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Taste Memory Formation: Role of Nucleus Accumbens

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Abstract

When a novel taste has been associated with postingestive malaise, animals recognize this taste as aversive. This associative learning is known as conditioned taste aversion. However, when an animal consumes a novel taste and no aversive consequences follow, it becomes recognized as a safe signal, leading to an increase in its consumption in subsequent presentations. In this review, we will discuss the results related to the taste memory formation focusing particularly on the nucleus accumbens (NAcc). The NAcc keeps projections with amygdala, insular cortex, parabrachial nucleus, and nucleus of the solitary tract areas important for taste memory formation. We will review the evidence relating to how the NAcc could be involved in taste memory formation, due to its role in the taste memory trace formation and its role in the association of the conditioned stimulus–unconditioned stimulus, and finally the retrieval of taste memory. In this context, we will review the participation of the cholinergic, dopaminergic, and glutamatergic systems in the NAcc during taste memory formation.

Key words: learning, memory formation, nucleus accumbens, taste memory trace

Introduction

A biologically important type of associative learning is the conditioned taste aversion (CTA). CTA is a robust type of learning in which the animal avoids consumption of a taste (conditioned stimulus [CS]) previously associated with gastric malaise (unconditioned stimulus [US]). However, when a novel taste is presented with no aversive consequences, it later becomes recognized as a safe signal, leading to an increase in its consumption.

Once a taste is ingested, it generates a taste memory trace (TMT), which is the neural representation of the taste and most likely remains temporally stored in parallel along several brain regions. This TMT has at least two components, safe and aversive, which share some common mechanisms, whereas differing in others (Gutierrez et al. 2003b; Bermudez-Rattoni 2004). Particularly, descriptions have been made referring to the fact that the safe TMT depends on cortical muscarinic receptor activity, whereas the aversive TMT is at least partially dependent on the N-methyl-D-aspartic acid (NMDA) receptor activity (Gutierrez et al. 2003a). Once the consequences of taste ingestion have been established, a taste memory is formed, which can be either safe or aversive depending on those consequences.

A structure that has been recently linked to taste memory formation is the nucleus accumbens (NAcc). Most of the research on the functions of the NAcc has focused on its role in reward (Kelley et al. 1997), addiction (Everitt et al. 1999), feeding (Saul'skaya and Mikhailova 2003), motivation (Salamone 1996) and learning (Setlow 1997; Martinez et al. 2002).

The NAcc

The NAcc is a structure in the rostrobasal forebrain and is the major component of the ventral striatum. Three fundamental subterritories of the NAcc have been described. The caudal two-third subregions are called core and shell, whereas the rostral pole comprises the third compartment (Delfs et al. 1998; Zahm 2000). The shell projects to the medial part of the ventral pallidum, the lateral hypothalamus, the ventral tegmental area (VTA), the parabrachial nucleus (PBN), and the substancia nigra pars compacta; on the other hand, the core projects to the dorsolateral part of the ventral pallidum, the entopenduncular nucleus, and substancia nigra pars compacta (Heimer et al. 1991; Usuda et al. 1998). Some studies have suggested that the medial region of the NAcc shell is more intimately connected to visceral and autonomic effector systems and the core to somatic motor effector systems (Zahm and Heimer 1990; Zahm 2000). Regarding neurotransmitter inputs, the NAcc receives dopaminergic

innervation from VTA (Zahm and Heimer 1993), and GABAergic and glutamatergic from basolateral amygdala (BLA) and from the insular cortex (IC) (Kelley and Domesick 1982; Wright and Groenewegen 1996). In addition, noradrenergic innervation from nucleus coeruleus and nucleus of the solitary tract (NTS) has been described (Pennartz et al. 1994). Among these structures, the IC, BLA, PBN, and NTS play a very important role in TMT processing (Yamamoto et al. 1994).

NAcc and taste memory formation

The development of a gustatory memory begins with the consumption of a food or drink, which has been suggested to be regulated by the NAcc system (Maldonado-Irizarry et al. 1995; Kelley and Swanson 1997; Rada et al. 1997; Stratford and Kelley 1997; Saul'skaya and Mikhailova 2003). Regarding CTA memory formation, taste and visceral information could reach the NAcc via 2 pathways: the NTS–PBN–central nucleus of amygdala–VTA–NAcc connection and the IC–BLA–NAcc pathway (McDonald 1991). The BLA sends a direct glutamatergic projection to the NAcc (Kelley and Domesick 1982; Robinson and Beart 1988; Groenewegen et al. 1996). The possibility that the connection from the BLA could regulate NAcc activity has also been shown (Louilot et al. 1985; Howland et al. 2002). In particular, the BLA and central amygdala modulate NAcc dopamine (DA) efflux; the latter modulates NAcc DA via a GABAergic projection to the VTA (Everitt et al. 1999). The regulation of NAcc activity by the amygdala, in synergism with the afferents from the agranular IC to the NAcc, has already been proposed to be an important factor in associative learning (Louilot and Besson 2000).

There are reports that suggest an important role of DA in the NAcc during associative processes. In this regard, increments of DA release during the formation of a conditioned association have been reported (Young et al. 1993, 1998; Datla 2002). For example, a neutral stimulus (tone or flashing light), which does not normally evoke any measurable change in DA in the NAcc, can evoke an increase above the one seen with the footshock alone, when they have previously been paired with it (Young et al. 1998). Conversely, in CTA, Mark et al. (1991) have demonstrated that intraoral saccharin (CS) increases DA levels in the NAcc before pairing it with an aversive stimulus (US), and once the 2 stimuli have been paired, saccharin consumption decreases DA levels in this nucleus. These results are in accord with those obtained with olfactory stimuli because conditioned odor stimulus when presented again decreases DA release in the NAcc (Louilot and Besson 2000). Thus, the involvement of NAcc in associative learning presents itself clearly, as well as the fact that this nucleus presents important changes in DA release as a consequence of CTA conditioning.

As mentioned before, the consumption of a novel taste can lead to two different outcomes, depending on its association, safe or aversive taste memory. Thus, the novelty of the stimulus would be important in the formation of TMT. In this regard, it has been shown that NAcc neurons respond to the consumption of a novel food, characterized by a decrease in their spontaneous neuronal activity (Lee et al. 1998). Differential responses in DA release after novel or familiar taste presentations have been shown. In this regard, Bassareo et al. (2002) found that the intraoral infusion of gustatory stimuli increased DA release in the NAcc core and shell, independently of the novelty or valence; like positive (20% of sucrose or sucrose plus chocolate) or negative (aversive such as saturated NaCl and quinine solutions). In accordance, licking of novel taste increased basal DA in dialysates from the NAcc (Hajnal and Norgren 2005). Exposure to a familiar intraoral solution after a single preexposure increased DA from dialysates of the NAcc core but not of the NAcc shell (Bassareo et al. 2002). However, it has been shown that a DA D1 antagonist (SCH 39166) in the NAcc shell but not in the NAcc core impairs CTA learning (Fenu et al. 2001). The exact role of DA in the 2 NAcc sub regions remains to be established in the acquisition, association, and consolidation of aversive taste memory formation.

Taste and visceral inputs coming from the PBN could be modulating the DA activity in the NAcc. It has been shown that rats with lesions in the PBN showed less intense NAcc DA release during sucrose licking (Hajnal and Norgren 2005). The PBN sends axons to the central nucleus of the amygdala, the lateral hypothalamus, the bed nucleus of the stria terminalis (Fulwiler and Saper 1984), and the VTA (Oades and Halliday 1987). In this regard, it has been proposed that the PBN might influence NAcc DA activity via direct connections to the VTA, but it is equally likely that the route is multisynaptic through their extensive connections in the ventral forebrain (Hajnal and Norgren 2005).

Consumption of food with an appetitive taste induces a decrease in glutamate levels in the NAcc (Rada et al. 1997; Saul'skaya and Mikhailova 2003), whereas natural or conditioned aversive food produces significant glutamate release (Saulskaya and Mikhailova 2002). Interestingly it has been demonstrated that glutamate release is mediated by D2 DA receptors (Saul'skaya and Mikhailova 2003). Accordingly, we recently found that the activity of NMDA receptors in the NAcc shell and core is necessary for the TMT processing. CTA allows to test short-term memory 4 h after the LiCl injection without interferences to long-term memory test 72 h after the acquisition day. We demonstrated that pretraining injection of DL-2-amino-5-phosphonopentanoic acid (APV), an NMDA receptor antagonist, on either NAcc shell or core, impaired short-term and long-term aversive taste memory, without affecting the safe taste memory formation. Conversely, posttraining injections of APV did not have any effect on either task (Ramirez-Lugo et al. 2006). These results suggest that the NMDA receptors in the NAcc shell and core have an important role in the processing of aversive TMT, but not of safe TMT.

Interestingly, the cholinergic muscarinic receptors are needed in the NAcc shell but not in the NAcc core for the formation of either safe or aversive taste memory (Ramirez-Lugo et al. 2006). Pretraining injection of scopolamine, a muscarinic receptor antagonist, on NAcc shell, but not core, disrupted both short-term and long-term aversive taste memory and also prevented the safe taste memory formation, whereas posttraining injections of scopolamine had no effects on either safe or aversive taste memory formation. These results suggest that the activation of muscarinic receptors in NAcc shell is necessary for the normal processing of a taste stimulus that can be later associated with either aversive or safe consequences (Ramirez-Lugo et al. 2006). Altogether these results support the proposed idea of the existence of two different memory traces generated by the consumption of a new taste (Gutierrez et al. 2003a, 2003b; Bermudez-Rattoni 2004) and that the NAcc is involved in both aversive and safe TMT (Ramirez-Lugo et al. 2006).

It is clear that the NAcc has an important role in taste memory formation, but its role should be mediated by its interactions with other structures. It is possible that, given the participation of BLA in processing the aversive stimulus (Miranda et al. 2002), the connection between BLA and NAcc could play a central role in relating the aversive TMT with the information of the malaise-inducing agent during aversive memory formation. Another possible mechanism for the participation of NAcc in taste learning is through its modulation to the nucleus basalis magnocellularis (NBM) that in turn projects cholinergic efferents to the cortical mantle, including the IC (see Figure 1). In this regard, it has been demonstrated that NAcc shell can regulate acetylcholine (ACh) release in the cortex via its modulation to NBM (Neigh-McCandless et al. 2002).

As mentioned above, the formation of the TMT takes place in several brain structures. However, if the taste stimulus is followed by gastric malaise (US), it will become the CS in order to form a conditioned taste aversion. Although where these stimuli convergence takes place remains to be established, several brain regions have been proposed as good candidates, like the insular and the perirhinal cortex (Gutierrez et al. 2003a, 2004; Bermudez-Rattoni 2004), the amygdala (Swank 2000), and the PBN (Yamamoto et al. 1994), and now the NAcc itself could also be participating in this process.

In addition, the role of the NAcc in the retrieval of aversive taste memory has been suggested. In this regard, the NAcc presents significative changes in ACh release when saccharin has been previously paired with LiCl but not with isotonic saline. Moreover, a significative increase in the ACh levels in the NAcc has been observed during intraoral infusion of saccharin and levels remained elevated for about 20 min (Mark et al. 1995). Similarly, the NAcc shows changes in c-fos expression during taste aversion retrieval but not after consumption an innately aversive tastant (quinine hydrochloride) consumption or LiCl-induced visceral stimulation in unconditioned animals (Yasoshima et al. 2006).

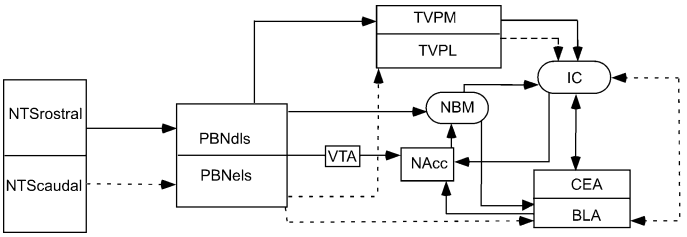

Figure 1 Schematic drawing of the principal taste and visceral brain pathways. BLA, basolateral amygdala; CEA, central nucleus of amygdala; dls, dorsolateral subnucleus; els, exterior lateral subnucleus; IC, insular cortex; NAcc, nucleus accumbens; NBM, nucleus basalis magnocellularis; NTS, nucleus of the solitary tract; PBN, parabrachial nucleus; VTA, ventral tegmental area; TVPL, ventral posterior lateral nucleus of the thalamus; TVPM, ventral posterior medial nucleus of the thalamus. Solid lines represent the gustatory projections, and the dashed lines represent the visceral projections. Modified from Bermudez-Rattoni (2004).

Conclusion

In this report, we have presented evidences of how the NAcc could be involved in processing the taste stimulus, as well as in the association of taste with visceral consequences. It has been proposed that TMT can be associated with either aversive or safe consequence (Bermudez-Rattoni 2004). Here we examine the current literature on the participation of 3 different neurotransmitter systems of the NAcc, dopaminergic, glutamatergic, and cholinergic, during the taste memory formation. In this regard, there is evidence that both aversive and safe memory traces are initially processed by cholinergic activation in the NAcc shell (Ramirez-Lugo et al. 2006). Additionally, the NAcc presents a significant increase in ACh release as a consequence of the consumption of a familiar-aversive conditioned taste but not as a consequence of familiar-safe unconditioned taste consumption (Mark et al. 1995). The cortical cholinergic activity related with the TMT formation is modulated by the NBM activity (Miranda and Bermudez-Rattoni 1999). Thus, the NAcc shell can regulate the ACh release in the cortex via its modulation through the NBM (Neigh-McCandless et al. 2002). Altogether, the results presented in this review suggest that the participation of NAcc in taste learning could be through its effect on cortical ACh release by its modulation of the NBM (see Figure 1).

There is an important participation of DA system during taste memory formation. It has been suggested that DA release into the NAcc is involved in aversive taste memory because its release decreases after presentation of conditioned aversive taste (Mark et al. 1991). Furthermore, a role for NAcc shell DA D1 receptors in CTA has been demonstrated by Fenu et al. (2001). Additionally, the consumption of a novel taste, independent of its intrinsic aversive/safe value, increases DA in both NAcc core and shell. However, familiar-aversive or -safe taste produces changes in DA release only into the NAcc core (Bassareo et al. 2002). The NAcc receives dopaminergic innervations from VTA

(Zahm and Heimer 1993), and it has been proposed that the PBN might influence NAcc DA activity via connections to the VTA (Hajnal and Norgren 2005).

The role of glutamate in the NAcc by its NMDA receptor activation seems to be involved in processing the aversive but not the safe taste memory formation (Ramirez-Lugo et al. 2006). In this regard, it has been demonstrated that natural or conditioned familiar-aversive stimulus produced significant increase of extracellular glutamate levels in NAcc (Saulskaya and Marsden 1995; Saul'skaya and Mikhailova 2004). These results could be related with the glutamatergic pathways coming to the NAcc. Thus, the possible mechanism for the participation of NAcc in aversive taste learning is related to the interaction between the glutamate inputs to the NAcc, from the IC and the BLA. However, it does not rule out the possibility that there could be other brain systems participating in the aversive taste memory along with the NAcc circuit (see Figure 1).

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