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Review

Noradrenergic modulation of extinction learning and exposure therapy

Devin Mueller*, Shawn P. Cahill

Department of Psychology, University of Wisconsin—Milwaukee, P.O. Box 413, Milwaukee, WI 53201-0413, United States

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ABSTRACT

Memory consolidation is enhanced by emotional arousal, an effect mediated by noradrenergic beta-receptor signaling. Norepinephrine strengthens consolidation of both appetitive and aversive learning, and is implicated in extinction of conditioned responses. In this review, we summarize work on the noradrenergic mechanisms of extinction learning and implications for extinction-based exposure therapy. The evidence suggests that norepinephrine release evoked by conditioned stimuli during extinction strengthens extinction memory via beta-receptor signaling. The modulatory effect of norepinephrine during extinction depends on predictable presentation of conditioned stimuli and optimal levels of norepinephrine release. Mechanistically, norepinephrine acts to increase cellular excitability and enhance synaptic plasticity within extinction-related neural circuitry. Currently, drugs that modulate norepinephrine are being used to treat symptoms of anxiety disorders, and are now being tested as pharmacotherapeutic prophalactics in the prevention of chronic posttraumatic stress reactions and as adjuncts to extinction-based exposure therapy. Studies of these new applications of noradrenergic drugs show a converging pattern of results with basic science suggesting ways in which basic laboratory findings can be translated into procedures to enhance clinical outcomes.

Contents

Abbreviations: BLA, basolateral amygdala; CREB, cAMP response element binding protein; CS, conditioned stimulus; IL-mPFC, infralimbic medial prefrontal cortex; LTP, long term potentiation; MAPK, mitogen-activated protein kinase; NE, norepinephrine; PKA, cAMP-dependent protein kinase A; PTSD, posttraumatic stress disorder; US, unconditioned stimulus.

* Corresponding author at: Department of Psychology, Garland Hall 224, University of Wisconsin—Milwaukee, P.O. Box 413, Milwaukee, WI 53201-0413, United States. Tel.: +1 414 229 6113; fax: +1 414 229 5219.
E-mail address: devinm@uwm.edu (D. Mueller).

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1. Introduction

Emotional regulation is necessary for adaptation and survival, and an important form of emotional regulation is extinction learning. Extinction of conditioned responses has been examined extensively since the time of Pavlov. In his classic study, Pavlov observed that responding to a conditioned stimulus (CS) diminished with repeated presentations of the CS in the absence of the unconditioned stimulus (US) [93]. Because responding was observed to spontaneously recover with the passage of time, Pavlov surmised that extinction learning results in the formation of a new inhibitory memory rather than an erasure of the original memory. The return of conditioned responses has also been observed following presentation of the US, or when the context is manipulated [10,113]. Thus, extinction does not erase the original CS-US association but constitutes new learning of a CS-no US contingency [88,109,111]. Extinction, therefore, can be thought of as a form of emotional regulation which gates the expression of conditioned memories.

The neural circuitry underlying extinction learning has been studied extensively [88,109], but less is known regarding the neurochemical signaling within that circuitry that leads to the formation of an extinction memory. Recent discoveries concerning the noradrenergic mechanisms of extinction have led to a renewed interest in the role that norepinephrine (NE) plays in this memory formation. Catecholaminergic cell bodies in the brain were first localized by Dahlstrom and Fuxe in 1964 [24], followed closely by initial research into the noradrenergic mechanisms of extinction learning in 1967 [79]. The purpose of this review is to examine the past four decades of research on the contribution of noradrenergic signaling to the formation of extinction memories. In addition, we will address the clinical implications of this work, and determine the therapeutic relevance of noradrenergic drugs in the treatment of anxiety disorders.

2. Norepinephrine and memory modulation

Emotionally arousing experiences are particularly well remembered, and are associated with elevated levels of NE [75,78]. Extensive research indicates that NE strengthens the formation of emotional memories [74]. Blockade of NE signaling through noradrenergic beta-receptors results in a loss of this enhancement in both animals [35,50,60] and humans [13,38]. Thus, arousal-evoked NE release strengthens acquisition of emotional memories via beta-receptor signaling. Moreover, direct infusion of NE in the basolateral amygdala (BLA) enhances memory [60,61,117], suggesting that the BLA is a critical site of NE action. In agreement with this notion, lesions of the BLA or infusions of beta-receptor antagonists into the BLA block enhancement of memory consolidation [81,117,119]. Memory consolidation can also be enhanced by administration of glucocorticoids [26,76], and this effect is mediated by beta-receptor signaling as well [106,120].

The memory enhancing effects of beta-receptor activation and other modulating treatments are not necessarily due to memory enhancement within the BLA itself. Notably, lesions of the stria terminalis, a target of BLA principal neurons, block memory enhancement induced by infusions of glucocorticoid receptor agonists into the BLA [118,133]. Studies indicate that the target sites of BLA modulatory effects include the hippocampus, caudate, and cerebral cortex [73,77]. These structures all receive direct NE input, and are implicated in numerous learning and memory tasks.

3. Norepinephrine and extinction

The neural mechanisms that underlie long-term behavioral changes after acquisition and extinction share some common

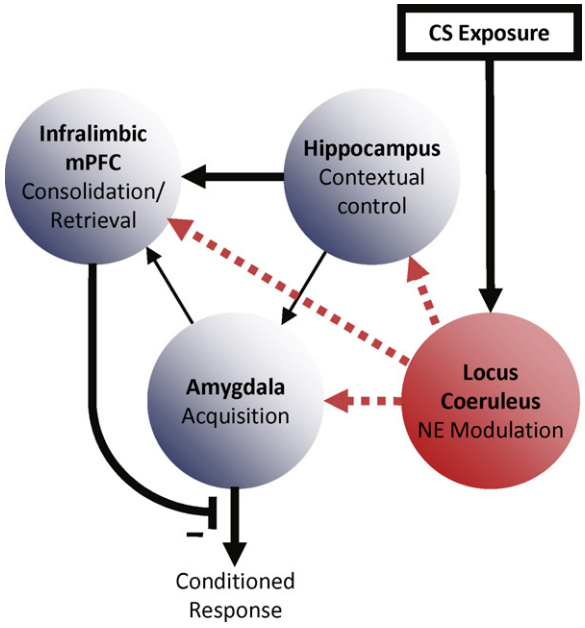

Fig. 1. The locus coeruleus innervates the neural structures responsible for extinction learning and retrieval, and CS-induced activation evokes NE release throughout the circuit. The amygdala stores both conditioning and extinction memories. The IL-mPFC integrates CS information with contextual information from the hippocampus in order to determine extinction retrieval. In the extinction context, the IL-mPFC inhibits amygdala output, to reduce conditioned responses.

mechanisms, but also display different characteristics [7,62]. Although consolidation of newly acquired information is enhanced by NE signaling [74], there is uncertainty whether NE has comparable effects in enhancing extinction memory consolidation. In contrast to acquisition, extinction leads to a decrease in responses to conditioned stimuli, and forms a new inhibitory memory [10,107,112]. Extinction of both appetitive and aversive conditioning involves the repeated presentation of a CS which evokes arousal and NE release [16,80]. Here we examine the necessity of NE signaling and the mechanisms by which NE modulates extinction learning. In particular, we examine the evidence that NE modulates extinction in aversive, appetitive and drug-related learning paradigms.

The majority of forebrain NE is provided by the locus coeruleus, a small pontine nucleus. This structure innervates the amygdala, hippocampus, and the infralimbic medial prefrontal cortex (IL-mPFC) [51,63] which are involved in extinction learning and retrieval (see Fig. 1) [88,109]. Whereas the amygdala is required for acquisition of extinction [54,139], the hippocampus provides contextual control of retrieval and expression of extinction [20,21,45]. The IL-mPFC is specifically involved in the consolidation of extinction, as plasticity in this region is important for subsequent extinction retrieval [47,124]. For example, neurons in IL-mPFC exhibit high-frequency bursting shortly after extinction that predicts retrieval of extinction the following day [12]. In addition, this structure inhibits amygdala output [108,154]. Thus, extinction learning and retrieval is amenable to NE modulation in these structures in response to repeated CS exposure.

3.1. Extinction of aversively-motivated behavior

Early work has implicated noradrenergic signaling in the modulation of extinction learning in aversive tasks. For example, systemic administration of NE increased the rate of extinction in a trace avoidance task [79]. In that same study, blockade of beta-receptors was found to impair extinction. Thus, initial find-