Role of cholinergic system on the construction of memories: Taste memory encoding

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Abstract

There is a large body of evidence suggesting that cholinergic activity is involved in memory processes. It seems that cholinergic activity is essential to learn several tasks and recent works suggest that acetylcholine plays an important role during the early stages of memory formation. In this review, we will discuss the results related to taste memory formation, focusing particularly on the conditioned taste aversion paradigm. We will first give evidence that nucleus basalis magnocellularis is involved in taste memory formation, due to its cholinergic projections. We then show that the cholinergic activity of the insular (gustatory) cortex is related to the taste novelty, and that the cholinergic signals initiated by novelty are crucial for taste memory formation. Then we present recent data indicating that cortical activation of muscarinic receptors is necessary for taste trace encoding, and also for its consolidation under certain circumstances. Finally, interactions between the cholinergic and other neuromodulatory systems inducing intracellular mechanisms related to plastic changes will be proposed as important processes underlying gustatory memory trace storage.

Keywords: Acetylcholine; Amygdala; Conditioned taste aversion; Gustatory learning; Insular cortex; Memory trace; Muscarinic receptor; Neophobia; NMDA receptor; Novelty; Scopolamine

1. Introduction

A substantial body of literature has suggested that in humans memory deficits associated with Alzheimer’s disease and normal aging can be attributed to degeneration of cholinergic basal forebrain neurons (for review: Muir, 1997). Thus, numerous anatomical and behavioral studies were developed to investigate in animals the relationship between the neurons located in this basal forebrain complex and the maintenance of normal cognitive functions. Furthermore, in recent years accumulated evidence demonstrates that the cholinergic receptors set off a series of intracellular events related to the plasticity of the central nervous system related with memory encoding.

Behavioral studies on animal models demonstrate that lesion-induced damage to the nucleus basalis magnocellularis (NBM), and their cholinergic projections from to the neocortex induce deficits related to cognitive impairments, especially on attentional processes (for review: Sarter & Bruno, 1997), as well as on learning and memory processes (for review: Dunnett, 1993; Dunnett, Everitt, & Robbins, 1991; Everitt & Robbins, 1997; Wenk, 1997; Woolf, 1998). The assumption that cortical cholinergic projections were involved in learning and memory was also reinforced by studies related to cortical acetylcholine (ACh) activity. In this regard, it has been demonstrated, for example, that ACh modifies cellular responses in vivo, and modulates receptive plastic changes in the auditory cortex (Metherate & Ashe, 1993; Weinberger & Bakin, 1998) and somatosensory cortex (Dykes, Metherate, & Tremblay, 1990). Cortical ACh was thus hypothesized to modulate the general efficacy of the cortical processing of sensory or...
associational information. Specifically, cortical cholinergic inputs could mediate the subjects’ abilities to detect and select stimuli and associations for extended processing and to allocate the appropriate processing resources to these functions. Some authors proposed that the cholinergic system participates in higher cognitive functions through neural network modeling (for review: Myers et al., 1996).

The purpose of this paper is to provide recent evidence about the stages in which the cholinergic activity is involved in memory formation. We will give evidence that the cholinergic system plays an important role during the early stages of taste memory formation, by modulating the signaling of the taste novelty, and then participating in several intracellular mechanisms related to plastic events that could be essential for taste memory encoding.

2. Conditioned taste aversion and forebrain structures

A reliable and robust paradigm to study the different processes during taste memory formation is the conditioned taste aversion (CTA). CTA is an example of adaptive learning in which an animal acquires aversion to a novel taste, the conditioned stimulus (CS), when it is followed by digestive malaise, generally induced by lithium chloride (LiCl), the unconditioned stimulus (US). The anatomical substrates responsible for CTA learning have been well established (see Bermudez-Rattoni & Yamamoto, 1998). From the taste receptor cells of the tongue and mouth, the VII, IX, and X cranial nerves carried the gustatory information, reaching first the nucleus of the solitary tract and then the dorso-lateral parabrachial nucleus in the midbrain. From the midbrain there are two taste pathways: one reaches the hypothalamus, zona incerta of stria terminalis and the amygdala, and another reaching the ventro-posterior-medial nucleus of the thalamus, which in turn reaches the insular gustatory neocortex (IC). The visceral pathways carrying the induced malaise information reaches the vagus nerve and that the nucleus of the solitary tract and the external lateral subnucleus of the parabrachial nucleus and finally reaching the central nucleus of the amygdala and the paraventricular hypothalamic nucleus (Bermudez-Rattoni & Yamamoto, 1998).

Grill and Norgren (1978) demonstrated that chronically descerebrate rats did not show CTA, stressing the importance of forebrain areas in this paradigm. Thereafter, a number of studies had focused on the role of amygdala and IC on CTA memory formation (Bahar, Samuel, Hazvi, & Dudai, 2003; Bermudez-Rattoni & McEachern, 1991; Bermudez-Rattoni & Yamamoto, 1998; Gallo, Roldan, & Bures, 1992; Yasoshima, Morimoto, & Yamamoto, 2000). Thus, permanent, reversible lesions or pharmacological manipulations of both structures severely impaired acquisition of CTA (for review: Bermudez-Rattoni & Yamamoto, 1998). As we will see later, some recent data suggest that the amygdala is more related to the US than the CS processing (Gallo et al., 1992; Miranda, Ferreira, Ramirez, & Bermudez-Rattoni, 2002; Roldan & Bures, 1994), although the precise roles of the central and basolateral nuclei of amygdala in CTA acquisition remain unclear (reviewed by Lamprecht & Dudai, 2000). Concerning the IC, located in the temporal cortex of the rat, at the confluence of the medial cerebral artery and the rhinal sulcus, several studies have confirmed that the IC is involved in taste processing and memory formation, and particularly mediation of associative aspects of taste responses, but not the innate hedonic responses to taste (Braun, Kiefer, & Ouellet, 1981). The amygdala and IC are not the only forebrain structures important for CTA acquisition. In the next section we will review recent studies showing the importance of the NBM in CTA memory formation, a structure which projects to both amygdala and IC.

3. Cholinergic basal forebrain structures

3.1. Nucleus basalis magnocellularis

The cholinergic basal forebrain complex is a group of relatively large neurons located in the ventral region of the mammalian brain. It includes the medial septal area, the vertical and horizontal limbs of the diagonal band of Broca, and the nucleus basalis of Meynert in humans and primates, also called the NBM in the other mammals. The basal forebrain complex provides widespread cholinergic, and also GABAergic, innervations throughout the brain: the septal area and the vertical limb of the diagonal band of Broca project essentially to the hippocampus, the horizontal limb of the diagonal band of Broca to the olfactory bulb and the NBM to amygdala and the whole neocortex (Mesulam, Volicer, Marquis, Mufson, & Green, 1986). Moreover, the IC receives one of the strongest cholinergic cortical projections from the NBM (Mesulam et al., 1986), which in turn receives inputs from only a few cortical regions, including the IC (Mesulam & Mufson, 1984). In several laboratories, it has been demonstrated that the ascending pathways from the NBM to the cortex are related with the ability to learn aversively motivated tasks, especially inhibitory avoidance learning (for review: Everitt & Robbins, 1997; Wenk, 1997). In CTA, it has been demonstrated that excitotoxic-induced lesions of the NBM performed before acquisition impaired CTA (Gonzalez, Miranda, Gutierrez, Ormsby, & Bermudez-Rattoni, 2000; Gutierrez et al., 1999a; Gutierrez et al., 1999b; Lopez-Garcia, Fernandez-Ruiz, Escobar, Bermudez-Rattoni, & Tapia, 1993; but see Kesner, Berman,
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