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Special Topics and Review

Role of the hippocampus in contextual modulation of fear extinction★★

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Abstract: Fear extinction is an important form of emotional learning, and affects neural plasticity. Cue fear extinction is a classical form of inhibitory learning that can be used as an exposure-based treatment for phobia, because the long-term extinction memory produced during cue fear extinction can limit the over-expression of fear. The expression of this inhibitory memory partly depends on the context in which the extinction learning occurs. Studies such as transient inhibition, electrophysiology and brain imaging have proved that the hippocampus – an important structure in the limbic system – facilitates memory retrieval by contextual cues. Mediation of the hippocampus-medial prefrontal lobe circuit may be the neurobiological basis of this process. This article has reviewed the role of the hippocampus in the learning and retrieval of fear extinction. Contextual modulation of fear extinction may rely on a neural network consisting of the hippocampus, the medial prefrontal cortex and the amygdala.

Key Words: hippocampus; fear; extinction; context-specific; exposure-based treatment

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INTRODUCTION

Cue fear extinction (CFE) is a form of fear inhibition that has been used in clinical treatment, such as exposure-based treatment, for a long time. In CFE, the conditioned stimulus (*e.g.* a tone) that has been paired with the aversive unconditioned stimulus (*e.g.* a foot-shock) in fear conditioning, is repeatedly presented alone. Consequently, fear level decreases in the test after fear extinction. It is widely accepted that fear extinction partly depends on new learning specific to the context in which the extinction occurs, and is not merely the reversal of the previous fear learning[1].

The hippocampus – a critical structure in the limbic system – plays a key role in the representation of context and the regulation of memory retrieval *via* contextual cues. Cue fear conditioning does not depend on hippocampal activities. After fear conditioning and fear extinction, the conditioned stimulus acquires two conflicting meanings, *i.e.* that it predicts or does not predict the occurrence of the unconditioned stimulus. According to Hirsh's information storage model of the nervous system, the hippocampus uses contextual indices to mark and retrieve the appropriate meaning associated with the retrieval context[2]. Therefore, the hippocampus might also play a crucial role in the acquisition and expression of extinction memory.

ACADEMIC BACKGROUND

As early as 1927, Pavlov demonstrated that extinction involves new learning and is not just a reversal of the previous learning. For the last 60 years, it has been generally accepted that the destruction of the learned association between the conditioned stimulus and the unconditioned stimulus is the main mechanism of extinction. However, since the 1990s, many scientists have accepted Pavlov's assertion that new learning occurs in fear extinction. Contextual modulation of the expression of the extinction proves that the previous learned association between the conditioned stimulus and unconditioned stimulus is not abolished by the extinction training. This indicates that the mechanism of extinction learning is different from that of fear conditioning. As a result, the neural mechanisms of extinction memory have become one of the most intensively studied areas of emotional learning. The amygdala, the foundation of

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the lateral nucleus of the amygdala, in which long-term potentiation (LTP) mediates the memory of fear, does show fear renewal in the test after fear extinction[3]. More importantly, the renewal of neural activity was also disrupted by temporal inhibition of the hippocampus. However, brain imaging studies on human and monkey subjects revealed that the hippocampus was activated not only in the expression of fear renewal, but also in the expression of fear extinction[4]. This indicated that the expression of extinction memory might also be related to activity in the hippocampus.

Recent data have shown that the DHC is also involved in contextual encoding of fear extinction[5]. A high level of fear was induced by a conditioned stimulus in any of the ABB, ABA or ABC designs if the activity of the hippocampus was temporarily inhibited before the extinction learning. Therefore, hippocampal inhibition before extinction training caused disruption of the context-dependent expression of fear because of failure in the expression of long-term extinction memory. In addition, the sub-regions of hippocampus (CA1 and CA3) play different roles in the learning and expression of extinction[6].

The neural circuit of fear extinction: hippocampus-medial prefrontal cortex-amygdala (HC-mPFC-A)

The neural circuit of context-dependent fear extinction consists of three functional modes: fear expression, fear inhibition and contextual gating. The amygdala mediates auditory fear conditioning and plays an important role in fear learning and expression. Fear inhibition is based on the neural network of the mPFC-A. Extinction learning causes neural plasticity changes in the mPFC. The mPFC activates the GABA system in the amygdala and inhibits fear expression. The hippocampus sends projections both to the mPFC and the amygdala and may play a significant role in the contextual gating of fear expression.

First, the hippocampus could modulate the activity of the amygdala indirectly *via* the mPFC. Fear inhibition is closely associated with neural plasticity of the mPFC, in particular the infralimbic cortex. Extinction learning induces LTP from the mediodorsal thalamic nucleus to the mPFC, which is closely related to fear inhibition. In addition, the LTP in this pathway at 1 week is greater than that at 1 day[7]. However, it seems that the hippocampus could modulate the neural plasticity in the mPFC. If the VHC is stimulated immediately by low frequency stimulation (LFS), LTP from the VHC to the mPFC induced by fear extinction, which disappeared after 1 week, is blocked, the mediodorsal thalamic nucleus-mPFC LTP is also impaired, and there is difficulty in expressing the extinction memory[8]. Extinction learning also induces LTP from the DHC to the mPFC[9]. In addition, immediate LFS after extinction learning can also block this LTP and cause difficulty in the expression of extinction memory. Due to the important role of the hippocampus in the learning and expression of CFE, neural plasticity in the hippocampus-mPFC may be the primary means of mediating the context-dependent component of fear extinction.

Second, the hippocampus could modulate the activity of the amygdala directly. There are many projections between the basal nucleus of the amygdala (BA) and the hippocampus. However, there is no evidence from lesion studies of the BA that the BA is necessary in fear learning and extinction[10]. Nevertheless, recent data have shown that lesion of the mPFC does not impair the formation and expression of extinction memory[11]. In addition, LTP and long-term depression in the DHC can modulate the learning and expression of extinction memory, in spite of the lesion in the mPFC. LFS of the DHC disrupts the LTP in the DHC-mPFC induced by extinction learning, and the expression of extinction memory. After several hours, the great stimulation of the DHC reverses the difficulty in expressing the extinction memory caused by the LFS of the DHC, but the neural plasticity in the mPFC is not re-established[7]. This indicates there is probably a direct modulation pathway from the hippocampus to the amygdala.

In summary, there is a triangular circuit consisting of the hippocampus, mPFC and amygdala. The hippocampus modulates activity of the amygdala directly or indirectly. The activity of neurons in the lateral nucleus of the amygdala shows a context-dependent fear response, which needs the hippocampus[12].

Clinical implications of the renewal effect for exposure-based therapies

Freud discovered that repeated presentation of a fear inducer (*e.g.* a spider) to a patient with panic disorder, a paradigm similar to fear extinction, can efficiently reduce the clinical symptoms. However, relapse of clinical symptoms always occurs following this exposure therapy[13]. More interestingly, the fear renewal could truly be reduced by the manipulation of some parameters of the behavioral paradigm of fear extinction.

First, increasing the number of contexts in which extinction training occurs can facilitate the expression of fear extinction in other contexts where no extinction learning has taken place[14]. Extinction learning in multiple contexts reduced the fear renewal in a non-extinction context. However, this phenomenon is not very stable and needs further validation[15-16].

Second, although the idea that new inhibitory memories are formed in fear extinction has been accepted, there is also some component of reversal of the previous learning, which is context-independent. The reversal component can be increased by shortening the time interval (< 1 hour) between the fear conditioning and extinction learning, resulting in a decrease in fear renewal[17-18]. However, the effect of a short interval can only be used with low or moderate levels of fear[19].

Finally, increasing the time of the conditioned stimulus in extinction learning can reduce the renewal effect. Some substances show an effect in reducing fear renewal, which may be used as auxiliary medicines in exposure-based therapies[20-21]. For example, injection of D-cycloserine, a partial agonist of N-methyl-D-aspartic acid, can significantly potentiate the expression of extinction memory and show potential in reducing fear renewal. If this effect can be confirmed, it would be a useful medicine in exposure-based therapies. Furthermore, some other substances, such as valproic acid and anisomycin, also show certain effects on

fear renewal reduction[22].

CONCLUSION

It is evident that the hippocampus mediates the contextual modulation of fear extinction. The hippocampus is necessary for learning of context-specific extinction memory and expression of fear after extinction. In addition, the hippocampus is the primary site of storage of the context-specific component of extinction memory. Its neural plasticity is the basis of the extinction memory-related neural plasticity in the mPFC. Moreover, the hippocampus, mPFC and amygdala comprise the neural circuit of context-specific fear extinction. Studies on the contextual dependence of fear and its neural basis are important for the effective treatment of anxiety disorders and reduction in relapse rates after exposure-based treatments.

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What is already known on this topic: Fear extinction is an important type of inhibitory learning with new memory formation. After fear conditioning and extinction, the conditioned stimulus has two conflicting meanings: that it either predicts or does not predict the unconditioned stimulus. The hippocampus plays a crucial role in the representation of the context and facilitation of memory retrieval by contextual cues. The hippocampus and the medial prefrontal cortex (mPFC) construct a complete nerve circuit of context-specific fear extinction.

What this study adds: Hippocampus-mPFC-amygdata might mediate the contextual modulation of fear extinction learning and expression. LTP is induced by fear extinction both in the pathway from the mediodorsal thalamic nucleus to the mPFC and from the hippocampus to the mPFC. Although LTP of the mediodorsal thalamic nucleus-mPFC lasts longer and is stronger than that of the hippocampus-mPFC, the hippocampus not only modulates the activity of the amygdala indirectly *via* the mPFC, but also affects the amygdala directly, implying a direct projection from the hippocampus to the amygdala, which is independent of the indirect pathway via the mPFC. Therefore, the amygdala, mPFC and hippocampus constitute a triangle of neural circuits mediating fear extinction. The hippocampus plays an integral role in the contextual modulation of fear extinction. It is of great importance to understand the context-dependence of fear extinction and its neural mechanisms to improve the efficiency and to reduce the relapse rate of exposure-based therapies.

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