

Amygdala-dependent Mechanisms Underlying Memory Retrieval of Conditioned Taste Aversion

Yasunobu Yasoshima¹, Takashi Yamamoto² and Kazuto Kobayashi¹

¹Department of Molecular Genetics, Institute of Biomedical Sciences, Fukushima Medical University, Fukushima 960-1295, Japan and ²Department of Behavioral Physiology, Graduate School of Human Sciences, Osaka University, Osaka, Japan

Correspondence to be sent to: Yasunobu Yasoshima, e-mail: yasosima@fmu.ac.jp

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Introduction

Conditioned taste aversion (CTA) is an associative learning phenomenon in which ingestion of a novel tasting food or fluid (conditioned stimulus, CS) is paired with visceral malaise (unconditioned stimulus, US) (Yamamoto *et al.*, 1994). Conditioned animals avoid ingesting the tastant previously associated with the condition of sickness. Since CTA is established by a single pairing of the CS and US, it is easy to distinguish different memory-related phases: acquisition, consolidation, reconsolidation and retrieval. This unique property of CTA is useful in identification and manipulation of the underlying physiological and molecular mechanisms responsible for each memory phase.

There is a large amount of evidence that the amygdala plays an important role in the acquisition and retention of CTA (see, for example, Miranda *et al.*, 2003). The amygdala receives a variety of sensory inputs, including gustatory and visceral information. It also has many kinds of transmitter systems, such as glutamatergic, noradrenergic (NAergic), dopaminergic and other innervations, and contains inhibitory interneurons containing γ -aminobutyric acid (GABA) as a neurotransmitter. Although there have been several reports about the roles of amygdalar transmitter systems in CTA acquisition, the functioning of the transmitter systems responsible for the retrieval has not been completely elucidated. In this paper, we summarize our findings regarding amygdalar mechanisms for retrieval of CTA memory.

Involvement of the amygdala in memory retrieval

There are several critical brain regions that affect CTA formation: the parabrachial nucleus, the parvocellular region of the ventroposteromedial nucleus of the thalamus (VPMpc), the basolateral nucleus of the amygdala (BLA) and the cortical gustatory area (CGA) in the insular cortex (Yamamoto *et al.*, 1994). Lesion of one of these structures before conditioning impedes the acquisition of CTA (Yamamoto *et al.*, 1994). However, the brain sites responsible for the retention of CTA remain unclear. Lesions in the CGA, hippocampus (HIP) or the central nucleus of the amygdala (CeA) that are formed after conditioning do not affect retention and retrieval of CTA in a first retention test; instead, lesion of the CGA or HIP accelerated extinction. On the other hand, lesion of the VPMpc or BLA formed after conditioning impaired retention and retrieval. Hence, these results suggest that the BLA, not the CGA, is involved in retrieval of CTA memory (Yamamoto, 1994).

In an electrophysiological study in freely behaving animals, the taste responses to the CS in BLA neurons during retrieval were enhanced after conditioning. In contrast, the activity of some CeA neurons was suppressed during CS presentation (Yasoshima *et al.*, 1995). These results are consistent with the notion that the BLA is involved in the retrieval process.

Transmitter systems in the amygdala

Glutamatergic transmission

When an AMPA receptor antagonist, CNQX, was infused into the BLA in conditioned rats before the retention test, the rats drank a larger amount of the CS, compared to rats infused with vehicle solution. However, the same rats infused with CNQX showed a strong aversion to the CS in a subsequent test without drug infusion. The reversible and transient memory deficit caused by intra-BLA CNQX infusion was also induced in the stronger CTA formation developed using the twice conditioning procedure. On the contrary, infusions of an NMDA receptor antagonist or a metabotropic receptor antagonist, MCPG, before the retention test did not cause memory disruption (Figure 1). These results suggest that the retrieval process is mediated by the activation of AMPA receptors, but not NMDA or metabotropic receptors, in the BLA (Yasoshima *et al.*, 2000). The results also suggest that blocking of AMPA receptors in the BLA does not modify the CTA memory trace, while blocking of NMDA receptors in the BLA during reactivation of CTA memory significantly attenuates retention of CTA memory (Figure 1). This latter result suggests that NMDA receptors in the BLA are involved in the reconsolidation of CTA memory.

NAergic transmission

Recent findings indicate that NAergic function is involved in CTA memory formation. Although there have been many studies about the involvement of NAergic transmission in the amygdala, the

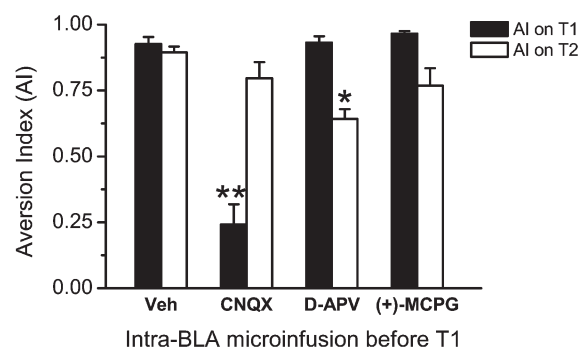


Figure 1 Effects of blocking glutamatergic receptor subtypes in the BLA on the retrieval of CTA memory. An AMPA receptor antagonist, CNQX, but not an NMDA receptor antagonist, D-APV, or a metabotropic receptor antagonist, (+)-MCPG, disrupted retrieval in the T1 test. The rats infused with CNQX in the T1 test showed a strong aversion to the CS in the T2 test. Veh, vehicle. * $P < 0.05$, ** $P < 0.01$, in comparison to the corresponding indices in the Veh-infused group, Tukey's test. [Data from an unpublished figure of Yasoshima *et al.* (2000).]

contribution of the NAergic system during each memory phase has not been clearly elucidated. Mice heterozygous for a mutation in the tyrosine hydroxylase gene showed rapid extinction of CTA (Kobayashi *et al.*, 2000). When the NAergic function in the mutants was upregulated by an i.p. injection of desipramine, an uptake inhibitor of NA, after conditioning, memory deficit was restored. These results suggest that the NAergic system plays an important role in retention of CTA memory.

GABA/benzodiazepine transmission

CTA retrieval was disrupted by an i.p. injection of midazolam (MDZ, 1.5 mg/kg), a benzodiazepine (BDZ) agonist, in conditioned animals. The disruption induced by MDZ was reversible and transient, because a strong aversion to the CS was apparent in a subsequent test in the same animals. When MDZ was infused into the rat BLA, the latency for rejection of intraorally infused CS was longer than that in PBS-infused rats (Yasoshima *et al.*, unpublished data). These results suggest that activation of GABA_A/BDZ receptors in the BLA reversibly impairs retrieval of CTA memory, although the transient activation of the inhibitory system in the BLA does not destroy the CTA memory trace.

Conclusion

Retrieval of the CTA memory and motor commands elicited by CTA memory reactivation is mediated by activation of AMPA receptors and inhibited by GABA_A/BDZ receptors in the BLA. The NAergic function in the amygdala facilitates memory formation.

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