

## Neurobiology of Taste-recognition Memory Formation

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### Introduction

Recognition memory is the ability to assert the familiarity of things previously encountered. In the case of food, when an animal encounters a new taste, it hesitates to eat it, showing a reduced consumption—a neophobic response. However, when the new taste has no negative consequences, it becomes recognized as a safe signal, leading to an increase in its consumption (attenuation of neophobia). But if the new taste is associated with malaise, animals develop a long-lasting aversion to that taste—the taste cue becomes an aversive signal—rejecting it the next time they encounter it, being the taste the conditioned stimulus (CS) and the malaise inducing agent the unconditioned stimulus (US). This form of recognition memory is referred to as conditioned taste aversion (CTA) (Bermudez-Rattoni, 2004).

Both aversive and safe taste memories depend on the neural representation of the taste that probably remains temporarily stored in several brain regions in parallel where it might be processed in either direction (safe or aversive taste memory) (Bermudez-Rattoni, 2004). This neural representation has been called the taste memory trace (TMT) (Bermudez-Rattoni, 2004). However, it still remains to be demonstrated whether the TMT has two independent components (aversive and safe), or if there is only one TMT, which could be converted into an aversive TMT when it is associated with visceral malaise.

### CS signals

Taste information reaches forebrain structures such as the amygdala and the insular cortex (IC) and permanent or reversible lesions of these two structures impair taste memory formation (see Bermudez-Rattoni, 2004). Inside these structures information is processed by different mechanisms, among which the cholinergic system has been widely studied. It has been demonstrated by using microdialysis in freely moving rats a marked increase in the release of acetylcholine (ACh) in the IC induced by the first presentation of a new taste, compared to the release elicited by the presentation of a familiar taste like water (Miranda *et al.*, 2000). This is highly significant because taste novelty is a determinant factor in the establishment of gustatory memory (Miranda *et al.*, 2000). After several presentations of a given taste, there was a significant decrease of ACh release as the taste became familiar (Miranda *et al.*, 2000). These data point to an inverse relationship between taste familiarity and cortical ACh release. Since no gastric malaise was induced after saccharin presentation, these results suggest a participation of the muscarinic ACh receptors in the insular cortex when a novel taste becomes a safe familiar one. In this regard, several experiments have shown that a 2–4 h continuous period in which noxious consequences of food ingestion are absent is required to classify a gustatory stimulus as safe or neutral (Bermudez-Rattoni, 2004).

After the injection of scopolamine, an antagonist of muscarinic ACh receptors, in the IC before the first presentation of a taste that produces a robust neophobic response, consumption remained unaltered in the acquisition session. However, 1 day later, when saccharin was presented again, the animals that received scopol-

amine showed a strong neophobic response, as if it were the first time that they experienced this taste, indicating that scopolamine prevented a new taste from becoming familiar. Importantly, the attenuation of neophobia was impaired only if scopolamine was administered before or up to 2 h after the new taste (Gutierrez *et al.*, 2003).

### CS–US association

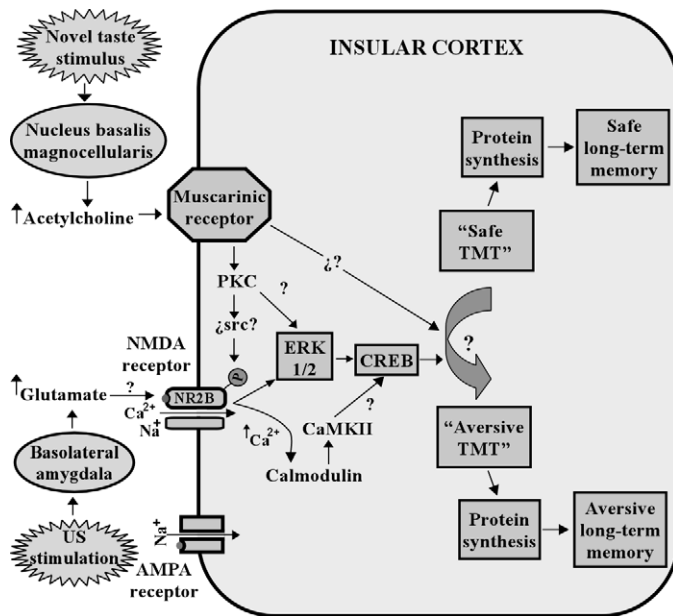
Synergistic interactions between cholinergic and glutamatergic systems seems to be critical for memory formation (for a review, see Woolf, 1996) and glutamate has been implicated in the consolidation of several memory tasks, such as inhibitory avoidance, the Morris water maze and CTA (Kim and McGaugh, 1992; Ferreira *et al.*, 2002).

Recently, it has been demonstrated by *in vivo* microdialysis that injection of LiCl, but not the presentation of saccharin, elicited a marked increase in glutamate release in the amygdala and a modest but significant release in the IC (Miranda *et al.*, 2002). In addition, while the injection of a low concentration of LiCl after saccharin presentation induces a weak CTA, a reliable and robust aversive CTA can be elicited with this low concentration of LiCl when accompanied by microinjections of glutamate directly into the amygdala (Miranda *et al.*, 2002). Furthermore, it has been shown that the application of AMPA, NMDA or metabotropic glutamate receptor antagonists into the amygdala after the new taste or before the LiCl is presented impaired the formation of long-term taste aversion memory (Yasoshima *et al.*, 2000). It was concluded that glutamatergic transmission is involved in the formation of the long-term gustatory memory that is associated with the altered hedonic change from safe to aversive TMT (Yasoshima *et al.*, 2000).

Similar results were found for NMDA receptors in the IC. Thus, NMDA receptor antagonists when applied in the IC either before or after the acquisition trial disrupted CTA (Ferreira *et al.*, 2002). For comparison, intracortical microinjection of the muscarinic antagonist scopolamine applied before the presentation of the new taste, but not afterwards, abolished aversive taste memory formation (Ferreira *et al.*, 2002). These results indicate that glutamate might convey the visceral input that eventually converges with the CS during the association and consolidation phases of aversive TMT formation. These data confirm that cholinergic activity is involved in the TMT formation, whereas glutamatergic activity participates in promoting the formation of an aversive TMT, probably suppressing the formation of a safe TMT (see Figure 1).

### Cortical (CS)–amygdala (US) interactions

Activity-dependent changes in the efficacy of synaptic transmission are considered to be of fundamental importance for memory formation. *In vivo* tetanic stimulation of the basolateral nucleus of amygdala induces long-term potentiation (LTP) in the insular cortex of adult rats, significantly increasing the synaptic responses to low



**Figure 1** Schematic representation of the intracellular elements of the proposed model for information processing in the IC during taste memory formation (TMT). The proposed two TMT are presented (safe TMT in the upper part and aversive TMT in the lower). For explanation see text.

frequency stimulation during a period of at least 1 h after stimulation and its induction in this projection before CTA training enhances the retention of this task (Escobar and Bermudez-Rattoni, 2000). These results suggest that the potentiation of the amygdala-cortical projection is a possible mechanism for memory-related functions performed by the insular cortex. Intracortical administration of NMDA receptor-competitive antagonist (3-2carboxypiperazin-4-yl-propyl-1-phosphonic acid, CPP) disrupts the acquisition of CTA, as well as the BLA-insular cortex-LTP induction *in vivo* (Escobar *et al.*, 2002). These results point to a cortical facilitation induced by amygdala stimulation that seems to be regulated by glutamate through its NMDA receptors in the IC.

As noted before, injection of a low dose of lithium chloride (25 mg/kg, i.p.) 30 min after novel taste consumption (saccharin 0.1%) induces a weak CTA, which can be improved by injection of glutamate into the amygdala (Miranda *et al.*, 2002). In an unpublished work, we showed that cortical microinjections of a NMDA antagonist reverse the memory-enhancing effect of BLA glutamate injection. This further supports an important amygdala-cortical interaction during CTA memory formation and a crucial role for glutamatergic system in the IC for CTA consolidation.

As shown in Figure 1, consumption of a new taste leads to sustained tyrosine phosphorylation of the NR2B subunit of the NMDA receptor in the IC (Rosenblum *et al.*, 1997) and application of tyrosine kinase inhibitors block aversive memories, including taste aversion (Yasoshima and Yamamoto, 1997). This phosphorylation is dependent on the muscarinic receptors activation by the taste and can be reproduced by the administration of carbachol in the IC (Rosenblum *et al.*, 1995). Together, these results indicate that there is

an inverse relationship between the familiarity of the taste and the phosphorylation of the NR2B subunits. Although the role of this phosphorylation remains to be established, it might facilitate the formation of the malaise-induced aversion (Miranda *et al.*, 2002; Gutierrez *et al.*, 2003), since this phosphorylation potentiates the NMDA channel activity and has also been related with the activation of intracellular signaling (Mizuno *et al.*, 2003). Thus, after phosphorylation, the NMDA receptor in the IC might generate an increased response to the stimulation coming from the amygdala and carrying the US information and transforming the safe in aversive TMT.

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