

Enhancement of extinction memory consolidation: The role of the noradrenergic and GABAergic systems within the basolateral amygdala

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Abstract

Evidence from previous studies indicates that the noradrenergic and GABAergic influences within the basolateral amygdala (BLA) modulate the consolidation of memory for fear conditioning. The present experiments investigated whether the same modulatory influences are involved in regulating the extinction of fear-based learning. To investigate this issue, male Sprague Dawley rats implanted with unilateral or bilateral cannula aimed at the BLA were trained on a contextual fear conditioning (CFC) task and 24 and 48 h later were given extinction training. Immediately following each extinction session they received intra-BLA infusions of the GABAergic antagonist bicuculline (50 ng), the β -adrenoceptor antagonist propranolol (500 ng), bicuculline with propranolol, norepinephrine (NE) (0.3, 1.0, and 3.0 μ g), the GABAergic agonist muscimol (125 ng), NE with muscimol or a control solution. To investigate the involvement of the dorsal hippocampus (DH) as a possible target of BLA activation during extinction, other animals were given infusions of muscimol (500 ng) via an ipsilateral cannula implanted in the DH. Bilateral BLA infusions of bicuculline significantly enhanced extinction, as did infusions into the right, but not left BLA. Propranolol infused into the right BLA together with bicuculline blocked the bicuculline-induced memory enhancement. Norepinephrine infused into the right BLA also enhanced extinction, and this effect was not blocked by co-infusions of muscimol. Additionally, muscimol infused into the DH did not attenuate the memory enhancing effects of norepinephrine infused into the BLA. These findings provide evidence that, as with original CFC learning, noradrenergic activation within the BLA modulates the consolidation of CFC extinction. The findings also suggest that the BLA influence on extinction is not mediated by an interaction with the dorsal hippocampus.

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1. Introduction

Contextual fear conditioning (CFC) is induced by pairing a context (conditioned stimulus; CS) with a fear-inducing stimulus (unconditioned stimulus; US), usually footshock. Subsequent elicitation of autonomic and behavioral fear responses, such as freezing, by the CS is typically used as an index of the CS–US association (Blanchard & Blanchard, 1972). CFC responses, like other forms of learned responses, can be extinguished by presenting the CS alone. The new information that the context no longer predicts a footshock

results in a decrease in the expression of the conditioned response (CR) (Pavlov, 1927). Extinction shares many common properties with original learning. Both require the formation of CS–US predictions and both require consolidation to achieve stability (McGaugh, 2000).

Considerable evidence indicates that the basolateral nucleus of the amygdala (BLA) plays an important role in modulating the consolidation of fear-based memories, including CFC (Berlau & McGaugh, 2003; Huff, Wright-Hardesty, Higgins, Matus-Amat, & Rudy, 2005; Kim & Jung, 2005; LaLumiere, Buen, & McGaugh, 2003; McGaugh, 2002; Vazdarjanova & McGaugh, 1999; Wilensky, Schafe, & LeDoux, 2000). There is extensive evidence that post-training noradrenergic agonists and antagonists enhance and impair, respectively, the consolidation

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of fear-based memory when infused into the BLA (Ferry, Roozendaal, & McGaugh, 1999; LaLumiere et al., 2003; Power, Thal, & McGaugh, 2002). Findings of studies using *in vivo* microdialysis and high-performance liquid chromatography (HPLC) provide additional evidence that endogenous NE release in the amygdala plays a role in memory modulation (Galvez, Mesches, & McGaugh, 1996; McIntyre, Hatfield, & McGaugh, 2002; Quirarte, Galvez, Roozendaal, & McGaugh, 1998).

Other neuromodulatory systems, including the GABAergic system, also modulate memory consolidation by regulating NE release within the amygdala. Post-training systemic administration or direct amygdala infusions of GABAergic agonists and antagonists impair and facilitate memory consolidation, respectively (Breen & McGaugh, 1961; Brioni & McGaugh, 1988; Brioni, Nagahara, & McGaugh, 1989; Castellano, Brioni, Nagahara, & McGaugh, 1989). Post-training intra-BLA (Cahill & McGaugh, 1996) or systemic (Introini-Collison, Castellano, & McGaugh, 1994) administration of a β -adrenergic antagonist blocks the memory-modulating effects of systemically administered GABAergic drugs. Such findings support the view that GABAergic influences on memory consolidation act upstream from noradrenergic activation by modulating NE release. Moreover, experiments using *in vivo* microdialysis have shown that systemic administration of the GABA_A antagonist picrotoxin increases the release of NE in the amygdala, whereas the GABA_A agonist muscimol decreases the release (Hatfield, Spanis, & McGaugh, 1999). In addition, GABAergic antagonists potentiate footshock-induced NE release in the amygdala (Quirarte et al., 1998).

There is extensive evidence that the BLA modulates memory consolidation via its efferent connections to other brain structures (McGaugh, 2000, 2004). The projections between the hippocampus and amygdala play an important and perhaps critical role in the consolidation of contextual fear memories (McIntyre et al., 2005; Roozendaal & McGaugh, 1997). This might be expected, in view of the extensive evidence that the hippocampus is engaged by contextual learning (Eichenbaum, Schoenbaum, Young, & Bunsey, 1996; Hirsh, 1974; Matus-Amat, Higgins, Barrientos, & Rudy, 2004; McNish, Gewirtz, & Davis, 1997; Phillips & LeDoux, 1992; Rudy & Sutherland, 1989) and receives substantial input from the BLA either directly or indirectly via the entorhinal cortex (Alheid, de Olmos, & Beltramino, 1995; Racine, Milgram, & Hafner, 1983; Thomas, Assaf, & Iversen, 1984). Infusions of β -adrenoceptor antagonists into the BLA block the memory modulating effects of drugs infused post-training into the hippocampus (Roozendaal, Nguyen, Power, & McGaugh, 1999).

There is also extensive evidence that the BLA is involved in extinction. Several studies have reported that infusions of drugs into the BLA affect extinction in experiments using tasks other than contextual fear conditioning, such as conditioned taste aversion (Bahar, Samuel, Hazvi, & Dudai, 2003). Infusions of the MAPK inhibitor PD98059 into the

BLA impair extinction of fear-potentiated startle (FPS) whereas such infusions administered the hippocampus do not affect FPS extinction (Lu, Walker, & Davis, 2001). Furthermore, intra-amygdala infusions of the NMDA receptor antagonist AP5 impair extinction of FPS, whereas infusions into a control brain region, such as the cerebellum, have no effect (Falls, Miserendino, & Davis, 1992). Administration of D-cycloserine (DCS), a partial NMDA receptor agonist, enhances extinction of FPS when administered either systemically or directly into the amygdala before extinction training (Walker, Ressler, Lu, & Davis, 2002).

In several studies, drugs were administered shortly after extinction training to affect memory consolidation without affecting processes influencing animals' experiences at the time of extinction training. Ledgerwood, Richardson, and Cranney (2003, 2005) reported that intra-amygdala infusions of the partial NMDA agonist DCS administered immediately following an extinction trial enhanced extinction retention. Additionally, an earlier study from our laboratory found that systemic administration of the GABA_A agonist picrotoxin immediately after extinction training enhanced the extinction of auditory fear conditioning (McGaugh, Castellano, & Brioni, 1990). Such findings clearly suggest that GABAergic influences modulate extinction memory consolidation in a similar manner to that of original memory consolidation (Brioni & McGaugh, 1988).

The present study investigated the involvement of the GABAergic and noradrenergic systems within the BLA in the consolidation of extinction memory. The experiments investigated whether, as with initial consolidation of fear-based memory (Brioni et al., 1989; Castellano et al., 1989), the consolidation of extinction involves GABAergic influences in the BLA and whether such effects are also mediated by noradrenergic influences (Introini-Collison et al., 1994). The experiments also examined the interaction between the BLA and the dorsal hippocampus (DH) in the consolidation of contextual fear extinction.

2. Materials and methods

2.1. Subjects

Subjects were 267 male Sprague Dawley rats (Charles River, Wilmington, MA) weighing 225–250 g on arrival. The animals were individually housed in a temperature (22 °C) and light (12:12 h light–dark cycle; lights on at 7 am) controlled vivarium. Rats received food and water *ad libitum* and acclimated to laboratory conditions for 1 week prior to surgery. The UC Irvine Institutional Animal Care and Use Committee approved all procedures.

2.2. Surgical procedures

2.2.1. Basolateral amygdala

The rats were anesthetized with sodium pentobarbital (50 mg/kg *ip.*), and received atropine sulfate (0.4 mg/kg *ip.*) to assist breathing. The rats were placed in a small animal stereotaxic frame (Kopf Instruments, Tujunga, CA) with the nose bar maintained at –3.3 mm relative to the interaural line. Guide cannulae aimed at the basolateral amygdala were implanted (2.8 mm posterior and 5.0 mm lateral to Bregma and 6.5 mm ventral to the skull surface) (Paxinos & Watson, 2004).

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