the activation of the gustatory cells that are 'triggered' to respond to a basic taste modality. Simultaneously, the olfactory cells are activated by specific mechanisms of this sensorial system. The neurophysiological studies of taste and smell highlight an important difference between chemosensory vs. visual and auditory cortical representations. Flavor recognition, e.g., the chemosensory information captured through multi-sensorial processing, distributed throughout plastic networks in different structures, induces early representations of both taste and smell in heteromodal regions of the limbic and paralimbic brain (Small and Prescott, 2005). It has been suggested that 'taste–odor integration occurs at earlier stages of processing and is likely to be influenced by experience and affective factors such as the physiological significance of a given stimulus…' (Mesulam, 1998). In this regard, during the processing of the flavor information, its hedonic and reinforcing value is integrated and also compared with the body's internal state, which supports the possibility of very early cortical integration of the sensory components (Small et al., 1999). It is clear that flavor memory is constantly updated by new experiences, which dramatically reflect the gastrointestinal consequences produced by the flavor and the degree of satiety or expectation. Quoting John Garcia 'Obviously, man has a highly specialized form of symbolic communication and the rat does not, yet man's cognitive specialization does not prevent him from developing aversions to food consumed before illness even when he knows that his illness was not caused by food.' (Garcia et al., 1974). A food is not only characterized by its flavor, but also by the sum of the odor, texture and visual appeal, as well as the context in which it is eaten, thus converting flavor into an experience integrated into the internal and emotional state of each individual.

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