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Review

Molecular mechanisms involved in taste learning and memory

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Abstract: Taste learning, and particularly conditioned taste aversion (CTA), is an adaptive learning involving complex brain mechanisms and molecular pathways. Taste learning and CTA are critical behaviors for survival, and the knowledge of the molecular bases involved in the acquisition, retention and extinction of CTA can help to understand the brain mechanisms of normal and altered taste learning. The aim of this review is to describe recent findings on the molecular mechanisms of taste learning, from the genetic, receptors, and intracellular and extracellular signaling biological levels. We can conclude that some molecular pathways and processes for the acquisition of taste learning and the formation of taste memories are well identified. However, new molecular, neurobiological and behavioral studies are needed to thoroughly elucidate the complexity of the taste system and the neural mechanisms of CTA.

Keywords: conditioned taste aversion; gene expression; molecular signaling; receptors; taste learning

1. Introduction

Conditioned taste aversion (CTA) is a form of taste learning identified in many species. CTA results from the association of a taste stimulus with gastro-intestinal malaise, which allows an organism to avoid potentially noxious foods. The acquisition of this conditioning reduces the risk of poisoning by possible dangerous taste stimuli and, therefore, is a critical learning for survival, especially in omnivorous species [1]. This learning depends on complex neural networks that include the brainstem and subcortical and cortical areas [1,2]. Several brain regions, as the gustatory insular cortex [3-5], the amygdala [6-9], thalamus [10], and the parabrachial nucleus [10,11], have been identified as part of the neurobiological networks involved in CTA. For example, the gustatory

insular cortex is a necessary structure for the acquisition of CTA [2], and it has been shown that the inactivation of this area disrupts or prevents the acquisition of taste aversion [3]. The pontine parabrachial nucleus is also a key region for CTA, and the functional connectivity between this nucleus and the gustatory insular cortex is selectively involved in the acquisition of CTA, but not in the formation of safe taste memory [12]. In addition to the critical structures necessary for the acquisition of CTA, as the gustatory insular cortex and the parabrachial nucleus, various studies have pointed to the possibility that the magnitude of a taste aversion can be modulated by other brain areas and connections [13-17]. Thus, the connections between the gustatory insular cortex and the amygdala [8,18,19] and between the amygdala and the brainstem nuclei involved in CTA [6,9,16] may influence in the intensity of a learned taste aversion.

The nucleus of the solitary tract (NTS), the posteromedial parabrachial nucleus, the lateral hypothalamus, the bed nucleus of the stria terminalis, and the ventroposteromedial and lateral thalamus, as well as the VII, IX and X cranial nerves, are part of the structures and pathways involved in processing taste and visceral information [1]. Taste processing starts in the taste cells of the tongue and the oral cavity, and the taste pathway projects to the NTS via the VII, IX and X cranial nerves [20], and then ipsilaterally to the parabrachial nucleus, the lateral hypothalamus, the bed nucleus of the stria terminalis, the amygdala and the thalamus. Finally, the taste pathway reaches the gustatory insular cortex [1,5]. In addition to the gustatory insular cortex and its connections, the brain substrate of taste learning includes other structures which are non-specific for CTA, as for example the medial prefrontal cortex and the nucleus accumbens. It has been shown that changes in extracellular signals of the prefrontal cortex and nucleus accumbens are related to the acquisition and expression of CTA [21].

Several molecular mechanisms involved in the acquisition of CTA and the formation of taste memory trace have recently been described [22]. These mechanisms involve gene expression processes, the activity of certain neurotransmitter receptors, and different intracellular and extracellular signaling pathways, among others. This review aims to describe recent findings on relevant molecular processes involved in taste learning in general, and CTA in particular. Knowledge of these mechanisms may be of interest to identify the complex neurobiological processes of normal and altered taste learning and memory.

2. Gene expression and taste learning

Recent studies show that specific transcriptional processes in the gustatory insular cortex of the rat seem to be necessary for taste learning, and taste experience and novel taste experience affect transcription in this cortical area during taste memory consolidation [23]. More specifically, novel or familiar taste learning seems to induce different actions of the transcriptome in this region. Consolidation of positive and negative taste learning also requires transcriptional activity in the gustatory insular cortex [23]. In rodent, novel taste learning induces biochemical changes in the gustatory insular cortex, such as increased cholinergic activity and alterations in protein phosphorylation [24,25], which facilitate taste memory consolidation [26,27]. Besides, it has been shown that taste memory consolidation can be affected after the inhibition of protein synthesis in the gustatory insular cortex [28,29]. In a recent study, the infusion of protein synthesis inhibitors into the gustatory insular cortex during long-term memory formation and consolidation of CTA impaired the formation of long-term memory, but had no effect on memory persistence when it was infused 3 days after the acquisition, and enhanced the memory persistence when it was infused 14 days after the

acquisition [30]. Thus, the long-term memory of CTA seems to be affected by protein synthesis inhibitors even several days following the acquisition of taste aversion memory.

Some of the immediate early genes of the gustatory insular cortex involved in different forms of taste learning, as the activity-regulated cytoskeleton associated protein (Arc)/Arg3.1, regulate the homeostasis of excitatory synapses and mediate processes of synaptic plasticity and the long term memory of CTA [31,32]. The specific role of the Arc/Arg3.1 may vary depending on the type of taste learning, because it has been found that novel taste learning increases and reduces the expression of Arc/Arg3.1 in the gustatory insular cortex according to different time points, and these transcriptional changes can last for hours and are greater compared to familiar taste [23]. Moreover, Inberg et al. have even shown a lateralization of the expression of Arc/Arg3.1 in the gustatory insular cortex through a left-right lateralization index during processing novel taste stimuli [33]. With respect to the acquisition of CTA, the involvement of the protein synthesis process in the gustatory insular cortex has been consistently demonstrated [34].

The expression of other molecules has also been identified with processes of neural plasticity and taste learning. In particular, the expression of brain-derived neurotrophic factor (BDNF) in the basolateral amygdala and the gustatory insular cortex induces long-term synaptic plasticity, and it has been shown that the acquisition of CTA prevents this long-lasting BDNF-induced strengthening of synaptic plasticity [35]. Therefore, the gene expression of BDNF in the gustatory insular cortex is one of the molecular mechanisms that induce long-term synaptic changes related to memory processes in CTA.

C-fos, Homer1a or the transcription factor Elk-1 are also some of the gene expression mechanisms described in the gustatory insular cortex in different taste learning forms [36-38]. The role of the proteins and factors derived from some of these gene expression processes is not completely understood, although possible functions on the structure and activity of synapses are suggested [39]. In summary, the gene expression in the gustatory insular cortex, as well as in others critical structures of the neural circuit of CTA, is a molecular mechanism of taste learning which may contribute to the long-trace CTA [26]. Table 1 summarizes the information of this section, as well as information of the following sections.

3. Receptors involved in taste learning and CTA

The acquisition of CTA and taste learning requires the activity of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-D-aspartate (NMDA) and muscarinic receptors in the gustatory insular cortex, and metabotropic glutamate receptors, β-adrenergic and dopaminergic receptors in the gustatory insular cortex contribute to the acquisition of novel taste memory but not to the retrieval [40]. For appetitive taste learning, it has been demonstrated the activity of muscarinic receptors [39,41], and the GABA-A and cholinergic receptors have opposite patterns of activity during novel vs. familiar taste recognition [42]. Muscarinic receptors of acetylcholine (mAChR) are also related to the taste neophobia phenomenon [39]. Thus, cholinergic neurotransmission seems to be a molecular mechanism of taste-recognition memory [39].

The specific plastic changes occurring in the synapses during acquisition and memory of taste learning are unknown. However, the glutamatergic neurotransmission seems to be a key molecular mechanism for synaptic plasticity in the taste pathway. For instance, the acquisition of CTA induces tyrosine phosphorylation of the NR2B subunit of the NMDA receptor (NMDAR) in the gustatory

Table 1. Molecules involved in taste learning and memory, and proposed brain regions and functions (in parentheses)

Gene expression	Receptors	Cell signaling
Arc/Arg3.1 (GIC; CTA memory)	AMPA (GIC; CTA acquisition)	CaMKIIα (GIC; SP, novel taste memory, CTA acquisition)
c-fos (GIC; SP and LT taste memory)	NMDA (GIC; CTA acquisition and taste learning)	PKA (GIC and amygdala CTA memory)
Homer 1a (GIC; SP and LT taste memory)	NR1 (PFC; SP in CTA acquisition)	PKC (GIC and amygdala; LT plasticity and CTA memory)
Transcription factor Elk-1 (GIC; SP and LT taste memory)	NR2A-2B (GIC; CTA acquisition and taste processing)	NSF (amygdala and PEC; SP and taste memory)
BDNF (GIC and amygdala; SP in taste memory and CTA)	GluR2 (amygdala and PEC; SP and taste memory)	cAMP (GIC; SP and taste memory)
	mACh (GIC; neophobia, SP and CTA acquisition)	Adenylyl cyclase (GIC; SP and taste memory)
	DA (GIC; novel taste memory)	ERK1/2 (GIC; novel taste processing, SP and taste memory)
	TrkB (GIC; taste memory)	Myosin II (IFC; structural plasticity and CTA memory)
	β-adrenergic (GIC; novel taste memory)	Actin (IFC; structural plasticity and CTA memory)
	D1 (GIC; novel taste processing and memory)	PSD-95 (GIC; SP and taste learning)
	GABA-A (GIC; taste recognition)	PI3K (GIC; SP and CTA memory)

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor; *(Arc)/Arg3.1*, activity-regulated cytoskeleton associated protein/Arg3.1, an immediate early gene (IEG); *BDNF*, brain-derived neurotrophic factor; *CaMKIIα*, calcium calmodulin-dependent protein kinase IIα; *CTA*, conditioned taste aversion; *DA*, dopamine receptor; *ERK*, extracellular signal-regulated kinases 1/2; *GIC*, gustatory insular cortex; *GluR2*, GluR2 subunit-containing AMPA receptor; *IFC*, infralimbic cortex; *LT*, long-term; *mACh*, muscarinic receptor of acetylcholine; *NMDA*, N-methyl-D-aspartate glutamate receptor; *NR1-2B-2A*, subunits of the NMDA receptor; *NSF*, N-ethylmaleimide-sensitive factor; *PEC*, perirhinal cortex; *PFC*, prefrontal cortex; *PI3K*, phosphoinositide 3-kinase; *PKA*, protein kinase A; *PKC*, protein kinase C; *PSD-95*, NR2B-associated protein; *SP*, synaptic plasticity; *TrkB*, BDNF receptor.

insular cortex [43,44], and expositions to a novel taste increase the phosphorylation of the NR2A and NR2B subunits also in the gustatory insular cortex [45]. The NMDAR-mediated mechanisms described in processing of novel taste information involve dopaminergic signaling. Specifically, David et al. have shown that the tyrosine phosphorylation of the NR2B Y1472 subunit of the NMDAR depend on the activity of the dopamine receptor D1, and this phosphorylation is necessary for the extracellular signal-regulated kinase 1/2 (ERK1/2) activation and for processing novel taste stimuli [44]. Other kind of glutamate receptor involved in the acquisition of CTA is the NR1 subunit, particularly in the synaptic plasticity process observed in the prefrontal cortex [46]. In taste learning, it is possible that these glutamatergic mechanisms of plasticity allow the association between stimuli optimizing necessary brain connections. Because the associative processes in CTA may emerge several hours after the taste experience, the NMDA-dependent plasticity in this learning could involve different time points. In rats, two parallel gustatory memory traces for novel tastes have been recently described in a recent study. A short-duration (around 3 hours) robust trace in the gustatory

insular cortex regulated by a calcium calmodulin-dependent protein kinase IIα (CaMKIIα)-AMPA glutamate receptor pathway, which in turn depends on the NMDAR, and a long-duration (up to 8 hours) trace which depends on the previous one [47]. The NMDAR activity in the basolateral amygdala-gustatory insular cortex projection critical for CTA memory-formation involves the activation of protein kinase C (PKC) and protein kinase A (PKA). In a recent study, Rodríguez-Durán and Escobar have shown that the activity of the NMDAR and the phosphorylation of PKC and PKA are necessary for the formation of CTA memory, and that the activity of NMDAR and PKC, but not PKA, is related to the long-term plasticity processes occurring in the gustatory insular cortex in CTA [48]. Visceral information induces NMDAR activation and PKA and PKC phosphorylation in the gustatory insular cortex through molecular mechanisms shared with the effect of taste stimulation during the acquisition of CTA [49].

Recently it has been shown that regulation of protein degradation via the ubiquitin proteasome system is a crucial mechanism of synaptic plasticity in different types of learning. This mechanism seems to depend on the activity of certain neurotransmitter receptors. More specifically, the NMDAR-dependent upregulation of proteasome activity observed in the gustatory insular cortex after novel taste learning is a necessary molecular mechanism for the association of novel taste with malaise during the acquisition of CTA [50]. In the CTA paradigm, Rosenberg et al. have shown that the proteasome activity in the gustatory insular cortex is increased 4 hour after the exposure to a novel taste [51]. This effect was dependent on the NMDAR and the CaMKII signaling during acquisition, and suggests that the acquisition of CTA involves NMDAR-dependent proteasome activity in the gustatory insular cortex. In another study, Rosenberg et al. found that the proteasome-mediated degradation in the gustatory insular cortex was reduced 20 min after the exposure to a novel taste [50]. This effect was dependent on the mAChR. Thus, the reduction of the proteasome-mediated degradation recorded in the gustatory insular cortex after novel taste consumption seems to depend on the mAChR but not the NMDAR activity [50]. These studies suggest that the memory of taste familiarity after novel taste exposures involves mAChR-dependent reduced proteasome activity.

4. Taste learning and intracellular signals

Recent complex molecular studies on taste learning and CTA have determined the involvement of numerous molecules in the intracellular and extracellular signaling pathways. Thus, increased activity of the N-ethylmaleimide-sensitive factor (NSF), a protein molecule participating in membrane fusion through SNAP receptor proteins (SNAREs), has been observed in the basolateral amygdala and the perirhinal cortex during habituation of taste neophobia and taste recognition memory [52]. The synaptic plasticity and memory processes mediated by NSF in these areas involve cellular signaling pathways that include the extracellular activation of GluR2 subunit-containing AMPA receptors [52].

Intracellular signaling that triggers taste memory formation is a complex process that includes a multitude of molecular mechanisms. It has been proposed that novel taste stimulation activates dopamine receptors in the gustatory insular cortex that increase cAMP levels through the activation of adenylyl cyclase, activating cAMP-dependent PKA [49]. As a result, PKA induces CREB phosphorylation and expression of genes related to synaptic plasticity and long-term taste memory formation. The mechanisms of synaptic plasticity for taste memory consolidation may also include the activation of mAChR and PKC, as well as an enhancement of the activity of the extracellular signal-regulated kinases (ERK) [49]. On the other hand, the visceral information induces CaMKII and

PKA activation and CREB phosphorylation, probably also promoting protein synthesis [49]. With respect to the mechanisms of signaling initiated by the above mentioned BDNF molecule, intracortical microinfusion of BDNF in the gustatory insular cortex reduces the magnitude of the taste aversion and enhances the extinction of CTA in rats [53]. BDNF reduces CTA even if administered 10 days after the acquisition stage, and it also has been shown that the activity of this molecule in the gustatory insular cortex is essential for the persistence of CTA several hours after the association between stimuli [54]. The contribution of BDNF to taste memory has also been described in a study in which microinfusion of this factor in the gustatory insular cortex previous to the acquisition of CTA enhanced the retention of the taste aversion [55]. The functional effects of the BDNF signaling on the gustatory insular cortex seem to be dependent on the activity of the TrkB receptor since these effects can be blocked by the infusion of K252a, an antagonist of BDNF receptors [53].

Recent studies have also described different molecular mechanisms of structural synaptic plasticity during CTA memory extinction. Actin rearrangement is one of the structural changes that may strengthen the synapses, and it also has been shown actin rearrangement and increased synaptic density in the infralimbic cortex, a subregion of the ventromedial prefrontal cortex, during the extinction of CTA memory [56]. A possible mechanism underlying to the structural plasticity which occurs during CTA memory extinction seems to involve myosin II phosphorylation. Microinfusion of inhibitors of the myosin II ATPase into the infralimbic cortex blocks the actin rearrangement and CTA memory extinction, which may indicate that increased myosin II in the infralimbic cortex induces structural cellular changes aimed to modulate the formation of new synapses through structural plasticity mechanisms during CTA memory extinction [56]. Other plasticity processes involving NMDAR and intracellular protein signaling have been described in novel taste learning. In the gustatory insular cortex, these processes include elevations of the postsynaptic density of the PSD-95 protein in association with phosphorylated NR2B subunit of the NMDAR [57]. Further signaling processes and receptors, as the D2 dopamine receptor, are also being investigated in the context of taste learning [58]. In CTA, intracellular phosphoinositide 3-kinase (PI3K) signaling through the phosphorylation of the AKT kinase is increased after the acquisition of CTA and decreased after CTA extinction, which suggests that the PI3K signaling is a molecular process implicated in the consolidation of aversive taste memories [59]. All of these are some of the signaling mechanisms described in taste learning.

5. Conclusion

Several molecular mechanisms of taste learning and memory have been identified in the last few years. These findings have improved our knowledge of the neurobiology of this kind of learning. The expression of specific genes seems to be necessary for the synaptic plasticity processes related to taste learning and, particularly, to CTA. Perhaps the best-known molecular mechanism of taste learning and memory include the activity of certain neurotransmitter receptors, as the mAChR, AMPAR and NMDAR. All these mechanisms initiate the activity of various intracellular and extracellular signaling pathways which result in the induction of structural and functional plasticity related to taste learning and memory. However, knowledge of the functioning of these and other signaling pathways underlying taste learning and memory is limited. The complexity of the molecular mechanisms associated with taste learning and memory requires new and advanced studies to discover the molecular details that underlie this peculiar type of learning.

Conflict of interest

The authors declare no conflict of interest.

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