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Review

Out with the old and in with the new: Synaptic mechanisms of extinction in the amygdala

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ABSTRACT

Considerable research indicates that long-term synaptic plasticity in the amygdala underlies the acquisition of emotional memories, including those learned during Pavlovian fear conditioning. Much less is known about the synaptic mechanisms involved in other forms of associative learning, including extinction, that update fear memories. Extinction learning might reverse conditioning-related changes (e.g., depotentiation) or induce plasticity at inhibitory synapses (e.g., long-term potentiation) to suppress conditioned fear responses. Either mechanism must account for fear recovery phenomena after extinction, as well as savings of extinction after fear recovery.

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1. Introduction

Pavlovian fear conditioning is a form of associative learning that is an instrumental model for understanding the molecular and synaptic basis of memory formation (Johansen et al., 2011; Maren, 2005; Pape and Pare, 2010; Sah et al., 2008). Among its many advantages, Pavlovian fear conditioning is rapidly acquired, requiring only a single aversive experience to generate a long-term memory. In this procedure, pairing an innocuous conditioned stimulus (CS), such as a tone, with an aversive footshock unconditioned stimulus (US) produces a robust and enduring conditioned fear response (CR) to the CS. The neural substrates underlying this form of learning are well-characterized, and considerable evidence indicates that neurons in the amygdaloid complex, particularly those in the basolateral amygdala (BLA), play an essential role in encoding the CS–US associations that underlie long-term fear memories (Davis and Whalen, 2001; Fanselow and Poulos, 2005; LeDoux, 2000; Maren, 2001; Maren and Quirk, 2004).

Within the amygdala, an abundance of research indicates that long-term potentiation (LTP) is a mechanism for fear conditioning (Blair et al., 2001; Davis and Whalen, 2001; Fanselow and Poulos, 2005; Goosens and Maren, 2002; LeDoux, 2000; Maren, 2001; 1999; Maren and Quirk, 2004; Sigurdsson et al., 2007). Amygdaloid LTP was first described in extracellular field recordings *in vivo* (Clugnet and LeDoux, 1990; Racine et al., 1983) and subsequently confirmed by intracellular recordings of synaptic currents in lateral nucleus (LA) neurons *in vitro* (Chapman and Bellavance, 1992; Chapman et al., 1990). Soon after the discovery of LTP, it was appreciated that its Hebbian nature would allow strong aversive stimuli, such as footshock USs, to associatively potentiate weak CS inputs thereby enabling the CS to drive fear CRs (Maren and Fanselow, 1996). Some key findings consistent with this view are that both fear conditioning and amygdaloid LTP are prevented by *N*-methyl-D-aspartate (NMDA) receptor antagonists (Chapman and Bellavance, 1992; Lee and Kim, 1998; Maren et al., 1996; Maren and Fanselow, 1995; Miserendino et al., 1990), the induction of amygdalar LTP is sensitive to stimulus contingencies that support fear conditioning (Bauer et al., 2001), fear conditioning induces LTP-like changes at amygdala synapses (McKernan and Shinnick-Gallagher, 1997; Rogan et al., 1997; Tsvetkov et al., 2002) including AMPA receptor insertion (Rumpel, 2005), and single-unit correlates of fear conditioning in the amygdala are eliminated by NMDA receptor antagonists (Goosens and Maren, 2004). Indeed, recent evidence indicates that optogenetic induction of LTP in auditory thalamic afferents in the amygdala is sufficient to support fear memory and that long-term depression (LTD) of these inputs after learning yields retention impairments (Nabavi et al., 2014).

Once fear conditioning has been acquired, however, it is much less clear how new learning about an aversive CS is encoded by amygdalar synapses that have already been modified by conditioning. One form of post-conditioning learning that has attracted considerable attention is extinction, a form of learning that occurs when a CS is arranged to no longer predict the US (i.e., the CS is presented alone) (Jovanovic and Ressler, 2010; Maren, 2011; Milad and Quirk, 2012; Orsini and Maren, 2012; Pape and Pare, 2010). After fear conditioning, extinction procedures lead to a reduction in the magnitude and frequency of conditioned responses, including freezing behavior. A parsimonious view of extinction learning is that extinction results from a loss of associative strength accrued during conditioning (Rescorla and Wagner, 1972). By this view, the loss of conditional responding after

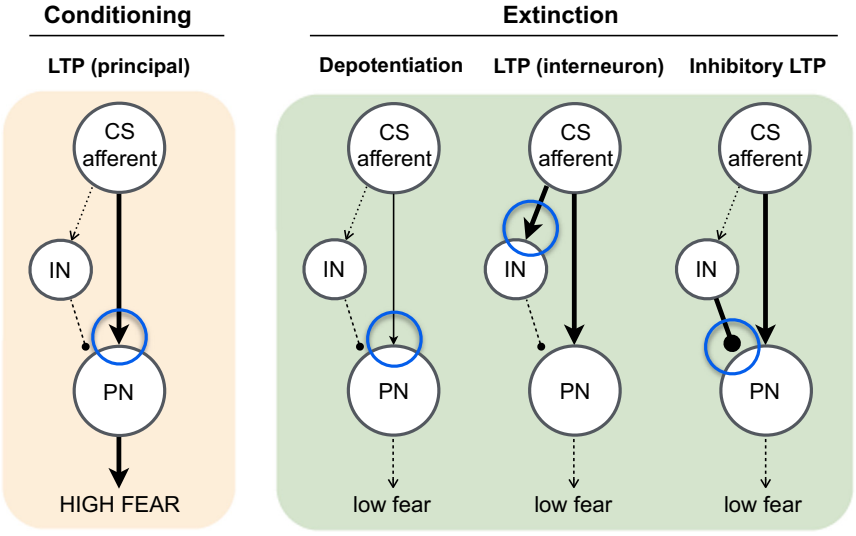

Fig. 1 – Synaptic mechanisms of conditioning and extinction. Conditioning (tan panel) is associated with long-term potentiation (LTP) at excitatory synapses from afferents carrying conditioned stimulus (CS) information that terminate on principal neurons (PN) in the basolateral amygdala [LTP (principal)]. Extinction (green panel) might result from a number of synaptic plasticity mechanisms including (1) depotentiation or long-term depression of previously potentiated PN synapses, (2) induction of LTP at CS afferents on interneurons (LTP-IN), or (3) LTP of inhibitory synaptic transmission ('inhibitory' LTP). Blue circles indicate the target synapses undergoing the forms of plasticity indicated above each microcircuit.