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Invited review

A current overview of cannabinoids and glucocorticoids in facilitating extinction of aversive memories: Potential extinction enhancers

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ABSTRACT

Emotional learning is extremely important for the survival of an individual. However, once acquired, emotional associations are not always expressed. The regulation of emotional responses under different environmental conditions is essential for mental health. Indeed, pathologic feelings of fear and anxiety are defining features of many serious psychiatric illness, including post-traumatic stress disorder (PTSD) and specific phobias. The simplest form of regulation of emotional responses is extinction, in which the conditioned response to a stimulus decreases when reinforcement (stimulus) is omitted. In addition to modulating basal anxiety states, recent studies suggest an important role for the endocannabinoid (eCB) and glucocorticoid systems in the modulation of emotional states and extinction of aversive memories in animals. The purpose of this review is to briefly outline the animal models of fear extinction and to describe how these have been used to examine the potential of extinction enhancing agents which specifically alter the eCB and glucocorticoid systems. Pharmacological manipulations of these systems by agents such as cannabinoid or glucocorticoid agonists can enhance the extinction process and avoid the retention of memories which have the potential to trigger trauma. A better understanding of these findings through animal models highlights the possibilities of using combined extinction enhancing agents in exposure-based psychotherapies for anxiety disorders related to inappropriate retention of aversive memories.

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1. Introduction

Aversive learning is necessary for an individual to survive, since it helps in the avoidance of potentially dangerous situations. When exposed to such situations, proper regulation of emotional responses is essential for healthy living, since the lost of emotional tuning may contribute to the development of trauma-related diseases, including anxiety and mood disorders (Quirk and Mueller, 2008). Upon recollection, previously acquired fear memories are labialized and may undergo two different concurrent processes: reconsolidation or extinction (Quirk and Mueller, 2008). Reconsolidation occurs when consolidated memories are re-stabilized after retrieval, which results in maintenance of the memory trace. On the other hand, extinction occurs when a consolidated memory is recalled but no longer represents meaningful information. For this reason, facilitation of fear memory extinction (i.e. gradual reduction in fear responses) has been regarded as a therapeutically useful way to regulate emotional responses. During extinction, conditioned fear response gradually decreases through re-learning with repeated omission of the aversive stimulus (Quirk and Mueller, 2008).

Memory extinction is not simply forgetting, but an update to the emotional component of the context–shock association (termed by some as context-no shock association). The strongest evidence against the idea that extinguished memories have been erased are the facts that: 1) re-learning of the same fear memory after its extinction occurs at a faster rate compared to the initial acquisition, and 2) extinguished fear memories spontaneously recover with the passage of time (Myers and Davis, 2007). This means that the original memory trace has not been erased during the extinction, but rather suppressed by a new memory that inhibits the context–shock association (Bouton and Swartzentruber, 1989; Brooks and Bouton, 1993; Napier et al., 1992). It is important to mention that some authors see extinction as a non-associative habituation – like cognitive mechanism (although this view might be restricted to the less complex unimodal form of fear conditioning) (Kamprath and Wotjak, 2004). Here we provided an introductory overview of the fear extinction concept, for a more complete review see Herry et al. (2010).

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2. Studying fear memory extinction in the laboratory

Animal models are widely used to study fear memory mechanisms and this often involves the use of a fear conditioning paradigm. The classical fear conditioning protocol is the pairing of previously-neutral conditioned stimulus (CS; discrete cue or context) with an unconditioned stimulus (US; often a foot shock), which induces rapid, robust, and long-lasting fear learning. Re-exposure to the conditioned stimulus (even in the absence of the foot shock reinforcement), leads to the expression of behavioral, hormonal and autonomic fear responses. Common behavioral readouts of conditioned fear are: 1) cued- or contextual-induced expression of freezing, or 2) potentiation of a loud tone-induced startle. A single mild foot shock is capable of inducing the acquisition of conditioned fear memory in rodents, which lasts for weeks or months depending on the intensity and training schedule (Maren, 2008; Pamplona et al., 2008).

Different examples of fear conditioning laboratory paradigms are available. For example, in tone fear conditioning, aversive memories are elicited by temporally-pairing a tone (CS) with a mild foot shock (US) (Barrett and Gonzalez-Lima, 2004; Cannich et al., 2004; Dubreucq et al., 2010; Kamprath et al., 2006; Marsicano et al., 2002; Niyuhire et al., 2007; Plendl and Wotjak, 2010). In contextual fear conditioning, the CS is ill-defined and constituted by the surrounding stimuli of various sensorial modalities (i.e. the environment) and the fear memory is therefore formed by the context–shock association (Bitencourt et al., 2008; Blundell et al., 2011; de Oliveira Alvares et al., 2008; Ninomiya et al., 2010; Pamplona et al., 2008, 2006; Suzuki et al., 2004). In fear-potentiated startle, a CS (usually a light) is paired with a foot shock and the experimenter measures the startle reaction induced by a loud tone (US) in the presence and absence of the CS (Chhatwal et al., 2005; Lin et al., 2009; Yang et al., 2006, 2007). The fear-potentiated startle response is enhanced compared to the startle response elicited by the loud tone alone (Davis et al., 2006). Conditioned fear is also studied with operant conditioning paradigms, in which the US presentation occurs when the animal express (or refuses to express) a given behavior. Inhibitory avoidance occurs when the US follows a natural behavior, such as moving to the dark compartment of a light-dark chamber or stepping down from a platform onto a grid floor, after which the animal rapidly learns to avoid expressing such behavior (Kim and Jung, 2006). Active avoidance implies the avoidance of a given environment (i.e. a shutter box compartment) upon receipt of a US-paired signal, often a light or tone. Re-exposure to the CS triggers behavioral and hormonal conditioned responses, whether it be a discrete unimodal tone/light or multimodal context (Blanchard and Blanchard, 1969). Prolonged or repeated exposure to the CS in the absence of reinforcement leads to the extinction of the conditioned responses (for a more complete view see Myers and Davis, 2007). In tone/contextual fear conditioning, extinction of conditioned responses is often evaluated as a time-dependent reduction in the freezing response; in the fear-potentiated startle, the repeated presentation of the CS results in a reduction in the frequency and amplitude of the startle response (Walker and Davis, 2002), whereas in the extinction of operant conditioning one observes a reduction in avoidance behavior (Cammarota et al., 2003; Rossato et al., 2006).

3. Neural substrates supporting fear memory extinction

A number of studies have characterized the neural substrates underlying fear memory extinction. A major focus has been on the amygdala (AMY), hippocampus (HPC) and pre-frontal cortex (PFC), which are the main components of the well-defined fear circuit in the mammalian brain (for review, see Herry et al., 2010; Myers and Davis, 2007; Quirk and Mueller, 2008; Quirk et al., 2010). Very briefly, the amygdala is important for the encoding of the aversive content of the fear memory, the hippocampus plays a role in the associative processing of multimodal information into contextual information and the PFC is critical for the retrieval and reassessment of the aversive memory (Shin and Liberzon, 2009).

Anatomically, the amygdala might be understood as an output "hub" of the fear network, receiving sensory inputs from diverse areas of the brain (e.g. thalamus, neocortex, olfactory cortex, hippocampus) and sending projections to mediate behavioral and autonomic fear responses (e.g. bed nucleus of stria terminalis for activating stress hormones, periaqueductal gray matter for freezing, lateral hypothalamus for sympathetic activation) (Kim and Jung, 2006; Pare et al., 2004). Both CS and US signals converge to the basolateral nucleus of the amygdala (BLA), where specific CS–US associations are formed. Inter-amygdaloid connections to the central nucleus (CeA), a primary fear output, allow the learned fear association to influence various autonomic and motor centers involved in fear responses (Davis et al., 2006; Kim and Jung, 2006; Pape and Pare, 2010). The lateral nucleus of the amygdala (LA) is another important site for fear conditioning, projecting directly and indirect to the CeA in support of conditioned fear acquisition. Basal nucleus (BA), on the other hand, is an important site for conditioned fear expression (Anglada-Figueroa and Quirk, 2005). Interestingly, although BA-lesioned animals "loose" previously recently-conditioned fear, they are able to learn new CS–US associations, maybe suggesting that BA is a transient post-training site of signal encoding within the fear circuit (Anglada-Figueroa and Quirk, 2005).

Amygdala is certainly the main integration site for fear conditioning, which is actively modulated by other brain areas to regulate the expression of conditioned fear responses. As a consequence of extinction training, experience-dependent plasticity in amygdala nuclei may serve to inhibit fear expression, whereas plasticity in the hippocampus or pre-frontal cortex may allow for contextual modulation of that inhibition (Bruchey et al., 2007). Within the amygdala, there are well-defined circuits for inhibition. These include local inhibitory neurons within the BLA and CeA, as well as the islands of GABAergic neurons situated between these two structures known as the intercalated (ITC) cells. ITC cells receive input from BLA as well as several cortical sites (McDonald et al., 1996; Pare and Smith, 1998), and inhibit central nucleus output neurons (Pare and Smith, 1993; Royer et al., 1999). In a similar manner, paracapsular ITC cells surround the BLA and inhibit BLA neurons (Marowsky et al., 2005). Thus, ITC cells can be seen as an "off switch" for the amygdala that is activated by cortical input.

The hippocampus can play a role integrating multimodal stimuli into a contextual representation, which is directly involved in contextual fear conditioning. The context representation as a whole is the CS, which is associated to the US in the lateral portion of the amygdala (LA). There are direct and indirect projections from the hippocampus to the amygdala. Indirect connections occur, for example, via the medial PFC (Quirk and Mueller, 2008). The role of the PFC in conditioned fear expression varies with the different internuclei (Morgan et al., 1993). Lesions in the ventral medial PFC (vmPFC), including the infralimbic (IL) and prelimbic (PL) areas, have no effect on the acquisition of tone fear conditioning, but do impair its extinction (Morgan et al., 1993). Animals with vmPFC lesions are nevertheless able to learn fear extinction eventually, but they require twice as many days of training (Lebron et al., 2004). On the other hand, direct activation of the IL PFC enhances extinction learning (Milad and Quirk, 2002; Milad et al., 2004; Mueller et al., 2008). This vmPFC effect on a time-dependent reduction of conditioned fear responses occurs via inhibition of amygdala neuronal firing (Pape and Pare, 2010). On the other hand, prelimbic

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