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Review

Modulation of the extinction of fear learning

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ABSTRACT

We review recent work on extinction learning with emphasis on its modulation. Extinction is the learned inhibition of responding to previously acquired tasks. Like other forms of learning, it can be modulated by a variety of neurotransmitter systems and behavioral procedures. This bears on its use in the treatment of fear memories, particularly in posttraumatic stress disorder (PTSD), for which it is the treatment of choice, often under the name of exposure therapy. There have not been many laboratories interested in the modulation of extinction, but the available data, although not very abundant, are quite conclusive. Most studies on the nature of extinction and on its modulation have been carried out on fear motivated behaviors, possibly because of their applicability to the therapy of PTSD. A role for D-serine and the glycine site of NMDA receptors has been ascertained in two forms of extinction in the ventromedial prefrontal cortex, basolateral amygdala and dorsal hippocampus. The serine analog, D-cycloserine, has received clinical trials as an enhancer of extinction. The brain histaminergic system acting via H2 receptors, and the endocannabinoid system using CB1 receptors in the ventromedial prefrontal cortex, hippocampus and basolateral amygdala enhance extinction. Dopaminergic D1 and β-noradrenergic receptors also modulate extinction by actions on these three structures. Isolated findings suggest roles for on serotonin-1A, dopaminergic-D2 and α- and β-noradrenergic receptors in extinction modulation. Importantly, behavioral tagging and capture mechanisms in the hippocampus have been shown to play a major modulatory role in extinction. In addition, extinction of at least one aversive task (inhibitory avoidance) can be made state dependent on peripheral epinephrine.

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1. Introduction

Pavlov discovered extinction first in alimentary and subsequently in footshock-motivated classical conditioning at the beginning of the 20th century (see Pavlov, 1927). Starting in 1937, his disciple Jerzy Konorski (for many, the discoverer of instrumental conditioning) made several fundamental additional findings on extinction (Konorski, 1948) and, decades later, Rescorla (2001, 2004) added other findings that shaped the knowledge and understanding of this important form of learning into what we think of it today. Perhaps the single most important additional finding since its discovery is the fact that extinction suffers spontaneous recovery, which indicates that it does not consist of an

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attenuation or erasure of a previously acquired memory, but rather on the inhibition of its expression. Other phenomena that point in the same direction are renewal (recovery of extinction by a change of context, Bouton and Ricker, 1994), reinstatement (recovery of the original task by exposure to the unconditioned stimulus, Bouton, 2004; Thanellou and Green, 2011), and the quickness of reacquisition of the original response after extinction (Izquierdo et al., 1965). These findings show that extinction is by no means a form of forgetting, but rather a form of inhibitory learning (Pavlov, 1927; Milad and Quirk, 2012; Myskiw et al., 2013a,b).

2. Neural mechanisms of extinction

Pavlov postulated that both conditioning and extinction depend on physiological changes in the cerebral cortex, by which he and his followers understood mainly the neocortex. Beginning with Brenda Milner' key findings on patient H.M. and her suggestions on the role of the temporal lobe in memory formation (see Penfield and Milner, 1958; Squire, 2009), the participation of the hippocampus and other areas of the limbic system began to be viewed as important for learning processes.

The main structures that were recognized by modern lesion, recording and microinfusion studies as crucial for the extinction of fear-motivated memories were the ventromedial prefrontal cortex (vmPFC, Santini et al., 2001), the hippocampus in humans (Milad et al., 2007) or the dorsal hippocampus (D-HIPP, Vianna et al., 2001) in rats and the basolateral amygdala (BLA, Vianna et al., 2004); and, for the extinction of conditioned taste aversion, the insular cortex (Berman and Dudai, 2001) or, more probably, the insular cortex together with the hippocampus and the entorhinal cortex, Garcia-Delatorre et al., 2010). A role for the entorhinal cortex in the extinction of inhibitory avoidance learning has been proposed in other tasks too (Bevilaqua et al., 2006); such a role was to be presumed from the multiple interconnections of that area with the hippocampus and with the rest of the cortex (Green, 1964). Changes in neuronal activity during extinction were studied at the single cell level in the vmPFC (Milad and Quirk, 2002; Santini et al., 2008; Li et al., 2009) and mostly at the electroencephalographic level in the hippocampus (see Green, 1964).

Two hallmarks of memory consolidation are the involvement of N-methyl-D-aspartate (NMDA) glutamatergic synapses in its early phases, and protein synthesis in the neuronal system(s) that participate in that process (Izquierdo and Medina, 1997; Kandel and Squire, 2000; Izquierdo et al., 2006).

It was recently found that the consolidation of two different fear extinction tasks is enhanced by the immediate posttraining microinfusion of D-serine into the vmPFC, the D-HIPP or the BLA, and is blocked by that of AP5 (2 amino-5 phosphono-pentanoic acid). D-Serine is a co-agonist acting at the glycine receptor site of the NMDA receptor, and AP5 is an antagonist at the glutamate (or NMDA) receptor site itself (Fiorenza et al., 2012). There is no evidence or suggestion that glutamatergic transmission at any of these sites precedes or depends on that at any of the others. The consolidation of extinction memory transfers it from a NMDA receptor-independent into a NMDA receptor-dependent process in the vmPFC (Quirk, 2002). In D-HIPP, BLA (Igaz et al., 2002; Szapiro et al., 2003; Vianna et al., 2004; Tronson et al., 2009) and vmPFC (Mueller et al., 2008) activation of RNA synthesis, of the cAMP-dependent protein kinase (PKA) and of the extracellular regulated kinases (Erk, Erk1) are as necessary for extinction as they are for LTP (long-term potentiation) and LTD (long-term depression) in some of those structures as well as in a variety of forms of learning (Izquierdo and Medina, 1997; Izquierdo et al., 2006; see also Potter et al., 2013). Extinction is widely regarded as secondary to LTD or to long-term depotentiation, at least in the hippocampus and amygdala (Tsumoto, 1990; Gruart et al., 2006; Dalton et al., 2008, 2012; Azad et al., 2008).

Ribosomal protein synthesis occurs early on after the acquisition of extinction of various fear-motivated tasks and is necessary for its consolidation in the vmPFC (Santini et al., 2001), D-HIPP (Vianna et al., 2001) and BLA (Vianna et al., 2004). The microinfusion of the ribosomal protein synthesis inhibitor, anisomycin immediately after extinction training into any of these three sites hinders the extinction of contextual fear conditioning and of inhibitory avoidance learning (Santini et al., 2001; Vianna et al., 2001, 2004; Myskiw et al., 2013a,b).

In addition, as occurs in numerous other forms of learning, the microinfusion into D-HIPP or BLA of inhibitors of the various protein kinase-dependent signaling pathways that regulate protein synthesis (Szapiro et al., 2003; Vianna et al., 2004) hinders the consolidation of extinction learning. Their influence has been much less studied in the vmPFC (see, however, Rudenko et al., 2013).

As has been repeatedly described for a variety of tasks (e.g. Yin et al., 1994; Bernabeu et al., 1997), the extinction of spatial learning of mice in a Morris water maze is accompanied by a long-lasting posttraining increase of pCREB (phosphorylated cAMP-response element binding protein) in the lateral amygdala (Porte et al., 2011). The first session of extinction of inhibitory avoidance, in which this task is consolidated, is also followed by an increase of pCREB in D-HIPP (Szapiro et al., 2002). As has been suggested for a variety of tasks (Yin et al., 1994; Bernabeu et al., 1997; Izquierdo and Medina, 1997), pCREB has been attributed a key role in consolidation in the extinction of spatial memory too (Porte et al., 2011).

Memory consolidation coexists with NMDA receptor-dependent plastic processes such as LTP and LTD mostly in the hippocampus (Izquierdo and Medina, 1995, 1997; Malenka and Bear, 2004; Gruart et al., 2006; Whitlock et al., 2006; Izquierdo et al., 2006) and, in the case of fear memories, also in the lateral or basolateral amygdala (Dalton et al., 2008, 2012). There are several hypotheses on the role of the interconnection of D-HIPP, BLA and vmPFC in the consolidation of conditioned fear memories and on the consolidation of their extinction. A recent very articulate account by Sotres-Bayon et al. (2012) suggests that the hippocampus and BLA gate activity in the vmPFC. What part of this putative function is played by hippocampal and amygdala NMDA-dependent plasticity is not really known; what is known is that this plasticity seems to be necessary both at the time of the original consolidation of the fear-motivated tasks and at the time of the consolidation of their extinction (see Maren, 2011; Myskiw et al., 2013a,b respectively). Recent evidence indicates that amygdalar NMDA GluN2A and GluN2B receptors play separate roles in the induction of LTP and the initial consolidation of fear motivated tasks, and of LTD and the consolidation of the extinction of conditioned fear respectively (Dalton et al., 2012). The possibility that LTD may underlie extinction has been hinted at by many over the years, particularly at times in which extinction was confused with forgetting (e.g. Tsumoto, 1990). The actual connection between LTD and extinction was only demonstrated to a reasonable extent by Dalton et al. (2008, 2012) in recent experiments.

Parenthetically, perhaps contrarily to what would have been expected from studies suggesting a role for LTP in regular consolidation and of LTD in extinction (see above), there is an increase of a slow hyperpolarizing after potential in layers II, III and IV of vmPFC neurons in the consolidation of fear conditioning, with reduced intrinsic excitability of the neurons, and a reduction of that after potential with increased neuron excitability of those neurons (Santini et al., 2008).

Gruart et al. (2006) observed an increase of the CA3 field potential evoked by CA1 stimulation in D-HIPP during the acquisition of