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Neuroscience and Biobehavioral Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Brain sites involved in fear memory reconsolidation and extinction of rodents

Q1 Elisabetta Baldi*, Corrado Bucherelli

Dipartimento di Medicina Sperimentale e Clinica, Sezione di Fisiologia, Università degli Studi di Firenze, Viale G.B. Morgagni 63, I-50134 Firenze, Italy

ARTICLE INFO

Article history:
Received 30 July 2014
Received in revised form 30 March 2015
Accepted 6 April 2015
Available online xxx

Keywords:
"One-trial" aversive conditioning
Fear memory reconsolidation
Fear memory extinction
Local temporary reversible treatments
Amygdala
Hippocampus
Infralimbic cortex
Prelimbic cortex
Entorhinal cortex

ABSTRACT

Fear memory is a motivational system essential for organisms survival having a central role in organization of defensive behaviors to threat. In the last years there has been a growing interest on conditioned fear memory reconsolidation and extinction, two specific phases of memorization process, both induced by memory retrieval. Understanding the mechanisms underlying these two mnemonic processes may allow to work out therapeutic interventions for treatment of human fear and anxiety disorders, such as specific phobias and post-traumatic stress disorder. Based on the use of one-trial conditioning paradigms, which allow to follow the evolution of a mnemonic trace in its various phases, the present paper has attempted to reorganize the current literature relative to the rodents highlighting both the role of several brain structures in conditioned fear memory reconsolidation and extinction and the selective cellular processes involved. A crucial role seems to be play by medial prefrontal cortex, in particular by prelimbic and infralimbic cortices, and by distinct connections between them and the amygdala, hippocampus and entorhinal cortex.

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* Corresponding author at: Dipartimento di Medicina Sperimentale e Clinica, Sezione di Fisiologia, Viale G.B. Morgagni 63, I-50134 Firenze, Italy. Tel.: +39 55 2751618; fax: +39 55 4379506.
E-mail address: e.baldi@unifi.it (E. Baldi).

http://dx.doi.org/10.1016/j.neubiorev.2015.04.003
0149-7634/

1. Prolegomena – introduction

Q2 Fear memory is one of the most studied memories in general and especially in rodents. It is easily and quickly learned and retained for a long time even for a lifetime. For these characteristics fear memory is frequently used as an experimental model to study the cerebral mechanisms involved in learning and memory (Baldi and Bucherelli, 2012; LeDoux, 2000). The characteristics of fear memories acquisition and retention are amenable to investigate both the brain sites involved and the phases in which they are implicated. Fear learning entails single pairing between the conditioned stimulus (CS) and the unconditioned stimulus (US) which is sufficient to establish it. In rodents "one-trial" paradigms are usually employed to induce aversive conditioning, such as "fear conditioning" and "inhibitory avoidance". The "one-trial" procedures have an important feature as they allow to follow the evolution of a memory trace in its various phases, from its origin to its disappearance, and it is very useful to know the exact starting point for engram formation (Ambrogi Lorenzini et al., 1998; Muller et al., 1997; Sacchetti et al., 1999a). This is not possible using multi-trial conditioning paradigms that require several temporally spaced training sessions. This aspect is not of secondary importance because the association phase between CS and US stimuli, called "acquisition", is followed by a phase defined "consolidation" during which the mnemonic trace is progressively stabilized becoming increasingly resistant to destruction. This strengthening allows a labile memory (working memory or short-term memory) turning into a consolidated memory (long-term memory) that can be stored and retained for a very long time (Abel and Lattal, 2001; McGaugh, 2000).

Indeed, in the brain the life of the engram is certainly more dynamic than shown by this simplistic treatment. A well-consolidated engram is not unchangeable. Many studies have demonstrated that a "dormant" memory trace in the brain is well protected from potential erasing, but when this trace is recalled (retrieved) it can change. The re-activation returns the engram to a labile state making it sensitive to disruption (Alberini, 2005; Nader and Hardt, 2009; Nader et al., 2000). It is necessary to make a distinction because if a new re-exposure to the CS reactivates the trace, the resulting effects depend on the re-exposure features. Short re-exposition to the CS also in the absence of the reinforcement elicits the conditioned response starting at the same time a new process of memory trace elaboration, called reconsolidation. On the contrary, prolonged or repeated re-exposures to CS alone determine a gradual weakening of the engram showing extinction (Eisenberg et al., 2003; Pedreira and Maldonado, 2003; Suzuki et al., 2004). As for the original phases of the process of engram formation (acquisition, consolidation, retrieval) reconsolidation and extinction as well can be selectively investigated employing experimental paradigms. In addition, in the processing of memory trace it is important to investigate the mechanisms that regulate it. In this regard, there is a wide scenario that involves neurotransmitters, neuromodulators, biochemical and genetic expression processes that continuously interfere with each other (Myers and Davis, 2007; Quirk and Mueller, 2008; Tronson and Taylor, 2007).

To assess whether a mechanism or a brain site is involved in a specific phase of the memorization process (acquisition, consolidation or retrieval of mnemonic trace), experimental techniques are used that affect selectively a phase of the process without interfering with the other ones preceding or following the investigated phase. For example, irreversible lesions of cerebral sites are not suitable for this purpose. On the contrary, temporary (reversible) inactivation allows to investigate not only the possible role of a particular brain structure in mnemonic process, but also in which phase or phases it is involved (Ambrogi Lorenzini et al., 1999).

In rodents, Pavlovian fear conditioning has been the main conditioning procedure used. In a typical experiment of fear conditioning to examine fear memory, an animal is placed in a conditioning apparatus and an emotionally neutral stimulus (such as a tone, a light or an odor) is paired with an aversive stimulus such as a mild electric footshock (the unconditioned stimulus, US). As a result of this pairing, the initially neutral stimulus (being now a conditioned stimulus, CS) acquires the ability to elicit a typical behavioral fear response. However, in this procedure the US is associated not only with a discrete CS but also with the environment in which the US is presented, i.e. the training context. Thus, the animal will exhibit conditioned fear to both CS (cued fear conditioning) and context (contextual fear conditioning) during the subsequent re-exposure to that CS or context. In this way, the same paradigm allows to obtain two distinct mnemonic traces, that can be studied separately, and to follow their temporal evolution (LeDoux, 2000; Sacchetti et al., 1999a, 1999b). The conditioned fear can be measured by quantifying specific behavioral responses such as fear-potentiated startle and freezing or immobility. The former consists in an increase in the amplitude of an acoustically elicited startle response, whereas the latter is defined as the complete absence of somatic movements except those requested for respiration (Fendt and Fanselow, 1999; Sacchetti et al., 1999a, 1999b). Contextual fear may also be induced by the presentation of a US alone. In addition to classical fear conditioning, this form of fear memory has been studied using the inhibitory avoidance paradigm. The animal learns that performing a response (for example, walking from an illuminated compartment to a spontaneously preferred darkened one of an apparatus or moving from a small elevated platform to a larger arena) is punished with a footshock. In this case the animal learns to avoid the punishment inhibiting its natural response (Tinsley et al., 2004).

As in all memories, fear memory retrieval of a consolidated mnemonic trace is a dynamic process that can initiate two processes: reconsolidation and extinction. In the reconsolidation, the retrieved fear memory transiently returns to a labile state and requires a new round of consolidation to be preserved. It has been proposed that reconsolidation allows the integration of new information into the original mnemonic trace, thus allowing memory updating, and also to strengthen or weaken it (Alberini, 2005; Alberini and LeDoux, 2013). Reconsolidation is not exactly

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a recapitulation or a repetition of initial consolidation. In fact, the time course of the two processes is different and the brain structures and molecular processes involved may be not necessarily coincident (Alberini, 2005; Bucherelli et al., 2006; Tronson and Taylor, 2007). On the other hand, during retrieval session, memory reactivation by means of longer re-exposition to the CS, without the US presentation, triggers the extinction process that leads to progressive reduction in the expression of conditioned fear response. However, extinction does not directly modify the original fear memory but leads to the formation of a new association (CS-no US) that competes with the original engram, masking it. Thus, extinction implies new learning. On the other hand, phenomena such as spontaneous recovery (that is, reappearance of an extinguished fear memory with the passage of time), renewal (recovery of an extinguished fear memory when the CS is presented in a context different from that in which extinction training took place) and reinstatement (reappearance of an extinguished fear memory following exposure to unsignaled US after extinction training) show that the original memory is not erased but remains encoded in the brain being not expressed during extinction (Baldi and Bucherelli, 2010; Myers and Davis, 2007; Quirk and Mueller, 2008).

The current understanding of the neural circuitry of fear memory reconsolidation and extinction is much poorer than that concerning the acquisition and consolidation phases. Experimental results indicated that these mnemonic phases are characterized by both distinctive and coincident features of the anatomical and molecular requirements (Alberini, 2005; Berman and Dudai, 2001; Bucherelli et al., 2006; Chen et al., 2005; Izquierdo et al., 2006; Lee et al., 2004; Lin et al., 2003b; Szapiro et al., 2003; Vianna et al., 2001). Understanding the mechanisms of fear memory reconsolidation and extinction may have clinical importance for the treatment of human anxiety disorders, such as specific phobias, panic disorder and post-traumatic stress disorder. In this contest treatments involving reconsolidation and extinction procedures have been recently used to reduce the expression of fear memory (Alberini, 2005; Auber et al., 2013; Davis et al., 2006; Hartley and Phelps, 2010; Monfils et al., 2009; Myskiw et al., 2014; Nader, 2003; Parsons and Ressler, 2013; Quirk et al., 2010; Rao-Ruiz et al., 2011; Rossato et al., 2010; Schiller et al., 2010; Todd et al., 2014). Thus, the identification of both neural structures underlying the two memory phases, and pharmacological agents that impair reconsolidation or potentiate extinction appears to be crucial. In this context, this review attempts to reorganize results in the literature aimed to highlight the role of several cerebral structures in fear memory reconsolidation and extinction in rodents, highlighting whenever possible the selective cellular processes involved. Following the principles exposed above, in this review we will consider studies related to one-trial aversive conditioning to investigate the role of brain structures in specific phases of memorization processes.

2. Brain structures involved in fear memory reconsolidation

Experimentally, reconsolidation process of fear memory can be verified by reactivating a well consolidated mnemonic trace. For this purpose, the previously conditioned animal is subjected to a reactivation session (usually at least 24 h after training) during which the CS is briefly re-presented usually in the absence of the US. Immediately after reactivation, a treatment known to disrupt memory consolidation is applied. Later (usually at least 24 h after the reactivation session) the memory retention is tested by presenting the CS again (Nader, 2003; Tronson and Taylor, 2007).

On the basis of literature results shown in Tables 1–3, it is clear that the amygdala and the hippocampus are the neural structures most investigated in this mnemonic phase. This is probably due to the fact that these sites play a central role in the fear responses learning. Indeed, the amygdala was demonstrated to be critical for the acquisition, consolidation and expression of cued and contextual fear conditioning. In addition, results obtained by inhibitory avoidance experiments show that this neural structure is also important for this form of fear memory, although in this case it seems to have a modulatory role as amygdala lesions attenuate, but do not block, inhibitory avoidance learning (Parent et al., 1994, 1995; Parent and McGaugh, 1994).

2.1. Amygdala

The involvement of the amygdala, in particular the basolateral complex (BLA), in the fear memories reconsolidation (Table 1) has been highlighted by means of tetrodotoxin (TTX) or lidocaine functional inactivation, blockers of voltage-dependent sodium channels, thus impeding the initiation and propagation of action potentials. Intra-BLA lidocaine or TTX infusion immediately after reactivation session of fear-related memory impairs both freezing response to context (Baldi et al., 2008; Bucherelli et al., 2006) and auditory CS (Sacchetti et al., 2007) and inhibitory avoidance response (Prado-Alacalà et al., 2006; Tzeng et al., 2012). However, Prado-Alacalà et al. (2006) have reported that post-reactivation administration of TTX into the amygdala produced a transient amnesic effect of inhibitory avoidance which recovered with repeated retention testing. Thus, according to the Authors, "the impairment induced by post-retrieval treatment is likely due to temporary impairment of memory retrieval". It was also shown that increasing the strength of conditioning, using an US strong enough to induce generalization, the BLA role in auditory fear reconsolidation is no longer crucial (Baldi et al., 2008; Sacchetti et al., 2007). This effect may be due to other neural sites which maintain this fear memory. On this point, some Authors (Sacchetti et al., 2007) have observed that stronger auditory fear memories are affected by the combined but not independent BLA and cerebellar vermis TTX blockade.

2.1.1. Neurotransmitter systems

The molecular mechanisms of fear memories reconsolidation are starting to be elucidated. Many studies have employed some post-retrieval treatments previously used to characterize memory consolidation. The results have provided evidence that the molecular mechanisms of these two mnemonic phases are similar, but not identical. Fear memory reconsolidation requires the activation of several neurotransmitter systems into the BLA, such as glutamate, noradrenaline and endocannabinoid. The glutamate acts through two types of ionotropic receptors: NMDA (N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid). The blockade of NMDA-receptors in the BLA before memory reactivation blocks the beginning of reconsolidation (Mamou et al., 2006), whereas the injection of a NMDA partial agonist, D-cycloserine (DCS), in the same neural site before the reactivation session enhances fear memories (Lee et al., 2006). Further studies reported that different subtypes of NMDA receptor within the BLA may mediate memory destabilization and re-stabilization after retrieval. In particular, into the BLA the NR2B subtype appears to be required for auditory fear memory destabilization, whereas the NR2A subtype seems to be involved in re-stabilization of this fear memory (Milton et al., 2013). On the contrary, AMPA receptor blockade (Mamou et al., 2006; Milton et al., 2013) does not seem to have any effect on memory reconsolidation. However, a recent study (Hong et al., 2013) showed that AMPA receptors may play an unexpected physiological role in guiding fear memory reconsolidation into the BLA. In fact, the authors demonstrated that an exchange from calcium impermeable AMPA (CI-AMPA) receptor to calcium permeable AMPA (CP-AMPA) receptor occurs during

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Table 1
Reconsolidation: effects of intra-amygdala post recall treatments on fear memory. The table lists the studies using local administration of pharmacological or genetic treatments to determine the role of amygdala and amygdaloid signaling molecules in fear memories reconsolidation.

Cerebral site	Behavioral paradigm	Treatment	Effect	Reference
Amygdala	Inhibitory avoidance	TTX	Impairment	Prado-Alacalà et al. (2006)
BLA	Inhibitory avoidance	Lidocaine	Impairment	Tzeng et al. (2012)
BLA	Auditory fear conditioning	TTX	Impairment	Sacchetti et al. (2007)
BLA	Auditory fear conditioning	TTX	No effect	Baldi et al. (2008)
BLA	Contextual fear conditioning	TTX	Impairment	Baldi et al. (2008) and Bucherelli et al. (2006)
BLA	Auditory fear conditioning	NMDA antagonist	Impairment	Mamou et al. (2006)
BLA	Auditory fear conditioning	NMDA agonist	Improvement	Lee et al. (2006)
BLA	Auditory fear conditioning	NR2A antagonist	Impairment	Milton et al. (2013)
		NR2B antagonist	No effect	
		AMPA antagonist	No effect	
LA	Auditory fear conditioning	CP-AMPA receptor blockade	Impairment	Hong et al. (2013)
BLA	Auditory fear conditioning	GR antagonist	Impairment	Jin et al. (2007)
BLA	Inhibitory avoidance	GR antagonist	Impairment	Tronel and Alberini (2007)
LA	Auditory fear conditioning	β-AR antagonist	Impairment	Debiec et al. (2011) and Debiec and LeDoux (2004)
		β-AR agonist	Improvement	
LA/BLA	Fear-potentiated startle	CB1 agonist	Impairment	Lin et al. (2006)
		CB1 antagonist	No effect	
BLA	Contextual fear conditioning	CB1 antagonist	Impairment	Bucherelli et al. (2006)
		H3 antagonist	No effect	
		Muscarinic antagonist	No effect	
BLA	Inhibitory avoidance	Noradrenaline	No effect	Cammarota et al. (2004)
BLA	Auditory fear conditioning	PKA activator	Improvement	Tronson et al. (2006)
		PKA inhibitor	Impairment	
LA	Auditory fear conditioning	MAPK inhibitor	Impairment	Diaz-Mataix et al. (2011) and Duvarci et al. (2005)
BLA	Contextual fear conditioning	PI-3K inhibitor	Impairment	Kritman and Maroun (2013)
BLA	Inhibitory avoidance	Protein synthesis inhibitor	No effect	Cammarota et al. (2004)
BLA	Auditory fear conditioning	Protein synthesis inhibitor	Impairment	Debiec et al. (2006), Duvarci et al. (2006), Duvarci and Nader (2004), Jarome et al. (2012), Mamou et al. (2006), Nader et al. (2000), Sacchetti et al. (2007) and Wang et al. (2009)
LA	Auditory fear conditioning	Protein synthesis inhibitors	Impairment	Debiec et al. (2010) and Duvarci et al. (2005)
Amygdala	Contextual fear conditioning	Protein synthesis inhibitor	Impairment	Mamiya et al. (2009) and Parsons et al. (2006a)
Amygdala	Auditory fear conditioning	mRNA synthesis inhibitors	No effect	Parsons et al. (2006a)
Amygdala	Contextual fear conditioning	mRNA synthesis inhibitors	No effect	Parsons et al. (2006a)
BLA	Auditory fear conditioning	mRNA synthesis inhibitors	Impairment	Duvarci et al. (2008)
BLA	Inhibitory avoidance	C/EBPβ antisense ODN	Impairment	Tronel et al. (2005)
LA	Auditory fear conditioning	EGR-1 (ZIF268) antisense ODN	Impairment	Maddox et al. (2011)
BLA	Auditory fear conditioning	CREB inhibition	Impairment	Tronson et al. (2012)
LA	Auditory fear conditioning	eIF4F inhibitor	No effect	Hoeffer et al. (2011)
LA	Auditory fear conditioning	FGF2	Impairment	Graham and Richardson (2011)
LA	Auditory fear conditioning	HDAC inhibitor	Improvement	Maddox and Schafe (2011) and Maddox et al. (2013, 2014)
		DNMT inhibitor	Impairment	
		HAT inhibitor	Impairment	
Amygdala	Auditory fear conditioning	mTOR inhibitor	Impairment	Parsons et al. (2006b)
BLA	Inhibitory avoidance	mTOR inhibitor	Impairment	Jobim et al. (2012)
BLA	Auditory fear conditioning	Actin inhibitor	Impairment	Rehberg et al. (2010)
BLA	Contextual fear conditioning	Actin inhibitor	Impairment	Motanis and Maroun (2012) and Rehberg et al. (2010)

Antisense ODN, antisense oligodeoxynucleotide; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; β-AR, β-adrenergic receptor; BLA, basolateral amygdala; CB1, cannabinoid receptor type 1; C/EBPβ, CCAAT enhancer-binding protein-β; CP-AMPA, calcium permeable AMPA receptors; CREB, cyclic AMP response element-binding protein; DNMT, DNA methyltransferase; EGR-1, early growth response gene-1; eIF4F, eukaryotic initiation factor 4F; FGF2, fibroblast growth factor 2; GR, glucocorticoid receptor; H3, histaminergic receptor type 3; HAT, histone acetyltransferase; HDAC, histone deacetylase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin kinase; NMDA, N-methyl-D-aspartate receptor; NR2A, NR2B, NMDA receptors subtype 2A, 2B; PI-3K, phosphatidylinositol 3 kinase; PKA, protein kinase A; TTX, tetrodotoxin; ZIF268, zinc finger 268.

fear memory reconsolidation. Moreover, the blockade of CP-AMPA receptor immediately after retrieval impairs the reconsolidation process of auditory fear memory.

Noradrenergic transmission is also involved in reconsolidation process; in fact, post-reactivation intra – BLA administration of β-adrenergic receptor (β-AR) antagonist or agonist reduces or enhances, respectively, fear memory (Debiec et al., 2011; Debiec and LeDoux, 2004). Also post-reactivation blockade of glucocorticoid receptors (GRs) in this neural site disrupts long-term fear memories retention (Jin et al., 2007; Tronel and Alberini, 2007). In our laboratory we studied the BLA cholinergic, histaminergic and cannabinoid systems involvement in contextual fear memory reconsolidation (Bucherelli et al., 2006). The results showed that the cannabinoid system participates in memory maintenance after reactivation, whereas cholinergic and histaminergic neurons do not. Amygdalar cannabinoid receptor type 1 (CB1) involvement was also demonstrated in the fear-potentiated startle reconsolidation (Lin et al., 2006), although in this case mnemonic impairment followed the activation of these receptors by CB1 agonists and was reverted by a selective CB1 antagonist. The difference between these results and ours is not clear but it could be due to the different fear responses studied (fear-potentiated startle vs. freezing response). Reconsolidation of different fear responses might require either activation or blockade of intra-amygdala CB1 receptors. Together these results suggest that several neurotransmitter systems within the BLA are critically involved in fear memory

Table 2
Reconsolidation: effects of intra-hippocampus post recall treatments on fear memory. The table lists the studies using local administration of pharmacological or genetic treatments to determine the role of hippocampus and hippocampal signaling molecules in fear memories reconsolidation.

Cerebral site	Behavioral paradigm	Treatment	Effect	Reference
DHC	Inhibitory avoidance	Muscimol	Impairment	Amaral et al. (2007)
DHC	Inhibitory avoidance	TTX	Impairment	Prado-Alcalà et al. (2006)
DHC	Contextual fear conditioning	NMDA antagonist	Impairment	Lee and Hynds (2013)
Hippocampus	Contextual fear conditioning	L-VGCC inhibitor	No effect	Suzuki et al. (2008)
DHC	Inhibitory avoidance	α7nAChR agonist (low footshock intensity)	Improvement	Boccia et al. (2010)
		α7nAChR antagonist (low footshock intensity)	Impairment	
		α7nAChR agonist (high footshock intensity)	Impairment	
		α7nAChR agonist (high footshock intensity)	Impairment	
DHC	Inhibitory avoidance	α7nAChR agonist	Improvement	Blake et al. (2012, 2013)
Hippocampus	Contextual fear conditioning	CB1 antagonist	Improvement	De Oliveira Alvares et al. (2008)
		CB1 agonist	Impairment	
Hippocampus	Contextual fear conditioning	CB1 inhibitor	No effect	Suzuki et al. (2008)
DHC	Inhibitory avoidance	MAPK inhibitor	No effect	Roesler and Quevedo (2009)
DHC	Contextual fear conditioning	MAPK inhibitor	No effect	Lee and Hynds (2013)
DHC	Contextual fear conditioning	IKK inhibitor	Impairment	Lee and Hynds (2013)
DHC	Inhibitory avoidance	IKK inhibitor	Impairment	Boccia et al. (2007)
DHC	Contextual fear conditioning	PI-3K inhibitor	No effect	Chen et al. (2005)
DHC	Inhibitory avoidance	Protein synthesis inhibitor	No effect	Cammarota et al. (2004) and Taubenfeld et al. (2001)
DHC	Inhibitory avoidance	Protein synthesis inhibitor	Impairment	Power et al. (2006)
DHC	Contextual fear conditioning	Protein synthesis inhibitor	Impairment	Chen et al. (2005) and Debiec et al. (2002), Frankland et al. (2006), Lee (2008), Lee et al. (2004, 2008), Mamiya et al. (2009), Stafford and Lattal (2009) and Suzuki et al. (2008)
DHC	Contextual fear conditioning	mRNA synthesis inhibitors	Impairment	De Oliveira Alvares et al. (2008) and Lee et al. (2004)
Hippocampus	Inhibitory avoidance	C/EBPβ antisense ODN	No effect	Taubenfeld et al. (2001)
DHC	Inhibitory avoidance	IGF-II	Improvement	Chen et al. (2011)
DHC	Contextual fear conditioning	BDNF antisense ODN	No effect	Barnes et al. (2012), Lee (2008) and Lee et al. (2004)
DHC	Contextual fear conditioning	ZIF268 antisense ODN	Impairment	Barnes et al. (2012), Kirtley and Thomas (2010), Lee (2008) and Lee et al. (2004)
DHC	Contextual fear conditioning	Proteasome inhibitor	No effect	Lee (2008) and Lee et al. (2008)
		Proteasome inhibitor + anisomycin	Anisomycin effect blockade	
DHC	Contextual fear conditioning	IL-1R antagonist	Impairment	Barnes et al. (2012) and Machado et al. (2010)
Hippocampus	Contextual fear conditioning	NF-kB inhibitor	Impairment	De la Fuente et al. (2011)
		NFAT inhibitor	No effect	
		Calcineurin inhibitor	No effect	
DHC	Inhibitory avoidance	NF-kB inhibitor	Impairment	Boccia et al. (2007)
DHC	Contextual fear conditioning	mTOR inhibitor	Impairment	Gafford et al. (2011)
DHC	Inhibitory avoidance	mTOR inhibitor	Impairment	Jobim et al. (2012)
Hippocampus	Contextual fear conditioning	Actin inhibitor	Impairment	Motanis and Maroun (2012)

α7nAChR, α7 nicotinic acetylcholine receptor; antisense ODN, antisense oligodeoxynucleotide; BDNF, brain-derived neurotrophic factor; CB1, cannabinoid receptor type 1; C/E≡Pβ, CCAAT enhancer-binding protein-β; DHC, dorsal hippocampus; IGF-II, insulin-like growth factor II; IKK, IκB protein kinase; IL-1R, interleukin 1 receptor; L-VGCC, L-type voltage-gated calcium channel; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin kinase; NFAT, nuclear factor of activated T-cells; NF-κB, nuclear factor κB; NMDA, N-methyl-D-aspartate receptor; PI-3K, phosphatidylinositol 3 kinase; TTX, tetrodotoxin; ZIF268, zinc finger 268.

Table 3
Reconsolidation: effects of intra several cerebral sites post recall treatments on fear memory. The table lists the studies using local administration of pharmacological or genetic treatments to determine the role of specific cerebral sites and signaling molecules in fear memories reconsolidation.

Cerebral site	Behavioral paradigm	Treatment	Effect	Reference
mPFC	Contextual fear conditioning	Protein synthesis inhibitor	No effect	Mamiya et al. (2009)
IL-mPFC	Contextual fear conditioning	Muscimol	No effect	Stern et al. (2014)
IL-mPFC	Contextual fear conditioning	PI-3K inhibitor	No effect	Kritman and Maroun (2013)
PL-mPFC	Contextual fear conditioning	Muscimol	Impairment	Stern et al. (2014)
PL-mPFC	Olfactory fear conditioning	α-AR antagonist	Impairment	Do Monte et al. (2013a,b)
Anterior cingulate cortex	Contextual fear conditioning	Protein synthesis inhibitor	No effect	Frankland et al. (2006)
Anterior cingulate cortex	Contextual fear conditioning	Protein synthesis inhibitor	Impairment	Einarsson and Nader (2012)
Anterior cingulate cortex	Olfactory fear conditioning	α_1-AR antagonist	No effect	Do Monte et al. (2013a,b)
ENT	Contextual fear conditioning	TTX	Impairment	Baldi and Bucherelli (2014)
ENT	Inhibitory avoidance	Protein synthesis inhibitor	No effect	Cammarota et al. (2004)
		Noradrenaline	No effect	
Perirhinal cortex	Auditory fear conditioning	TTX	No effect	Sacchetti et al. (2007)
		Protein synthesis inhibitor	No effect	
Cerebellar vermis	Auditory fear conditioning	TTX	Impairment	Sacchetti et al. (2007)
		Protein synthesis inhibitor	Impairment	
Nucleus basalis magnocellularis	Auditory fear conditioning	TTX	No effect	Baldi et al. (2008)
Nucleus basalis magnocellularis	Contextual fear conditioning	TTX	No effect	Baldi et al. (2008)

α-AR, α-adrenergic receptor; α_1-AR, α_1-adrenergic receptor; ENT, entorhinal cortex; IL-mPFC, infralimbic subregion of the medial prefrontal cortex; mPFC, medial prefrontal cortex; PI-3K, phosphatidylinositol 3 kinase; PL-mPFC, prelimbic subregion of the medial prefrontal cortex; TTX, tetrodotoxin.

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reconsolidation, and also show that this process cannot be considered a recapitulation of consolidation, although some mechanisms in BLA are in common.

2.1.2. Protein kinases

The activation/inhibition of several neurotransmitter systems in the amygdala during fear memory reconsolidation is thought to lead, either directly or indirectly, to the activation of downstream signaling cascades. Two protein kinases are of particular interest: protein kinase A (PKA) and mitogen-activated protein kinase (MAPK). These kinases were shown to contribute to fear memory consolidation engaging cellular processes necessary for long-term synaptic plasticity and memory formation. PKA and MAPK are required for conditioned auditory fear reconsolidation into the BLA. In this brain structure, PKA activation enhances reconsolidation processes (Tronson et al., 2006), whereas PKA or MAPK inhibition impairs memory reconsolidation (Diaz-Mataix et al., 2011; Doyere et al., 2007; Duvarci et al., 2005; Tronson et al., 2006). Moreover, auditory fear memory reconsolidation impairment induced by MAPK inhibition was obtained using both discrete CS and US for reactivating the mnemonic trace (Diaz-Mataix et al., 2011; Doyere et al., 2007). The consequent successive loss of reinstatement suggests that this loss of fear memory, and its neurophysiological correlate in the BLA induced by the MAPK inhibitor after (US or CS) reactivation, does not reflect a retrieval blockade. Also, the phosphatidylinositol-3 kinase (PI-3K) and its target, AKT/PKB (protein serine/threonine kinase), are critical for memory reconsolidation. In fact, Kritman and Maroun (2013) reported that PI-3K inhibition into the BLA before retrieval of a contextual fear task impairs reconsolidation of this memory. Because PI-3K and AKT/PKB are upstream targets of the mammalian target of rapamycin (mTOR) pathway, these results prove that PI-3K-AKT/PKB-mTOR pathway has a crucial role in fear memory reconsolidation at least into the BLA.

2.1.3. Gene expression and protein synthesis

PKA and MAPK act directly or indirectly activating several transcription factors, such as CREB (cyclic AMP-response element binding protein) and zif268 (zinc finger 268) that initiate gene transcription. Some of these transcription factors within the BLA are implicated in fear memory reconsolidation. For example, CREB inhibition or ICER (inducible CREB early repressor) overexpression into the BLA induced impairment of auditory fear memory reconsolidation (Tronson et al., 2012). Moreover, the inhibition of CREB activity did not disrupt memory retrieval. Thus, these results support the idea that disruption of reconsolidation is due to post-retrieval storage failure and not to retrieval impairment (Alberini, 2008; Hardt et al., 2009; Nader et al., 2000; Riccio et al., 2002).

Another transcription factor that is believed to be critical for regulating the transcription of late-response genes that promote functional and/or structural changes underlying memory formation is zif268 (also known as EGR-1). Regulation of zif268 mRNA in the BLA following auditory and contextual fear memory retrieval (Hall et al., 2001; Maddox et al., 2011) suggests that zif268 is critical for the reconsolidation process in the BLA.

Targeted disruption of the transcription factor CCAAT enhancer binding protein β (C/EBPβ) in the BLA impairs reconsolidation of fear memory, specifically of inhibitory avoidance. Within the BLA C/EBPβ appears to be required for reconsolidation but not for consolidation of this mnemonic task (Tronel et al., 2005). This result has been considered as an example of dissociation between the two processes. In other words, the different C/EBPβ requirement in the BLA during these memory phases can be used to dissociate the two processes both at the anatomical and molecular level.

Gene transcription can also be controlled by epigenetic mechanisms and recent studies have focused on those that might be involved in memory reconsolidation. Epigenetic mechanisms include modifications in chromatin structure and DNA methylation. Chromatin consists of DNA packaged around a core of eight histones and it is post-translationally regulated by acetylation of histones on their N-terminal tails via histone acetyltransferases (HATs). This induces the relaxation of chromatin structure, leading to enhanced transcription, and can be reversed by histone deacetylases (HDACs) (Levenson and Sweatt, 2005). On the other hand, DNA methylation is associated with transcriptional repression which is catalyzed by DNA methyltransferases (DNMTs) (Levenson and Sweatt, 2005). Histone acetylation of chromatin is thought to positively regulate transcription, whereas DNA methylation has a negative effect on transcription regulation. Recently, these two processes were shown to be crucial for fear memories reconsolidation in the amygdala. Maddox and coworkers (Maddox and Schafe, 2011; Maddox et al., 2014) reported that intra-LA infusion of inhibitors of HDAC and DNMT activity enhanced and impaired auditory fear memory reconsolidation, respectively. Moreover, the same authors showed that p300/CBP histone acetyltransferase activity within the BLA is critical for reconsolidation of auditory fear conditioning (Maddox et al., 2013), as intra-LA infusion of an inhibitor of the p300/CBP HAT impaired memory reconsolidation.

Post-retrieval inhibition of protein synthesis has been one of the most frequently used treatments to investigate the nature of memory reconsolidation. This use of protein synthesis inhibitors relies on the fact that protein synthesis is considered a marker of consolidation processes, necessary to render structural cellular changes permanent, and of the involvement of a neural region in mnemonic phase. Most of these studies showed that the local injections of protein synthesis inhibitors (anisomycin or cycloheximide) into the BLA after retrieval of a consolidated auditory or contextual fear memory impaired the original memory (Debiec et al., 2006, 2010; Duvarci et al., 2006; Duvarci and Nader, 2004; Duvarci et al., 2005; Jarome et al., 2012; Mamiya et al., 2009; Mamou et al., 2006; Nader et al., 2000; Parsons et al., 2006a; Sacchetti et al., 2007; Wang et al., 2009). Thus, these results provided evidence that fear memories, once reactivated, must undergo protein synthesis-dependent reconsolidation in the BLA to be maintained for subsequent retrieval. Moreover, this reconsolidation process has a temporal window during which blockade of protein synthesis is effective.

There are also negative results. Cammarota et al. (2004) reported that the intra-BLA infusion of anisomycin performed before or after a reactivation session of an inhibitory avoidance task does not affect subsequent memory retention; accordingly it does not seem there is a retrieval-induced, protein synthesis-dependent process that would cause reconsolidation of this fear memory.

During reconsolidation does protein synthesis depend on already existing mRNAs or on synthesis of new mRNAs in the BLA? On this point, contradictory results were obtained; in fact, Parsons et al. (2006a) have shown that auditory and contextual fear memory reconsolidation is independent on mRNA synthesis in the amygdala, whereas according to Duvarci et al. (2008) this process requires de novo mRNA synthesis in this neural structure. Likely, as underlined by the authors, the different results may be ascribed to procedural differences because it is possible that even small changes in experimental procedures can alter the molecular mechanisms engaged (Tronson and Taylor, 2007). There are at least two forms of protein synthesis: the primary mode of translation initiation requires formation of a multi-protein complex of eukaryotic initial factors (eIFs) bound to the 5′ methylated-GTP cap of target mRNAs. Specifically, the interaction between eIF4E and eIF4G facilitates eIF4A RNA helicase activity, recruitment of the 40 S ribosomal subunit, scanning, and peptide elongation. Molecules that block the formation of eIF4F (eIF4E+eIF4G+eIF4A), such as the endogenous regulator 4E-binding protein, which binds to

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and sequesters eIF4E, therefore effectively inhibits cap-dependent translation. Likewise, the small molecule, 4EGI-1, which selectively disrupts eIF4E–eIF4G interactions (eIF4F formation) in vitro, also inhibits cap-dependent translation. The second route by which mRNAs can be translated occurs via internal ribosomal entry sites (IRES), which are unaffected by disruptions to the 5′ cap translation machinery, such as blockade of eIF4E–eIF4G interactions. Very little is known about the specific mechanistic constraints on the phases of the memory processes. By microinfusing 4EGI-1 into the LA, the authors investigated the role of cap-dependent translation and eIF4F formation in reconsolidation of the cued (tone) fear conditioning. 4EGI-1 impaired consolidation but not reconsolidation. Thus, these two memory processes require different translational control mechanisms. In other words, consolidation is dependent on eIF4E–eIF4G interactions or required for cap-dependent protein synthesis; instead, reconsolidation does not seem to require cap-dependent protein synthesis, although it is possible that eIF4E–eIF4G interactions are increased during this memory phase in a temporal window outside those considered in the experiments (Hoeffer et al., 2011).

Neurons protein synthesis is regulated at the translational level through phosphorylation of several intracellular targets. In particular, the signaling pathway controlled by mTOR kinase regulates protein translation by controlling the phosphorylation state of the eIF4E-binding protein 1 (4E-BP1) and p70s6 kinase (p70s6K) (Raught et al., 2001). Post-retrieval intra-BLA infusion of rapamycin, an inhibitor of the mTOR pathway, disrupts reconsolidation of auditory fear memory after retrieval (Parsons et al., 2006b). As considerable evidence shows that many of the effects of mTOR on plasticity are localized to dendrites, this result seems to suggest that mTOR pathway may be involved in regulating the local protein synthesis that supports memory reconsolidation (Parsons et al., 2006b). This same signaling pathway is thought to be also involved in inhibitory avoidance as rapamycin impaired long-term retention of this memory when given before or immediately after retrieval into the BLA (Jobim et al., 2012).

During memory formation, structural changes at synapses occur and transcriptional and translation processes might serve to re-stabilize these changes and to maintain the memory trace. These synaptic alterations may involve re-arrangement of the actin cytoskeleton. Actin filaments are critically involved in several synaptic functions, such as control of neurotransmitter exocytosis (Morales et al., 2000), vesicles recycling (Shupliakov et al., 2002), trafficking of neurotransmitters receptors and structural modification of post-synaptic spines (Honkura et al., 2008; Zhou et al., 2001). Intra-BLA injection of toxin cytochalasin D, which depolymerizes actin filaments, blocks contextual fear memory reconsolidation (Motanis and Maroun, 2012). Similar results were obtained using the death cap toxin phalloidin that arrests actin filaments (Rehberg et al., 2010). Intra-BLA application of phalloidin impairs reconsolidation of auditory and contextual fear memory when performed 30 min after reactivation session; the same treatment performed 6 h after reactivation impairs reconsolidation of auditory memory trace, but not reconsolidation of contextual ones (Rehberg et al., 2010). Thus, these results suggest a crucial role of actin re-arrangement in reconsolidation process of fear memories.

2.2. Hippocampus

Whereas the amygdala is crucial for fear memory associated to either a discrete CS and contextual CS, the hippocampus is necessary for contextual fear memory (inhibitory avoidance included), but not for auditory fear conditioning. Several studies used inactivating agents (such as TTX and muscimol, $GABA_A$ receptor agonist) which depress neuronal excitability to study the hippocampal role in fear memory reconsolidation (Table 2). The results showed that post-reactivation infusion of these pharmacological agents into the dorsal hippocampus disrupted retention of inhibitory avoidance memory (Amaral et al., 2007; Prado-Alacalà et al., 2006). However, the deficit was temporary as it reversed spontaneously with time in the absence of multiple testing (Amaral et al., 2007) and it was attenuated progressively with repeated retention testing (Prado-Alacalà et al., 2006).

2.2.1. Neurotransmitter systems

Hippocampal-dependent fear memories reconsolidation requires several neurotransmitter systems. The contextual fear reconsolidation is impaired by the injection of NMDA antagonist in the hippocampus 15 min before the reactivation session (Lee and Hynds, 2013) demonstrating the importance of this receptor in this mnemonic phase. A critical role in reconsolidation of inhibitory avoidance is played by the hippocampal α7 nicotinic acetylcholine receptor (α7nAChR). Specifically, hippocampal α7nAChR activation by the agonist choline after reactivation of an inhibitory avoidance memory, impaired subsequent retention test in mice trained with a high footshock intensity, whereas the memory retention was improved in mice trained with a low footshock intensity (Boccia et al., 2010). However, Blake et al. (2012, 2013) observed memory reconsolidation improvement following α7nAChR agonist administration also using high shock intensity. On the contrary, intra-hippocampus injection of an α7nAChR antagonist impaired memory reconsolidation regardless of footshock intensity (Boccia et al., 2010).

Contradictory results were obtained about CB1 receptor role in contextual fear memory reconsolidation. Suzuki et al. (2008) found that hippocampal CB1 antagonist administration immediately after a brief re-exposure to training context had no effect on memory retention. However, when the CB1 antagonist was co-administered with anisomycin after context re-exposure, it protected contextual memory against the amnesic effects of anisomycin. The same authors showed similar results using a L-type voltage-gated calcium channel (L-VGCC) antagonist: the blockade of this ionic channel had no effect per se on contextual memory reconsolidation, but its co-administration with protein synthesis inhibitor anisomycin prevented the disruption of reactivated memory. Thus, in the hippocampus, CB1 and L-VGCC mediate destabilization of contextual fear memory which occurs following the reactivation session. On the other hand, De Oliveira Alvares et al. (2008) reported that a CB1 antagonist infused intra-hippocampus after a reactivation session caused facilitation of contextual memory reconsolidation. The local administration of a CB1 agonist caused disruption of this mnemonic process and this effect was abolished by the combined administration of a CB1 agonist and antagonist.

2.2.2. Protein kinases

Unlike what has been observed in the in amygdala, PI-3K inhibitors injection into the hippocampus has no effect on contextual memory reconsolidation (Chen et al., 2005).

Although fear memory consolidation and reconsolidation show an overlap concerning some molecular mechanisms, independent cellular processes were reported within the hippocampus in the two phases of contextual fear memorization. Dissociation was observed for the requirement of MAPK and IκB kinase (IKK) (Lee and Hynds, 2013). Administration of MAPK inhibitor into the dorsal hippocampus did not affect either contextual nor inhibitory avoidance reconsolidation, but impaired their initial consolidation (Lee and Hynds, 2013; Roesler and Quevedo, 2009). Instead, inhibition of hippocampal IKK induced impairment of memory reconsolidation without affecting consolidation (Boccia et al., 2007; Lee and Hynds, 2013).

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2.2.3. Gene expression and protein synthesis

A double dissociation was shown between the transcription factors BDNF (brain-derived neurotrophic factor) and zif268; whereas contextual fear memory consolidation depends on BDNF (Barnes et al., 2012; Lee, 2008; Lee et al., 2004), its reconsolidation requires zif268 (Barnes et al., 2012; Kirtley and Thomas, 2010; Lee, 2008; Lee et al., 2004). Finally, dissociation was observed in the hippocampal C/EBPβ. Using an inhibitory avoidance task, Taubenfeld et al. (2001) reported that this transcription factor in the hippocampus is required for consolidation of a new inhibitory avoidance memory, but nor for a reactivated fear memory.

Using microarray analysis, Barnes et al. (2012) showed that in the hippocampus activation of some genes is shared between consolidation and reconsolidation of contextual fear memory. These genes, however, are regulated in opposite directions. In particular, among the shared genes, there are those associated with pro-inflammatory cytokine pathway that appear to be downregulated during consolidation and upregulated during reconsolidation of contextual fear memory. Also, the injection of an interleukin 1a (IL-1a) receptor antagonist into the hippocampus immediately after retrieval reduced retention of the recalled contextual memory indicating that in the hippocampus the contextual fear memory reconsolidation depends on IL-1a receptor pathway. However, there is no direct experimental evidence about IL-1a antagonism on contextual fear conditioning consolidation. Involvement of the cytokines in contextual fear memory reconsolidation was shown by Machado et al. (2010). These authors reported that intra-hippocampus administration of interleukin 1β up to 30 min after reactivation session decreased subsequent memory retention. This effect was reversed by α-melanocyte-stimulating hormone that had no effect per se on contextual fear memory reconsolidation.

A putative C/EBPβ gene is the insulin-like growth factor II (IGF-II) which has relatively high concentration within the hippocampus. Chen et al. (2011) investigated the functional role of this growth factor in memory reconsolidation. They showed that hippocampal injection of IGF-II after retrieval of inhibitory avoidance memory enhanced subsequent memory retention. However, whether the treatment was performed immediately post-retrieval, two weeks after training, did not induce memory enhancement during retention testing. Thus, memory improvement induced by hippocampal IGF-II occurs only when the temporal window during which inhibitory avoidance memory undergoes reconsolidation.

Cellular imaging has shown that some immediate early genes are activated after retrieval of a previously consolidated memory. In the hippocampus, the retrieval of contextual fear memory is followed by c-Fos and JunB activation, while c-Jun or JunD are not activated (Strekalova et al., 2003). Other IEGs considered were serum- and glucocorticoid-induced kinase 3 (SGK3) and nerve growth factor inducible gene B (NGFI-B). Among these IEGs, SGK3 is upregulated both after training and retrieval of contextual fear in the hippocampus, whereas NGFI-B is regulated only during consolidation (Von Hertzen and Giese, 2005).

Post-retrieval inhibition of protein synthesis has been one of the most used treatments to analyze hippocampus-dependent fear memories reconsolidation, such as just contextual fear conditioning and inhibitory avoidance. It was demonstrated that intra-hippocampus anisomycin injection performed after reactivation of contextual fear memory caused a mnemonic impairment at subsequent retention test (Chen et al., 2005; Debiec et al., 2002; Frankland et al., 2006; Lee, 2008; Lee et al., 2004, 2008; Mamiya et al., 2009; Stafford and Lattal, 2009; Suzuki et al., 2008). Thus, it was concluded that the contextual fear memory stored in the hippocampus undergoes a protein synthesis-dependent reconsolidation process whenever it is reactivated. In other words, hippocampal memory reconsolidation depends on de novo protein synthesis. In contrast, it was shown that injections of anisomycin into the hippocampus were ineffective in blocking reconsolidation of inhibitory avoidance (Cammarota et al., 2004; Taubenfeld et al., 2001) or the blockade is temporary (Power et al., 2006). These results provide evidence that hippocampal protein synthesis is not requested for inhibitory avoidance reconsolidation. Moreover, they also raised the hypothesis that reconsolidation, as a protein synthesis-dependent process, does not occur in this neural site. However, it must be underlined that inhibitory avoidance memory is impaired by systemic administration of anisomycin performed following memory recall (Taubenfeld et al., 2001). The different hippocampal involvement in the reconsolidation of the two paradigms might be due to the different requirements of the tasks. In fact, the inhibitory avoidance is much more complex than classical contextual fear conditioning and requires an instrumental response. The transience of retrieval impairment has been used by some authors to argue against reconsolidation process on the basis that its blockade does not produce the same effects as blocking consolidation (Power et al., 2006). However, the reversibility of amnesia does not necessarily constitute evidence against the reconsolidation hypothesis because these same studies have shown that this effect is dependent on memory reactivation (Amaral et al., 2007; Power et al., 2006).

De novo protein synthesis which occurs during hippocampal contextual fear memory reconsolidation appears to depend on de novo mRNA synthesis. Local injections of mRNA synthesis inhibitors after re-exposure trial impair retention of this memory (De Oliveira Alvares et al., 2008; Lee et al., 2004).

The memory reconsolidation consists of two phases: a destabilization process and re-stabilization ones (Hong et al., 2013; Lee, 2008). It has been hypothesized that during memory re-stabilization/reconsolidation process, removal of existing proteins and incorporation of new proteins occur. For this purpose some authors investigated the involvement of hippocampal proteasome system (the main cellular mechanism controlling protein turnover) in the contextual fear memory destabilization/re-stabilization after retrieval. The results showed that hippocampal injection of the proteasome inhibitor βlac immediately after retrieval/reactivation session has no effect on subsequent contextual memory retention. However, the co-administration of βlac and anisomycin prevented memory reconsolidation impairment induced by anisomycin alone (Lee, 2008; Lee et al., 2008). Thus, proteasome-dependent protein degradation after memory retrieval destabilizes preexisting contextual fear memory which then undergoes reconsolidation process (Lee et al., 2008). Moreover, inhibition of memory destabilization may maintain the strength of a previously acquired memory supporting the concept that memory reconsolidation allows the strengthening of memory (Lee, 2008).

As for the amygdala, it was demonstrated that hippocampal protein synthesis is regulated, at least in part, by mTOR pathway. Intra-hippocampus administration of either transcription factor NF-κB (nuclear factor-κB) inhibitor (Boccia et al., 2007; De la Fuente et al., 2011) or transcriptional inhibitor rapamycin (Gafford et al., 2011; Jobim et al., 2012) impaired reconsolidation of contextual and inhibitory avoidance memories (Boccia et al., 2007; De la Fuente et al., 2011; Gafford et al., 2011; Jobim et al., 2012). Probably, the hippocampal mTOR pathway is not activated by PI-3K since it was reported that PI-3K inhibitors injection into the hippocampus has no effect on contextual memory reconsolidation (Chen et al., 2005). Instead, it was shown that within this neural site translation control through mTOR pathway is also crucial for consolidation of contextual and inhibitory avoidance memories (Boccia et al., 2007; Gafford et al., 2011). Therefore, in the hippocampus there is an overlap between molecular mechanisms underlying the fear memory consolidation and reconsolidation.

Structural changes of synapses also occur during hippocampus-dependent memories reconsolidation. The hippocampal actin

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rearrangement plays an important role since the infusion of the actin rearrangement antagonist after reactivation session blocks subsequent memory retention (Motanis and Maroun, 2012).

2.3. Cortex and other neural sites

Recently, researchers have investigated the potential role of other brain regions in fear memories reconsolidation (Table 3). Among these, several cortical regions have been considered. The medial Prefrontal Cortex (mPFC) appears to be involved in cued fear memory reconsolidation, whereas there are contradictory results about its role in contextual fear reconsolidation. Using an olfactory fear conditioning paradigm Do Monte et al. (2013b) studied the involvement of two mPFC sub-regions, the prelimbic region (PL) and the anterior cingulate cortex (ACC). The results showed that post-retrieval blockade of α_1-adrenergic receptor within PL-mPFC impaired fear memory reconsolidation, whereas the same treatment performed intra-ACC did not affect subsequent memory retention (Do Monte et al., 2013b). Concerning contextual fear memory reconsolidation, infusion of muscimol into the PL-mPFC, but not into IL-mPFC, after reactivation of this memory trace disrupts its subsequent retention (Stern et al., 2014). Moreover, contextual fear memory reactivation is followed by increased expression of zif268/EGR1 in the PL-mPFC but not in IL-mPFC (Stern et al., 2014). In contrast, Mamiya et al. (2009) reported that (i) CREB-mediated gene expression is not activated in the mPFC (both PL and infralimbic regions) when contextual memory is reconsolidated, and (ii) blocking protein synthesis in the mPFC does not affect reconsolidation of this mnemonic trace. Also, the post-reactivation blockade of protein synthesis in the ACC has no effect on contextual memory reconsolidation (Frankland et al., 2006). However, a recent study has shown that injection of anisomycin into the ACC immediately post-reactivation session blocked reconsolidation of this engram (Einarsson and Nader, 2012). The differences between these studies may be attributed to the different parameters employed. Finally, Kritman and Maroun (2013) have demonstrated that PI-3K inhibition in the IL-mPFC before retrieval of contextual fear memory does not influence either retrieval or reconsolidation of the mnemonic trace. Thus, together these results suggest that fear reconsolidation occurs in the mPFC, although the specific subregion recruited may depend on the conditioned stimulus.

In our laboratory, we have recently investigated the Entorhinal Cortex (ENT) role during reconsolidation of fear memories. We found that TTX inactivation of the ENT immediately after a brief reactivation session impairs reconsolidation of contextual fear conditioning (Baldi and Bucherelli, 2014). This result does not confirm those by Cammarota et al. (2004) in inhibitory avoidance which show that infusion of anisomycin or noradrenaline (a well-known retrieval enhancer) in this cortical site performed 15 min or 3 h after the reactivation session does not affect subsequent memory retention.

Another cortical site whose potential involvement in reconsolidation was studied is the perirhinal cortex. This neural site is not involved in auditory fear reconsolidation, as local TTX inactivation or anisomycin injection do not alter retrieved fear trace (Sacchetti et al., 2007). The same authors also investigated the role of the cerebellum (more specifically the cerebellar vermis). TTX cerebellar vermis blockade or cerebellar anisomycin injections induced amnesia if performed immediately after the retrieval of auditory fear memory. This effect did not recover over time, even after a reminder footshock administration. Moreover, using a stronger conditioning, the fear memory reconsolidation was affected by the combined but not independent cerebellar and amygdala blockade. Together these results suggest that the cerebellar vermis is a critical neural sites for fear memory reconsolidation and it may support this process even in the absence of the amygdala (Sacchetti et al., 2007).

In our laboratory the nucleus basalis magnocellularis (NBM) role in fear memory reconsolidation was studied. This interest is derived from our previous demonstration that this neural site, which constitutes the main source of cholinergic projections to the cortex and amygdala, is involved in the consolidation of both auditory and contextual engrams in fear conditioning (Baldi et al., 2007). We found that the NBM is not involved in the post-reactivation phase of fear memories. The TTX NBM inactivation performed immediately post-reactivation is not followed by an impairment of either acoustic CS or contextual memory trace (Baldi et al., 2008). Thus, unlike the consolidation phase, the relationship between NBM and amygdala might not be equally important during the reconsolidation ones.

3. Brain structures involved in fear memory extinction

As mentioned above, fear memory retrieval can initiate another process in addition to the mnemonic trace reconsolidation: memory extinction. Operationally, the engram reactivation is very similar to an extinction session. However, the results are quite different. While the reconsolidation allows, at least partially, the strengthening of the original memory, the extinction weakens its expression. An important factor for the fate of the engram following its retrieval is the duration of re-exposure to the conditioned stimulus in the absence of reinforcement. If the re-exposure is short the reconsolidation process will be triggered, while longer re-exposures will induce extinction (Debiec et al., 2002; De la Fuente et al., 2011; Eisenberg et al., 2003; Lee et al., 2006; Pedreira and Maldonado, 2003; Suzuki et al., 2004).

Experimentally, fear memory extinction can be studied by exposing a previously conditioned subject to the repeated non-reinforced presentation of CS. Cued fear extinction is obtained through the repeated exposure to the cue (tone, visual stimulus or odor) in a new environment, whereas contextual fear extinction is obtained by repeatedly presenting the training context. The subsequent extinction memory can be tested either in presence of the discrete CS or in the acquisition context, respectively. Because in the rodent it is thought that extinction is mainly a new learning, two phases have been distinguished: acquisition and consolidation (Myers and Davis, 2007; Pape and Pare, 2010; Quirk and Mueller, 2008). Depending on the phase studied, the treatment will be applied or before extinction training (acquisition), or immediately after extinction training (consolidation). Several evidence indicates that the amygdala, hippocampus and medial prefrontal cortex play a central role in fear extinction (Tables 4–9). Nevertheless, there is no consensus about the specific role of each brain region in the two phases (acquisition, consolidation) of memory extinction.

3.1. Amygdala

The BLA seems to be critical in fear extinction (Tables 4 and 7). Using cued and contextual fear conditioning paradigms, it was reported that muscimol-induced inactivation of the BLA performed before extinction training causes impairment of fear memory extinction (Herry et al., 2008; Holmes et al., 2013; Laurent et al., 2008; Laurent and Westbrook, 2008, 2010; Sierra-Mercado et al., 2011). Thus, the neuronal activity in the BLA seems to be necessary for acquisition of fear extinction. However, contradictory results were obtained when the BLA inactivation was induced immediately after extinction training. Whereas Sierra-Mercado et al. (2011) reported no effect on retention of auditory fear extinction, Akirav et al. (2006) found that intra-BLA muscimol infusion performed immediately after a short extinction training, but not after a long one, facilitates the auditory fear extinction retention. These authors

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Table 4
Extinction acquisition: effects of intra-amygdala pre-extinction training treatments on fear memory extinction. The table shows the studies using local administration of pharmacological or genetic treatments to determine the role of the amygdala and amygdaloid signaling molecules in fear memories extinction acquisition.

Cerebral site	Behavioral paradigm	Treatment	Effect	References
BLA/BA	Auditory fear conditioning	Muscimol	Impairment	Herry et al. (2008) and Sierra-Mercado et al. (2011)
BLA	Cued fear conditioning (CS: light)	Muscimol	Impairment	Holmes et al. (2013) and Laurent and Westbrook (2010)
BLA	Auditory fear conditioning	Muscimol	No effect	Akirav et al. (2006)
BLA	Contextual fear conditioning	Muscimol	Impairment	Laurent et al. (2008) and Laurent and Westbrook (2008)
BLA	Contextual fear conditioning	BZs	Impairment	Hart et al. (2009, 2010)
BLA	Fear-potentiated startle	NMDA agonist	Improvement	Davis (2002), Mao et al. (2006) and Walker et al. (2002)
BLA	Auditory fear conditioning	NMDA agonist	Improvement	Lee et al. (2006)
BLA	Contextual fear conditioning	NMDA agonist	Impairment	Bolkan and Lattal (2014)
BLA	Fear-potentiated startle	NMDA antagonist	Impairment	Davis (2002), Falls et al. (1992), Lin et al. (2003b) and Mao et al. (2006)
BLA	Inhibitory avoidance	NMDA antagonist	Impairment	Myskiw et al. (2010)
BLA	Contextual fear conditioning	NMDA antagonist	Impairment	Laurent et al. (2008) and Lee and Kim (1998)
BLA	Auditory fear conditioning	NMDA antagonist	Impairment	Lee and Kim (1998), Kwapis et al. (2014) and Zimmerman and Maren (2010)
BLA	Cued fear conditioning (CS: light)	NMDA antagonist	Impairment	Holmes et al. (2013) and Lee and Kim (1998)
CEA	Auditory fear conditioning	NMDA antagonist	No effect	Zimmerman and Maren (2010)
LA	Auditory fear conditioning	NR2B antagonist	Impairment	Sotres-Bayon et al. (2007, (2009)
BLA	Cued fear conditioning (CS: light)	NR2B antagonist	Impairment	Holmes et al. (2013)
BLA	Auditory fear conditioning	L-VGCC antagonists	Impairment	Davis and Bauer (2012)
BLA	Contextual fear conditioning	NR2B antagonist	Impairment	Laurent et al. (2008) and Laurent and Westbrook (2008)
Amygdala	Contextual fear conditioning	AMPA potentiator	Improvement	Zushida et al. (2007)
BLA	Auditory fear conditioning	AMPA potentiator blockade	Impairment	Kim et al. (2007a,b)
BLA	Fear-potentiated startle	AMPA antagonist	No effect	Falls et al. (1992)
BLA	Auditory fear conditioning	AMPA antagonist	No effect	Zimmerman and Maren (2010)
BLA	Auditory fear conditioning	AMPA antagonist	Impairment	Kwapis et al. (2014)
CEA	Auditory fear conditioning	AMPA antagonist	No effect	Zimmerman and Maren (2010)
LA	Auditory fear conditioning	mGluR1 antagonist	Impairment	Kim et al. (2007a)
BLA	Fear-potentiated startle	CB1 agonist	No effect	Kuhnert et al. (2013)
		CB1 antagonist	No effect	
BLA	Inhibitory avoidance	CB1 agonist	No effect	Ganon-Elazar and Akirav (2009)
		CB1 antagonist	Impairment	
BLA	Auditory fear conditioning	NPS	Improvement	Jungling et al. (2008)
		NPS inhibitor	Impairment	
BLA	Fear-potentiated startle	GR agonist	Improvement	Yang et al. (2006)
		GR antagonist	Impairment	
BLA	Fear-potentiated startle	MAPK inhibitor	Impairment	Davis (2002), Lin et al. (2003b) and Lu et al. (2001)
BLA	Auditory fear conditioning	MAPK inhibitor	Impairment	Herry et al. (2006)
BLA	Inhibitory avoidance	PKA inhibitor	Impairment	Myskiw et al. (2010)
BLA	Inhibitory avoidance	CaMKII inhibitor	Impairment	Myskiw et al. (2010)
BLA	Fear-potentiated startle	PI-3K inhibitor	Impairment	Lin et al. (2003b), Mao et al. (2006) and Yang and Lu (2005)
BLA	Fear-potentiated startle	Calcineurin inhibitor	Impairment	Lin et al. (2003a)
BLA	Fear-potentiated startle	Protein synthesis inhibitor	Impairment	Lin et al. (2003b) and Yang and Lu (2005)
BLA	Fear-potentiated startle	mRNA synthesis inhibitor	No effect	Lin et al. (2003b)
BLA	Fear-potentiated startle	mRNA synthesis inhibitor	Impairment	Yang and Lu (2005)
BLA	Auditory fear conditioning	CREB viral vectors	No effect	Tronson et al. (2012)
BLA	Fear-potentiated startle	BDNF/TrkB viral inhibitor	Impairment	Chhatwal et al. (2006)
BLA	Auditory fear conditioning	PSA-NCAM cleavage	Improvement	Markram et al. (2007)

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; BA, basal amygdala; BDNF, brain-derived neurotrophic factor; BLA, basolateral amygdala; BZs, benzodiazepines; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CB1, cannabinoid receptor type 1; CEA, central amygdala; CREB, cyclic AMP response element-binding protein; GR, glucocorticoid receptor; LA, lateral amygdala; L-VGCC, L-type voltage-gated calcium channel; MAPK, mitogen-activated protein kinase; mGluR1, metabotropic glutamate receptor subtype 1; NMDA, N-methyl-D-aspartate receptor; NPS, neuropeptide S; NR2B, NMDA receptor subtype 2B; PI-3K, phosphatidylinositol 3 kinase; PKA, protein kinase A; PSA-NCAM, polysialylated neural cell adhesion molecule; TrkB, tyrosine kinase B receptor.

concluded that the BLA is involved in extinction consolidation and that $GABA_A$ transmission facilitates this specific phase of extinction process. Different results were obtained in contextual fear extinction as well. Laurent and Westbrook (2008) showed that intra-BLA post-extinction injection of muscimol impairs extinction retention of this memory; on the contrary, no effect was reported by Berlau and McGaugh (2006). A BLA role in contextual memory extinction consolidation was demonstrated in our laboratory. Bilateral BLA TTX inactivation, performed after extinction training of this memory task, almost completely impaired extinction (Baldi and Bucherelli, 2010).

3.1.1. Neurotransmitter systems

Concerning the different BLA neurotransmitter systems involved in the fear extinction, one of the most investigated is glutamate and particularly its action at NMDA receptors. Among the first experiments dealing with amygdalar NMDA receptors role in fear extinction there are those by Falls et al. (1992). They employed the fear-potentiated startle paradigm and found that infusion of a NMDA antagonist before extinction training into the BLA blocks extinction of conditioned fear. These results were subsequently replicated not only in fear potentiated startle (Davis, 2002; Lin et al., 2003b) but also using inhibitory avoidance (Myskiw et al.,

Table 5
Extinction acquisition: effects of intra-hippocampus pre-extinction training treatments on fear memory extinction. The table shows the studies using local administration of pharmacological or genetic treatments to determine the role of the hippocampus and hippocampal signaling molecules in fear memories extinction acquisition.

Cerebral site	Behavioral paradigm	Treatment	Effect	References
DHC	Auditory fear conditioning	Muscimol	Impairment	Corcoran et al. (2005) and Xue et al. (2014)
VHC	Auditory fear conditioning	Muscimol	Impairment	Sierra-Mercado et al. (2011)
DHC	Auditory fear conditioning	NMDA agonist	Improvement	Ren et al. (2013)
DHC	Contextual fear conditioning	NMDA agonist	Improvement	Bolkan and Lattal (2014)
DHC	Inhibitory avoidance	NMDA antagonist	Impairment	Cammarota et al. (2005), Myskiw et al. (2010) and Szapiro et al. (2003)
DHC	Inhibitory avoidance	CB1 agonist	Improvement	Abush and Akirav (2010)
		CB1 antagonist	Impairment	
DHC	Inhibitory avoidance	MAPK inhibitor	Impairment	Szapiro et al. (2003)
DHC	Fear-potentiated startle	MAPK inhibitor	No effect	Shen et al. (2011)
DHC	Inhibitory avoidance	PKA inhibitor	Impairment	Myskiw et al. (2010) and Szapiro et al. (2003)
DHC	Inhibitory avoidance	CaMKII	Impairment	Myskiw et al. (2010) and Szapiro et al. (2003)
DHC	Fear-potentiated startle	Ginkgo biloba extract	Improvement	Shen et al. (2011)
DHC	Contextual fear conditioning	SFKs inhibitor	Improvement	Isosaka et al. (2009)
DHC	Contextual fear conditioning	Protein tyrosine phosphatases inhibitor	Impairment	De la Fuente et al. (2011) and Isosaka and Yuasa (2010)
DHC	Inhibitory avoidance	Protein synthesis inhibitor	Impairment	Cammarota et al. (2005) and Vianna et al. (2001, 2003)
DHC	Inhibitory avoidance	mRNA synthesis inhibitor	Impairment	Vianna et al. (2003)
DHC	Contextual fear conditioning	rBDNF	Impairment	Kirtley and Thomas (2010)
		Zif268-ASO	No effect	
DHC	Contextual fear conditioning	NFAT inhibitor	Impairment	De la Fuente et al. (2011)
DHC	Contextual fear conditioning	HDAC inhibitor	Improvement	Lattal et al. (2007)

BDNF, brain-derived neurotrophic factor; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CB1, cannabinoid receptor type 1; DHC, dorsal hippocampus; HDAC, histone deacetylase; MAPK, mitogen-activated protein kinase; NFAT, nuclear factor of activated T-cells; NMDA, N-methyl-D-aspartate receptor; PKA, protein kinase A; rBDNF, recombinant BDNF protein; SFKs, Src-family tyrosine kinases; VHC, ventral hippocampus; ZIF268, zinc finger 268; ZIF268-ASO, antisense oligonucleotide targeting ZIF268.

2010), contextual (Kwapis et al., 2014; Laurent et al., 2008; Lee and Kim, 1998) and cued (Holmes et al., 2013; Lee and Kim, 1998; Zimmerman and Maren, 2010) fear conditioning paradigms. These results support the idea that BLA NMDA receptors are involved in acquisition of fear memory extinction. Nevertheless, there is also evidence for amygdalar NMDA receptors role in fear memory extinction consolidation. Intra-BLA infusion of the NMDA antagonist immediately following the first of two sessions of extinction produces impairment of inhibitory avoidance and contextual fear extinction (Fiorenza et al., 2012). Further evidence for BLA NMDA receptors role in fear extinction was obtained employing a partial agonist, DCS. DCS facilitates extinction of fear potentiated startle and auditory fear when administered into the BLA before extinction training (Davis, 2002; Lee et al., 2006; Mao et al., 2006; Walker et al., 2002) confirming a role of these receptors in extinction acquisition. Moreover, fear extinction facilitation was observed when DCS is injected after extinction training (Akirav et al., 2009; Fiorenza et al., 2012; Ledgerwood et al., 2003; Mao et al., 2006). This last effect seems to reflect modulation of extinction consolidation (Myskiw et al., 2014). Different results have been obtained using contextual fear paradigm. In fact, intra-BLA DCS administration performed before or immediately after extinction training impairs contextual fear memory extinction. These effects seem to depend on the behavior of the animals during extinction training (Bolkan and Lattal, 2014).

The functional role of NMDA receptors seems to depend on their subunit composition (Cull-Candy and Leszkiewicz, 2004). Specifically, the 2B subunit appears to be involved in learning and associated plasticity in several brain sites (Tang et al., 1999; Ge et al., 2007). The NR2B pharmacological manipulation is a relatively selective tool for studying the contribution of NMDA receptor-mediated plasticity to extinction. The selective inactivation of NMDA receptor containing NR2B subunit in the LA/BLA before extinction training impairs acquisition of conditioned fear extinction to both acoustic CS (Sotres-Bayon et al., 2007) and context (Laurent et al., 2008; Laurent and Westbrook, 2008); on the other hand, the same treatment performed immediately after extinction training has no effect on the extinction of the two fear memory tasks (Laurent and Westbrook, 2008; Sotres-Bayon et al., 2009). These findings suggest that amygdalar NMDA receptors containing NR2B subunit are involved in acquisition, but not consolidation of fear memory extinction. NMDA receptors activation allows calcium influx resulting in an increased intracellular concentration of the ion. However, calcium influx is also associated with L-VGCCs activation. The L-VGCCs role in fear extinction is controversial because contradictory results of their involvement were obtained (Schafe, 2008) using genetic and pharmacological approaches. A recent work (Davis and Bauer, 2012) employed local infusions into the BLA of L-VGCCs antagonists to test the involvement of these channels in auditory fear extinction. It was found that pre-extinction training L-VGCCs blockade into this neural site induces impairment of long-term extinction retention. However, since the animals subjected to this treatment showed extinction acquisition, the results suggest that L-VGCCs are necessary for the fear extinction consolidation.

The AMPA receptor is another subtype of glutamate receptors involved in experience-dependent forms of synaptic plasticity (Zushida et al., 2007). Falls et al. (1992) showed that administration of AMPA receptor antagonist into the BLA before extinction training has no effect on subsequent extinction retention of fear potentiated startle. Similar results were obtained in an auditory fear task (Zimmerman and Maren, 2010). Together these results reveal that AMPA receptor in the BLA is not required for fear extinction. However, a recent finding indicates that intra-BLA pre-extinction training administration of AMPA antagonist impairs contextual fear extinction retention (Kwapis et al., 2014). Moreover, intra-amygdala pre-extinction training injection of an AMPA receptor "potentiator" facilitates contextual fear memory extinction (Zushida et al., 2007). This "potentiator" might exert its effect on fear extinction by promoting AMPA receptors internalization (Kim et al., 2007b; Maren, 2005; Yeh et al., 2006). Recently a synthetic peptide that blocks the internalization of these receptors was employed and it was found that intra-BLA infusion before extinction training impairs auditory fear extinction (Kim et al., 2007b). So the potential role of amygdala AMPA receptors in fear memory extinction requires further investigation.

As recent work has evidenced that glutamate receptors in the CEA are also implicated in the acquisition of fear conditioning, Zimmerman and Maren (2010) investigated the potential role of

Table 6
Extinction acquisition: effects of intra several cerebral sites pre-extinction training treatments on fear memory extinction. The table shows the studies using local administration of pharmacological or genetic treatments to determine the role of specific cerebral sites and signaling molecules in fear memories extinction acquisition.

Cerebral site	Behavioral paradigm	Treatment	Effect	References
mPFC	Auditory fear conditioning	Muscimol	Improvement	Akirav et al. (2006)
mPFC	Auditory fear conditioning	TTX	Impairment	Sierra-Mercado et al. (2006)
mPFC	Contextual fear conditioning	Muscimol	Impairment	Laurent and Westbrook (2008)
IL-mPFC	Auditory fear conditioning	Muscimol	Impairment	Sierra-Mercado et al. (2011)
IL-mPFC	Contextual fear conditioning	Muscimol	Impairment	Laurent and Westbrook (2009)
PL-mPFC	Auditory fear conditioning	Muscimol	No effect	Sierra-Mercado et al. (2011)
PL-mPFC	Contextual fear conditioning	Muscimol	No effect	Laurent and Westbrook (2009)
IL-mPFC	Auditory fear conditioning	M-type K^+ channels agonist	Impairment	Santini and Porter (2010)
		M-type K^+ channels antagonist	Improvement	
mPFC	Auditory fear conditioning	NMDA agonist	No effect	Chang and Maren (2011)
mPFC	Auditory fear conditioning	NMDA antagonist	Impairment	Burgos-Robles et al. (2007)
mPFC	Auditory fear conditioning	NR2B antagonist	No effect	Sotres-Bayon et al. (2009)
mPFC	Contextual fear conditioning	NR2B antagonist	No effect	Laurent and Westbrook (2008)
IL-mPFC	Contextual fear conditioning	AMPA potentiator	Improvement	Zushida et al. (2007)
IL-mPFC	Auditory fear conditioning	β-AR antagonist	Impairment	Mueller et al. (2008)
mPFC	Contextual fear conditioning	α-AR antagonist	Impairment	Do Monte et al. (2010)
IL-mPFC	Auditory fear conditioning	D1 antagonist	Impairment	Hikind and Maroun (2008)
IL-mPFC	Auditory fear conditioning	D2 antagonist	Impairment	Mueller et al. (2010)
IL-mPFC	Auditory fear conditioning	D4 antagonist	Impairment	Pfeiffer and Fendt (2006)
IL-mPFC	Auditory fear conditioning	Muscarinic antagonist	Impairment	Santini et al. (2012)
IL-mPFC	Fear-potentiated startle	CB1 agonist	Improvement	Lin et al. (2009)
IL-mPFC	Fear-potentiated startle	CB1 agonist	No effect	Kuhnert et al. (2013)
IL-mPFC	Fear-potentiated startle	CB1 antagonist	Impairment	Kuhnert et al. (2013) and Lin et al. (2009)
IL-mPFC	Contextual fear conditioning	Cannabidiol	Improvement	Do Monte et al. (2013a,b)
IL-mPFC	Auditory fear conditioning	PKA inhibitor	Impairment	Mueller et al. (2008)
IL-mPFC	Auditory fear conditioning	CaMKII inhibitor	No effect	Mueller et al. (2008)
IL-mPFC	Auditory fear conditioning	Protein synthesis inhibitor	Impairment	Mueller et al. (2008) and Santini et al. (2004)
IL-mPFC	Auditory fear conditioning	mRNA synthesis inhibitor	Impairment	Mueller et al. (2008)
IL-mPFC	Auditory fear conditioning	BDNF	Improvement	Peters et al. (2010)
Parietal cortex	Inhibitory avoidance	NMDA antagonist	No effect	Myskiw et al. (2010)
		CaMKII antagonist	No effect	
		PKA inhibitor	No effect	
Cingulate cortex	Inhibitory avoidance	NMDA antagonist	No effect	Myskiw et al. (2010)
		CaMKII antagonist	No effect	
		PKA inhibitor	No effect	
Nucleus accumbens	Auditory fear conditioning	D2 antagonist	Impairment	Holtzman-Assif et al. (2010)
Medial geniculate nucleus	Auditory fear conditioning	NMDA antagonist	Impairment	Orsini and Maren (2009)
		AMPA antagonist	Impairment	
		Protein synthesis inhibitor	No effect	
		MAPK inhibitor	No effect	
Midline thalamic nuclei	Auditory fear conditioning	Muscimol	No effect	Padilla-Coreano et al. (2012)
dPAG	Auditory fear conditioning	ORs antagonist	No effect	McNally et al. (2004)
vlPAG	Auditory fear conditioning	ORs antagonist	Impairment	McNally et al. (2004)
vlPAG	Auditory fear conditioning	μ-ORs antagonist	Impairment	McNally et al. (2005)
		δ-ORs antagonist	No effect	
		κ-ORs antagonist	No effect	
vlPAG	Auditory fear conditioning	cAMP analog	Impairment	McNally et al. (2005)
		PKA activator	No effect	
		MAPK inhibitor	No effect	
vlPAG	Auditory fear conditioning	Endogenous opioid catabolizing enzymes inhibitor	Improvement	McNally (2005)
Cerebellar interpositus nucleus	Fear-potentiated startle	NMDA antagonist	No effect	Falls et al. (1992)

α-AR, α-adrenergic receptor; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; β-AR, β-adrenergic receptor; BDNF, brain-derived neurotrophic factor; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; cAMP, cyclic AMP; CB1, cannabinoid receptor type 1; δ-ORs, opioid receptors subtype δ; D1, D2, D4, dopaminergic receptors type 1, 2, 4; dPAG, dorsal periaqueductal gray; IL-mPFC, infralimbic subregion of the medial prefrontal cortex; κ-ORs, opioid receptors subtype κ; μ-ORs, opioid receptors subtype μ; MAPK, mitogen-activated protein kinase; mPFC, medial prefrontal cortex; NMDA, N-methyl-D-aspartate receptor; NR2B, NMDA receptor subtype 2B; ORs, opioid receptors; PKA, protein kinase A; PL-mPFC, prelimbic subregion of the medial prefrontal cortex; TTX, tetrodotoxin; vlPAG, ventro-lateral periaqueductal gray.

NMDA and AMPA receptors within this amygdaloid nucleus in fear extinction. Neither pre-extinction training NMDA antagonist nor AMPA antagonist injected into the CEA affect auditory fear extinction. Thus, whereas the BLA may have a broader role in acquiring both fear and extinction memories, CEA plays a selective role in fear acquisition.

The literature about the involvement of the metabotropic glutamate receptors (mGluRs) in fear memory extinction is quite limited. The only report, to our knowledge, showed that local infusion of a mGluR1 antagonist into the LA before extinction training impairs the extinction of auditory fear memory (Kim et al., 2007a). Moreover, mGluR1 activity seems to be linked specifically to mechanisms underlying extinction, because intra-LA administration of the same antagonist before fear conditioning has no effect on fear acquisition (Kim et al., 2007a).

γ-Aminobutyric acid (GABA) is considered the major inhibitory neurotransmitter in the mammalian central nervous system. GABA seems to play a complex role in fear extinction and although the results obtained are mixed and sometimes contradictory, this neurotransmitter appears to interfere with the acquisition and consolidation of fear extinction memory. Increasing GABAergic transmission before extinction training disrupts extinction retention. For example, Hart et al. (2009, 2010) observed that midazolam (a benzodiazepine) injected intra-BLA before extinction training

Table 7
Extinction consolidation: effects of intra-amygdala post-extinction treatments on fear memory extinction. The table shows the studies using local administration of pharmacological or genetic treatments to determine the role of the amygdala and amygdaloid signaling molecules in fear memories extinction consolidation.

Cerebral site	Behavioral paradigm	Treatment	Effect	References
BLA	Auditory fear conditioning	Muscimol	No effect	Sierra-Mercado et al. (2011)
BLA	Auditory fear conditioning	Muscimol	Improvement	Akirav et al. (2006)
BLA	Contextual fear conditioning	Muscimol	No effect	Berlau and McGaugh (2006)
BLA	Contextual fear conditioning	Muscimol	Impairment	Laurent and Westbrook (2008)
BLA	Contextual fear conditioning	TTX	Impairment	Baldi and Bucherelli (2010)
BLA	Contextual fear conditioning	GABA antagonist	Improvement	Berlau and McGaugh (2006)
BLA	Fear-potentiated startle	NMDA agonist	Improvement	Mao et al. (2006)
BLA	Inhibitory avoidance	NMDA agonist	Improvement	Fiorenza et al. (2012)
BLA	Cued fear conditioning (CS: light)	NMDA agonist	Improvement	Ledgerwood et al. (2003)
BLA	Contextual fear conditioning	NMDA agonist	Improvement	Akirav et al. (2009) and Fiorenza et al. (2012)
BLA	Contextual fear conditioning	NMDA agonist	Impairment	Bolkan and Lattal (2014)
BLA	Inhibitory avoidance	NMDA antagonist	Impairment	Fiorenza et al. (2012)
BLA	Contextual fear conditioning	NMDA antagonist	Impairment	Fiorenza et al. (2012)
LA	Auditory fear conditioning	NR2B antagonist	No effect	Sotres-Bayon et al. (2009)
BLA	Contextual fear conditioning	NR2B antagonist	No effect	Laurent and Westbrook (2008)
LA	Auditory fear conditioning	β-AR agonist	Impairment	Debiec et al. (2011)
BLA	Contextual fear conditioning	β-AR antagonist	Improvement	Fiorenza et al. (2012)
BLA	Contextual fear conditioning	β-AR antagonist	No effect	Berlau and McGaugh (2006)
BLA	Inhibitory avoidance	β-AR antagonist	Improvement	Fiorenza et al. (2012)
BLA	Contextual fear conditioning	Norepinephrine	No effect	Fiorenza et al. (2012)
BLA	Contextual fear conditioning	Norepinephrine	Improvement	Berlau and McGaugh (2006)
BLA	Inhibitory avoidance	Norepinephrine	Impairment	Fiorenza et al. (2012)
BLA	Contextual fear conditioning	D1 agonist	No effect	Fiorenza et al. (2012)
BLA	Inhibitory avoidance	D1 agonist	No effect	Fiorenza et al. (2012)
BLA	Auditory fear conditioning	D1 antagonist	Impairment	Hikind and Maroun (2008)
BLA	Contextual fear conditioning	D1 antagonist	No effect	Fiorenza et al. (2012)
BLA	Inhibitory avoidance	D1 antagonist	Impairment	Fiorenza et al. (2012)
BLA	Contextual fear conditioning	Muscarinic agonist	Improvement	Boccia et al. (2009)
BLA	Contextual fear conditioning	H2 antagonist	Improvement	Fiorenza et al. (2012)
BLA	Inhibitory avoidance	H2 antagonist	Impairment	Fiorenza et al. (2012)
BLA	Contextual fear conditioning	Histamine N-methyltransferase inhibitor	Improvement	Fiorenza et al. (2012)
BLA	Inhibitory avoidance	Histamine N-methyltransferase inhibitor	Improvement	Fiorenza et al. (2012)
BLA	Auditory fear conditioning	PKA activator	No effect	Tronson et al. (2006)
BLA	Fear-potentiated startle	PI-3K inhibitor	Impairment	Mao et al. (2006)
BLA	Contextual fear conditioning	PI-3K inhibitor	Impairment	Kritman and Maroun (2013)
BLA	Auditory fear conditioning	Protein synthesis inhibitor	Impairment	Duvarci et al. (2006)
BLA	Contextual fear conditioning	Protein synthesis inhibitor	Impairment	Mamiya et al. (2009)
BLA	Auditory fear conditioning	FGF2	Improvement	Graham and Richardson (2011)

β-AR, β-adrenergic receptor; BLA, basolateral amygdala; D1, dopaminergic receptor type 1; FGF2, fibroblast growth factor 2; GABA, γ-aminobutyric acid; H2, histaminergic receptor type 2; LA, lateral amygdala; NMDA, N-methyl-D-aspartate receptor; NR2B, NMDA receptor subtype 2B; PI-3K, phosphatidylinositol 3 kinase; PKA, protein kinase A; TTX, tetrodotoxin.

impairs extinction of contextual fear, but spares and facilitates the re-learning of extinction. Thus intra-BLA GABAergic transmission appears to be involved in fear extinction acquisition. However, a study by Akirav et al. (2006) reported findings that seem to contradict this conclusion. In fact, these authors demonstrated that administration of muscimol (a $GABA_A$ agonist) into the BLA before an extinction training session does not alter extinction learning of auditory fear conditioning. On the other hand, it was shown that in this neural site the levels of gephyrin protein and mRNA and mRNAs of other GABAergic markers (such as GABA-synthesizing enzymes) are significantly increased following extinction training of fear-potentiated startle (Chhatwal et al., 2005; Heldt and Ressler, 2007). That is, gephyrin and other GABAergic markers are upregulated after fear extinction training in the BLA suggesting an increased GABAergic transmission (Chhatwal et al., 2005; Heldt and Ressler, 2007).

GABAergic transmission in the BLA has been implicated in the consolidation of fear extinction as well. Berlau and McGaugh (2006) observed enhanced extinction of contextual fear memory by unilateral intra-BLA infusion of the GABA receptor antagonist bicuculline when performed immediately but not 3 h after extinction training. These results support the idea that intra-BLA GABA antagonists facilitate extinction consolidation. Accordingly, the agonists should impair extinction. Instead, the results by Akirav et al. (2006) showed that administration of muscimol into the BLA after a short extinction session, but not a long one, leads to a significant improvement of the auditory fear extinction retention. That is, increasing amygdalar GABAergic transmission after extinction improves extinction retention. Maybe these unexpected results are due to the methodology used to induce extinction. The authors employed a short extinction session which is more similar to a reactivation session than an extinction one. Therefore they might have disrupted the reconsolidation of the original mnemonic trace rather than facilitated the extinction consolidation.

Norepinephrine is implicated in fear learning and memory (Debiec et al., 2011). Noradrenergic involvement in fear extinction was the topic of some recent studies which employed both Pavlovian fear conditioning and inhibitory avoidance. Results by Berlau and McGaugh (2006) showed that intra-BLA adrenergic activation promotes, whereas adrenergic blockade hinders memory consolidation in fear extinction. Using a contextual fear conditioning paradigm, the authors reported that unilateral intra-BLA infusion of norepinephrine following extinction training enhances extinction retention. On the contrary, administration of β-AR antagonist propranolol does not significantly affect extinction retention per se, but it prevents the extinction facilitation by intra-BLA bicuculline (GABAergic antagonist) whether the two compounds are co-administered. Thus, noradrenergic signaling seems to mediate memory modulatory effects of GABA. Different results were obtained by Fiorenza et al. (2012) who considered extinction of two different fear-motivated tasks: contextual fear conditioning and inhibitory avoidance. Intra-BLA post-extinction injection of

Table 8
Extinction consolidation: effects of intra-hippocampus post-extinction treatments on fear memory extinction. The table shows the studies using local administration of pharmacological or genetic treatments to determine the role of the hippocampus and hippocampal signaling molecules in fear memories extinction consolidation.

Cerebral site	Behavioral paradigm	Treatment	Effect	References
DHC	Contextual fear conditioning	Muscimol	No effect	Berlau and McGaugh (2006)
VHC	Auditory fear conditioning	Muscimol	No effect	Sierra-Mercado et al. (2011)
DHC	Inhibitory avoidance	NMDA agonist	Improvement	Fiorenza et al. (2012)
DHC	Contextual fear conditioning	NMDA agonist	Improvement	Bolkan and Lattal (2014) and Fiorenza et al. (2012)
DHC	Inhibitory avoidance	NMDA antagonist	Impairment	Fiorenza et al. (2012) and Szapiro et al. (2003)
DHC	Contextual fear conditioning	NMDA antagonist	Impairment	De Carvalho Myskiw et al. (2014) and Fiorenza et al. (2012)
DHC	Contextual fear conditioning	NR2A antagonist	Impairment	Leadrebrand et al. (2014)
		NR2B antagonist	No effect	
DHC	Inhibitory avoidance	NR2B agonist	No effect	Bonini et al. (2011)
		NR2B antagonist	No effect	
DHC	Contextual fear conditioning	L-VGCC inhibitor	Impairment	De Carvalho Myskiw et al. (2014)
DHC	Inhibitory avoidance	mGluR5 antagonist	No effect	Simonyi et al. (2007)
		mGluR1 antagonist	Impairment	
DHC	Inhibitory avoidance	Norepinephrine	No effect	Fiorenza et al. (2012)
		β-AR antagonist	Impairment	
DHC	Contextual fear conditioning	Norepinephrine	No effect	Fiorenza et al. (2012)
		β-AR antagonist	No effect	
DHC	Contextual fear conditioning	β-AR antagonist	Impairment	Ouyang and Thomas (2005)
DHC	Inhibitory avoidance	D1agonist	Improvement	Fiorenza et al. (2012)
		D1 antagonist	Impairment	
DHC	Inhibitory avoidance	nAChR agonists	Improvement	De Aguiar et al. (2013)
		nAChR antagonists	No effect	
DHC	Contextual fear conditioning	D1 agonist	Improvement	Fiorenza et al. (2012)
		D1 antagonist	Impairment	
DHC	Contextual fear conditioning	CB1 agonist	Improvement	De Oliveira Alvares et al. (2008)
		CB1 antagonist	Impairment	
DHC	Inhibitory avoidance	Histamine N-methyl-transferase inhibitor	Improvement	Bonini et al. (2011) and Fiorenza et al. (2012)
		H2 antagonist	Impairment	
DHC	Inhibitory avoidance	Histamine, H2 agonist	Improvement	Bonini et al. (2011)
DHC	Inhibitory avoidance	H3 agonist	Impairment	Bonini et al. (2011)
DHC	Inhibitory avoidance	H1 agonist, H1 antagonist, H3 antagonist	No effect	Bonini et al. (2011)
DHC	Contextual fear conditioning	Histamine N-methyl-transferase inhibitor	Improvement	Fiorenza et al. (2012)
		H2 antagonist	Impairment	
DHC	Inhibitory avoidance	GRPR inhibitor	Impairment	Luft et al. (2006)
DHC	Inhibitory avoidance	MAPK inhibitor	Impairment	Bevilaqua et al. (2007), Bonini et al. (2011), Rossato et al. (2006) and Szapiro et al. (2003)
DHC	Contextual fear conditioning	MAPK inhibitor	Impairment	Fischer et al. (2007) and Huh et al. (2009)
DHC	Inhibitory avoidance	PKA inhibitor	Impairment	Szapiro et al. (2003)
DHC	Contextual fear conditioning	AKAPs inhibitor	Improvement	Nijholt et al. (2008)
DHC	Inhibitory avoidance	CaMKII inhibitor	Impairment	Szapiro et al. (2003)
DHC	Contextual fear conditioning	PI-3K inhibitor	Impairment	Chen et al. (2005)
DHC	Inhibitory avoidance	Protein synthesis inhibitor	Impairment	Luft et al. (2006), Power et al. (2006) and Vianna et al. (2001)
DHC	Contextual fear conditioning	Protein synthesis inhibitors	Improvement	Fischer et al. (2004)
DHC	Contextual fear conditioning	Protein synthesis inhibitor	Impairment	De Carvalho Myskiw et al. (2014)
Hippocampus	Contextual fear conditioning	Protein synthesis inhibitor	No effect	Mamiya et al. (2009)
DHC	Inhibitory avoidance	mRNA synthesis inhibitor	No effect	Vianna et al. (2003)
DHC	Contextual fear conditioning	Proteasome inhibitor	Impairment	Lee et al. (2008)
DHC	Contextual fear conditioning	Proteasome inhibitor	No effect	De Carvalho Myskiw et al. (2014)
DHC	Contextual fear conditioning	CdK5 inhibitor	Improvement	Sananbenesi et al. (2007)
DHC	Contextual fear conditioning	GTPase Rac-1 inhibitor	Improvement	Sananbenesi et al. (2007)
DHC	Contextual fear conditioning	PAK-1 inhibitor	Impairment	Sananbenesi et al. (2007)
DHC	Contextual fear conditioning	Actin dynamics inhibitors	Impairment	Fischer et al. (2004)
DHC	Inhibitory avoidance	SFKs inhibitor	Impairment	Bevilaqua et al. (2005)
DHC	Contextual fear conditioning	NF-κB inhibitor	Improvement	De la Fuente et al. (2011)

AKAPs, A-kinase anchoring proteins; β-AR, β-adrenergic receptor; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CB1, cannabinoid receptor type 1; Cdk5, cyclin-dependent kinase 5; D1, dopaminergic receptor type 1; DHC, dorsal hippocampus; GRPR, gastrin-releasing peptide receptor; GTPase Rac-1, guanosine triphosphatase Rac-1; H1, H2, H3, histaminergic receptors type 1, 2, 3; L-VGCC, L-type voltage-gated calcium channel; MAPK, mitogen-activated protein kinase; mGluR1, mGluR5, metabotropic glutamate receptors subtype 1, 5; nAChR, nicotinic acetylcholine receptor; NF-κB, nuclear factor κB; NMDA, N-methyl-D-aspartate receptor; NR2A, NR2B, NMDA receptors subtype 2A, 2B; PAK-1, p21 activated kinase-1; PI-3K, phosphatidylinositol 3 kinase; PKA, protein kinase A; SFKs, Src-family tyrosine kinases; VHC, ventral hippocampus.

norepinephrine impairs extinction of the inhibitory avoidance, but has no effect on extinction of contextual fear paradigm. Instead, administration of β-AR antagonist timolol in the same neural site enhances extinction of both tasks. Finally, amygdala noradrenergic signaling involvement in fear extinction was shown by Debiec et al. (2011) using an auditory fear conditioning paradigm. β-AR agonist isoproterenol infused into the LA after retrieval of conditioned fear impairs its extinction. Although these studies report slightly different results, all seem to indicate an involvement of amygdalar noradrenergic system in the fear extinction consolidation.

Cholinergic activation within the BLA appears to modulate the consolidation of contextual fear memory as well. In fact, intra-BLA infusions of the muscarinic cholinergic agonist oxotremorine performed after each of two extinction sessions cause enhanced

Table 9
Extinction consolidation: effects of intra several cerebral sites post-extinction treatments on fear memory extinction. The table shows the studies using local administration of pharmacological or genetic treatments to determine the role of specific cerebral sites and signaling molecules in fear memories extinction consolidation.

Cerebral site	Behavioral paradigm	Treatment	Effect	References
mPFC	Auditory fear conditioning	Muscimol	No effect	Akirav et al. (2006)
mPFC	Auditory fear conditioning	TTX	No effect	Sierra-Mercado et al. (2006)
mPFC	Contextual fear conditioning	Muscimol	Impairment	Laurent and Westbrook (2008)
IL-mPFC	Auditory fear conditioning	Muscimol	No effect	Sierra-Mercado et al. (2011)
IL-mPFC	Contextual fear conditioning	Muscimol	Impairment	Laurent and Westbrook (2009)
IL-mPFC	Auditory fear conditioning	M-type K^+ channels antagonist	No effect	Santini and Porter (2010)
IL-mPFC	Auditory fear conditioning	GABA antagonist	Improvement	Chang and Maren (2011)
IL-mPFC	Contextual fear conditioning	GABA antagonist	Improvement	Thompson et al. (2010)
PL-mPFC	Contextual fear conditioning	GABA antagonist	No effect	Thompson et al. (2010)
mPFC	Contextual fear conditioning	NMDA agonist	Improvement	Fiorenza et al. (2012)
mPFC	Inhibitory avoidance	NMDA agonist	Improvement	Fiorenza et al. (2012)
mPFC	Auditory fear conditioning	NMDA antagonist	Impairment	Burgos-Robles et al. (2007) and Holmes et al. (2012)
mPFC	Contextual fear conditioning	NMDA antagonist	Impairment	Fiorenza et al. (2012)
mPFC	Inhibitory avoidance	NMDA antagonist	Impairment	Fiorenza et al. (2012)
mPFC	Auditory fear conditioning	NR2B antagonist	Impairment	Sotres-Bayon et al. (2009)
mPFC	Contextual fear conditioning	NR2B antagonist	Impairment	Laurent and Westbrook (2008)
IL-mPFC	Auditory fear conditioning	β-AR antagonist	No effect	Mueller et al. (2008)
mPFC	Contextual fear conditioning	β-AR antagonist	Improvement	Fiorenza et al. (2012)
mPFC	Inhibitory avoidance	β-AR antagonist	Impairment	Fiorenza et al. (2012)
mPFC	Contextual fear conditioning	Norepinephrine	Impairment	Fiorenza et al. (2012)
mPFC	Inhibitory avoidance	Norepinephrine	No effect	Fiorenza et al. (2012)
mPFC	Contextual fear conditioning	D1 agonist	No effect	Fiorenza et al. (2012)
mPFC	Inhibitory avoidance	D1 agonist	No effect	Fiorenza et al. (2012)
IL-mPFC	Auditory fear conditioning	D1 antagonist	Impairment	Hikind and Maroun (2008)
mPFC	Contextual fear conditioning	D1 antagonist	No effect	Fiorenza et al. (2012)
mPFC	Inhibitory avoidance	D1 antagonist	Impairment	Fiorenza et al. (2012)
mPFC	Contextual fear conditioning	H2 antagonist	Impairment	Fiorenza et al. (2012)
mPFC	Inhibitory avoidance	H2 antagonist	Impairment	Fiorenza et al. (2012)
mPFC	Contextual fear conditioning	Histamine N-methyltransferase inhibitor	Improvement	Fiorenza et al. (2012)
mPFC	Inhibitory avoidance	Histamine N-methyltransferase inhibitor	No effect	Fiorenza et al. (2012)
mPFC	Auditory fear conditioning	MAPK inhibitor	Impairment	Hugues et al. (2004)
IL-mPFC	Contextual fear conditioning	PI-3K inhibitor	Impairment	Kritman and Maroun (2013)
mPFC	Contextual fear conditioning	Protein synthesis inhibitor	Impairment	Mamiya et al. (2009)
ENT	Inhibitory avoidance	Protein synthesis inhibitor	Impairment	Bevilaqua et al. (2006)
		NMDA antagonist	Impairment	
		CaMKII antagonist	Impairment	
		MAPK inhibitor	No effect	
ENT	Contextual fear conditioning	TTX	Impairment	Baldi and Bucherelli (2014)
Nucleus basalis magnocellularis	Contextual fear conditioning	TTX	No effect	Baldi and Bucherelli (2010)
Substantia nigra	Contextual fear conditioning	TTX	No effect	Baldi and Bucherelli (2010)

β-AR, β-adrenergic receptor; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; D1, dopaminergic receptor type 1; ENT, entorhinal cortex; GABA, γ-aminobutyric acid; H2, histaminergic receptor type 2; IL-mPFC, infralimbic subregion of the medial prefrontal cortex; MAPK, mitogen-activated protein kinase; mPFC, medial prefrontal cortex; NMDA, N-methyl-D-aspartate receptor; NR2B, NMDA receptor subtype 2B; PI-3K, phosphatidylinositol 3 kinase; PL-mPFC, prelimbic subregion of the medial prefrontal cortex; TTX, tetrodotoxin.

fear extinction (Boccia et al., 2009). The effect is time-dependent because the same treatment administered 180 min after extinction does not affect extinction memory. This provides evidence that oxotremorine facilitates consolidation of extinction.

Previous results have shown that the histaminergic system modulates consolidation of some fear memories (Cangioli et al., 2002; Passani et al., 2001). Recent researches have reported that this system modulates fear extinction as well. Post-extinction infusions into the BLA of a histaminergic H2 receptor antagonist hinder extinction retention of both contextual fear conditioning and inhibitory avoidance (Fiorenza et al., 2012). On the contrary, intra-BLA administration of a histamine-N-methyltransferase inhibitor after extinction training enhances extinction memory retention of both tasks (Fiorenza et al., 2012). Thus, the histaminergic system modulates through H2 receptor extinction consolidation of fear memory (Myskiw et al., 2014).

The dopaminergic system modulates learning during fear extinction (Abraham et al., 2014). This evidence comes from studies employing either systemic administration of dopaminergic receptors agonists or antagonists, or mice lacking these receptors (Hikind and Maroun, 2008). The dopaminergic receptors are highly expressed in the amygdala; specifically, the BLA expresses D1 receptors, whereas the CEA mainly expresses D2 receptors. It was shown that microinfusions of a D1 antagonist in the BLA before an extinction session of an auditory fear task cause impairment in extinction acquisition. However, the same treatment performed immediately after the extinction session has no effect on the subsequent extinction retention (Hikind and Maroun, 2008). Thus, these results are consistent with the idea that fear extinction acquisition, but not consolidation, depends on the BLA D1 receptors. Further analysis of fear extinction consolidation was performed by Fiorenza et al. (2012) employing the contextual fear conditioning and inhibitory avoidance paradigms. These authors injected intra-BLA D1 agonist or antagonist after the first of two sessions of extinction in each task to influence extinction consolidation. While D1 agonist had no effect on the extinction of the two tasks, the D1 antagonist impaired extinction consolidation of inhibitory avoidance, but not contextual fear conditioning. Together these results implicate amygdalar dopaminergic signaling as a critical modulatory component in fear extinction.

Recently, the endocannabinoid system has emerged as an important system in the regulation of extinction learning. Mutant mice lacking the gene for the CB1 receptor ($CB1^{-/-}$) acquire and retain an auditory fear conditioning task, but show an impairment of extinction acquisition and retention (Marsicano et al., 2002). Moreover, the wild type mice ($CB1^{+/+}$) exhibit an impaired

extinction of fear memory when administered a CB1 antagonist before, but not after, extinction training. In wild type mice an increased expression of two endocannabinoids in the BLA was reported following extinction training. Subsequently, it was found that a CB1 antagonist injected into the BLA either before or after extinction training impaired extinction of inhibitory avoidance (Ganon-Elazar and Akirav, 2009). Thus, the CB1 receptor in this neural site is crucially involved in extinction of this memory task. However, the administration in the BLA of a CB1/CB2 agonist had no effect on inhibitory avoidance extinction (Ganon-Elazar and Akirav, 2009). Similar results were obtained using an inhibitor of cannabinoid reuptake and enzymatic degradation (Ganon-Elazar and Akirav, 2009). The amygdalar CB1 receptors involvement in fear-potentiated startle appears to be different. In fact, in this memory task neither CB1 antagonist nor agonist administration into the BLA affects extinction retention (Kuhnert et al., 2013).

Neuropeptide S (NPS) has anxiolytic-like effects and seems to be involved in fear memory extinction (Jungling et al., 2008). Pre-extinction training infusion of NPS within the BLA facilitated auditory fear extinction retention; in addition, the intra-BLA administration of a NPS receptor antagonist induced a significant impairment of extinction learning (Jungling et al., 2008).

Evidence has emerged correlating glucocorticoids release to the fear extinction memory (Rodrigues et al., 2009). The BLA is one of the neural sites containing GRs and thus it may represent a site where extinction memory is modulated. An increase in plasma corticosterone levels was observed following extinction training of the fear potentiated startle in rat suggesting an involvement of this hormone in the plasticity related to the extinction. Consistent with this, systemic administration of a glucocorticoid agonist performed pre- or post-extinction training facilitated fear extinction. Probably this effect is mediated at the level of the amygdala because intra-BLA infusion of a glucocorticoid agonist before extinction training improves extinction (Yang et al., 2006). Moreover, administration of glucocorticoid antagonist either systemically or intra-BLA before extinction training impairs extinction of conditioned fear (Yang et al., 2006). Thus, corticosterone contributes to fear extinction acting at amygdaloid GRs.

3.1.2. Protein kinases and phosphatases

Several intracellular signaling pathways have been implicated in fear extinction. MAPK is one of the second messengers activated by increased intracellular calcium concentration following extinction training. It was demonstrated that intra-BLA administration of MAPK inhibitors before extinction training impaired extinction retention in both fear-potentiated startle (Davis, 2002; Lin et al., 2003b; Lu et al., 2001) and auditory fear paradigm (Herry et al., 2006). Moreover, a few studies indicate that phosphorylated MAPK is upregulated into this neural site following extinction training (Cannich et al., 2004; Davis and Bauer, 2012; Kwapis et al., 2014; Yang and Lu, 2005).

Little evidence is available for a role of PKA in fear extinction. Tronson et al. (2006) found that intra-BLA infusions of a specific PKA activator after each of four daily extinction training sessions have no effect on auditory fear extinction. On the other hand, Myskiw et al. (2010) reported that administration of a PKA inhibitor within this neural site prior to the first of several extinction sessions hinders inhibitory avoidance extinction. However, the Authors did not report any change in the amygdaloid phosphorylated PKA levels and suggested that "probably the basal levels of PKA activity in BLA are necessary and sufficient for extinction processes to develop in this task". This conclusion, however, was not confirmed by experiments in which transgenic mice with reduced PKA activity in forebrain neurons were used. In fact, in these mice the reduction of PKA activity facilitates extinction retention of contextual fear (Isiegas et al., 2006). Myskiw et al. (2010) also investigated the amygdaloid CaMKII role in inhibitory avoidance extinction. Using the same protocol of inhibitory avoidance they showed that intra-BLA pre-extinction CaMKII inhibition impairs extinction of this task. This effect is correlated with an increase in phosphorylated CaMKII levels 90 and 180 min after testing.

It has been suggested that fear extinction is correlated with amygdaloid PI-3K activation. Some studies reported that intra-BLA administration of PI-3K inhibitors performed before extinction training impairs extinction of both fear-potentiated startle (Lin et al., 2003b; Mao et al., 2006) and contextual fear conditioning (Kritman and Maroun, 2013). On the other hand, Yang and Lu (2005) showed that intra-BLA blockade reduces fear-potentiated startle extinction facilitation induced by systemic, pre-extinction training injection of DCS. PI-3K activity is often evaluated employing pAKT levels as an indirect measure, however inconsistent results were obtained. Indeed, following extinction amygdaloid pAKT may increase (Yang and Lu, 2005), decrease (Lin et al., 2003a) or remain unchanged (Cannich et al., 2004).

These results suggest that several kinases in the BLA are involved in fear extinction. Many of these kinases are dephosphorylated, that is inactivated, by the protein phosphatase calcineurin. This phosphatase in the BLA has been implicated in fear extinction. Several works reported that extinction is associated with enhanced BLA calcineurin levels and enzymatic activity (and consequent reduced phosphorylation of MAPK and AKT) (Cannich et al., 2004; Lin et al., 2003a, 2003b). Furthermore, pre-extinction intra-BLA administration of inhibitors of this phosphatase blocks extinction of fear-potentiated startle (Lin et al., 2003a). These results suggested that fear extinction may involve the reversal of acquisition-related plasticity through upregulation of calcineurin, hence weakening the original fear memory (Lin et al., 2003a, 2003b).

3.1.3. Gene expression and protein synthesis

As recalled previously, the protein kinases activate some transcription factors, such as CREB which plays a critical role in fear memory consolidation (Kida et al., 2002). In fear extinction the role of CREB is contradictory. Some studies reported increased CREB phosphorylation after fear extinction (Hall et al., 2001; Mamiya et al., 2009) but others demonstrated a decreased CREB activity after extinction (Izumi et al., 2008; Lin et al., 2003b). Recently, a study by Tronson et al. (2012) attempted to clarify the role of amygdalar CREB in this phase of fear memory. Using an auditory fear conditioning task and intra-BLA CREB viral vectors injection, the authors showed that extinction is not affected by either disruption or overexpression of CREB. These results, therefore, seem to support the hypothesis that CREB activity in the BLA is not required for fear extinction. On the contrary, transcription factor BDNF appears to be implicated in fear memory extinction. In fact, it was found that BDNF mRNA expression within the BLA is increased in a time-dependent manner following fear-potentiated startle extinction (Chhatwal et al., 2006). As BDNF acts on tyrosine kinase B (TrkB) receptor, the involvement of this receptor in extinction was investigated as well. It was reported that intra-BLA infusion of TrkB lentiviral vector before extinction training induces a retention, but not acquisition, deficit of extinction suggesting a BDNF role in fear memory extinction consolidation (Chhatwal et al., 2006).

BDNF is not the only neurotrophic factor implicated in fear extinction. A recent work suggested that the fibroblastic growth factor 2 (FGF2) might be an attractive candidate for enhancing the learning processes underlying fear extinction (Graham and Richardson, 2011). Adult FGF2-treated rats exhibit facilitated auditory fear extinction consolidation when this neurotrophic factor is administered within the BLA immediately after extinction training. These animals also show attenuated renewal and reinstatement of fear. Therefore, FGF2 appears to be a powerful modulator of fear extinction.

Please cite this article in press as: Baldi, E., Bucherelli, C., Brain sites involved in fear memory reconsolidation and extinction of rodents. Neurosci. Biobehav. Rev. (2015), http://dx.doi.org/10.1016/j.neubiorev.2015.04.003

Fear extinction is partly explained as a new learning which involves the formation of a second, inhibitory association. This new association has opposite effects than the excitatory one, as the CS presentation no longer predicts the US and no fear is expressed. As a new learning, fear extinction requires new protein synthesis. Many studies using intra-BLA pre- or post-extinction training infusion of the protein synthesis inhibitor anisomycin showed an extinction impairment considering several conditioned fear paradigms, such as fear-potentiated startle (Lin et al., 2003b; Yang and Lu, 2005), auditory (Duvarci et al., 2006) and contextual fear conditioning (Mamiya et al., 2009). Probably protein synthesis that occurs during extinction depends on the transcription of new RNA. In this regard, the experiments employing transcription inhibitors showed conflicting results. Lin et al. (2003b) showed that intra-BLA administration of actinomycin D before extinction training has no effect on fear-potentiated startle extinction. It should be underlined that these authors measured extinction retention 20 min after extinction training. In general, short-term memory extinction (which is independent on transcription) is evaluated at a brief interval. Using a fear-potentiated startle paradigm, Yang and Lu (2005) found that extinction facilitation induced by intra-BLA pre-extinction training administration of DCS is blocked by pre-injection of actinomycin D into the BLA. These results seem to support the idea that fear memory extinction requires new mRNA synthesis in this neural structure.

Several post-translational modification occur during memory formation. The neural cell adhesion molecule (NCAM), a glycoprotein of the immunoglobulin superfamily, participates in changes. For example, polysialylated NCAM (PSA-NCAM) is upregulated within the amygdala (BLA and CEA) and hippocampus 24 h after training of auditory fear conditioning and spatial memory, respectively (Markram et al., 2007; Venero et al., 2006). In the amygdala this upregulation is not necessary for the acquisition, consolidation and recall of fear memories, but it is involved in extinction of these memories. In fact, pre- and post-training cleavage of PSA from NCAM induced by enzyme endoneuraminidase N (endoN) does not interfere with the acquisition or the consolidation of auditory and contextual fear memories. On the contrary, pre-extinction intra-BLA administration of endoN improves tone fear memory extinction (Markram et al., 2007). Thus, PSA-NCAM might be considered a molecular process that plays different roles in the acquisition and extinction of auditory fear memories, as it occurs with other mechanisms (Lin et al., 2003a).

3.2. Hippocampus

Fear extinction is a context-dependent process; a contextual change causes a renewal of extinguished conditioned fear responses that are again expressed (Herry et al., 2010; Myers and Davis, 2007). The hippocampus plays a critical role in the formation of contextual representations (Fanselow, 2000; Kim and Fanselow, 1992; Phillips and LeDoux, 1992), therefore many studies investigated its role in the contextual modulation of fear extinction (Bouton et al., 2006; Ji and Maren, 2007). Nevertheless, the hippocampus appears directly implicated in extinction acquisition, but not consolidation, of some type of fear memory (Tables 5 and 8). Pre-extinction training muscimol-induced inactivation of dorsal hippocampus (DHC) attenuates the extinction acquisition of conditioned freezing response to an acoustic CS (Corcoran et al., 2005; Xue et al., 2014). Instead, unilateral infusion of muscimol into the DHC immediately after contextual fear extinction training does not affect this conditioned response (Berlau and McGaugh, 2006). Whereas pre-extinction muscimol infusion within ventral hippocampus (VHC) impairs auditory fear extinction retention, the same treatment performed immediately after extinction training has no effect on extinction memory (Sierra-Mercado et al., 2011). Thus, the activity necessary for fear extinction processing in the hippocampus seems to occur during extinction training.

3.2.1. Neurotransmitter systems

In the hippocampus, as in the amygdala, various neurotransmitter systems appear critical for fear extinction, depending on the nature of the mnemonic task. Hippocampal glutamatergic neurotransmission is involved in extinction of fear memory, although the ionotropic and metabotropic receptors of glutamate appear to be implicated to a different extent. Hippocampal NMDA receptor activation is necessary for the transduction cascade that mediates the plasticity underlying fear memory extinction. Pre- (Cammarota et al., 2005; Myskiw et al., 2010; Szapiro et al., 2003) or post-extinction (De Carvalho Myskiw et al., 2014; Fiorenza et al., 2012; Szapiro et al., 2003) DHC infusion of NMDA antagonists impairs inhibitory avoidance and contextual fear long-term extinction. This effect does not seem to be mediated by the NR2B subunit (Bonini et al., 2011; Leadrebrand et al., 2014). However, hippocampal NR2A activity seems to be required for contextual fear extinction because its blockade performed each day after the extinction session impairs extinction (Leadrebrand et al., 2014). Also, intra-hippocampus infusion of DCS before extinction facilitates acquisition and retrieval of auditory and contextual fear extinction memory (Bolkan and Lattal, 2014; Ren et al., 2013). Similarly, post-extinction injections of DCS or D-serine in the same neural site enhance extinction consolidation of inhibitory avoidance and contextual fear task (Bolkan and Lattal, 2014; Fiorenza et al., 2012).

The role of hippocampal mGluRs is less clear. It was shown that mGluR5 knock-out mice exhibit a complete deficit in auditory and contextual fear extinction (Xu et al., 2009). However, this receptor is not involved in extinction of inhibitory avoidance. In fact, mGluR5 antagonist injected intra-DHC after the first extinction session has no effect on subsequent extinction retention of this task (Simonyi et al., 2007). On the contrary, mGluR1 blockade induces a significant impairment of inhibitory avoidance extinction (Simonyi et al., 2007). Thus, extinction of Pavlovian fear conditioning and inhibitory avoidance seems to involve different mGluR subtypes.

Also hippocampal L-VGCCs are crucial for contextual fear extinction. Intra-DHC infusion of nifedipine given after extinction session impairs consolidation of this memory phase (De Carvalho Myskiw et al., 2014). This effect is blocked by the co-administration of the proteasome inhibitor β-lac suggesting that L-VGCCs action depends on concomitant synaptic protein turnover (De Carvalho Myskiw et al., 2014).

Immediately post-extinction training administration of norepinephrine within the DHC has no effect on the extinction of either contextual freezing or inhibitory avoidance (Fiorenza et al., 2012). However, hippocampal β-ARs blockade results in the impairment of extinction consolidation of inhibitory avoidance, but not of contextual freezing response (Fiorenza et al., 2012). In the latter paradigm Ouyang and Thomas (2005) reported that β-adrenergic antagonism within DHC blocks extinction when the treatment is performed 3 h after extinction training, but not when performed before extinction training.

There is little evidence on hippocampal dopaminergic transmission involvement in fear extinction. The only study, to our knowledge, showed that intra-hippocampus administration of D1 receptor agonists or antagonists after extinction training enhances or impairs, respectively, extinction of both contextual fear and inhibitory avoidance (Fiorenza et al., 2012). Just as there are few studies on the role of hippocampal cholinergic receptors. De Aguiar et al. (2013) found that nicotine and its metabolite cotinine (nicotinic acetylcholine receptors (nAChRs) agonists) enhance extinction of inhibitory avoidance when they are injected

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intra-DHC after the first extinction session. Instead, nAChRs antagonists do not significantly interfere with this mnemonic process.

As reported for the BLA, hippocampal cannabinoid system is involved in fear extinction as well. In fact, infusion into the CA1 of CB1 antagonist before the first extinction session impairs the extinction of inhibitory avoidance, while CB1 agonist or an inhibitor of endocannabinoid reuptake facilitate it (Abush and Akirav, 2010). Similar findings were obtained using a contextual fear paradigm and post-extinction training injections: CB1 antagonists block whereas CB1 agonists enhance the extinction of this memory task (De Oliveira Alvares et al., 2008).

The hippocampal activity is also modulated by histamine. Recently, it was reported that histaminergic system of this neural site is involved in fear extinction consolidation. In particular, it seems that histamine facilitates fear extinction consolidation through a mechanism involving hippocampal H2 receptors. Animals subjected to post-extinction administration of histamine or histamine N-methyl-transferase inhibitor or H2 agonists exhibit enhanced extinction of inhibitory avoidance and contextual freezing response (Bonini et al., 2011; Fiorenza et al., 2012). Opposite effects were observed following injections of H2 antagonist and H3 agonist; moreover, H2 antagonism blocks histamine-induced facilitation (Bonini et al., 2011; Fiorenza et al., 2012). On the contrary, H1 agonists and antagonists or H3 antagonists have no effect on fear extinction (Bonini et al., 2011).

Hippocampal molecular mechanisms mediating extinction of inhibitory avoidance include activation of the gastrin-releasing peptide receptor (GRPR) because its inhibition immediately after the first extinction session blocks this memory phase (Luft et al., 2006).

3.2.2. Protein kinases

The many neurotransmitter systems mentioned above activate signaling pathways such as MAPK, PKA and CaMKII. It was reported that inhibitory avoidance and contextual fear extinction is blocked by intra-DHC MAPK (Bevilaqua et al., 2007; Bonini et al., 2011; Fischer et al., 2007; Huh et al., 2009; Rossato et al., 2006; Szapiro et al., 2003), PKA (Myskiw et al., 2010; Szapiro et al., 2003), and CaMKII (Myskiw et al., 2010; Szapiro et al., 2003) inhibitors regardless of whether they were given before or after extinction sessions. However, intra-DHC pre-extinction administration of a MAPK (in particular ERK1/2) inhibitor does not affect extinction of fear potentiated startle (Shen et al., 2011). This might be due to the fact that diverse memory tasks use different MAPK subfamilies to produce extinction. It was reported that the subfamily ERK1/2 is not involved in the facilitation effect of Ginkgo biloba extract on fear extinction. In fact, intra-hippocampal infusion of this extract given prior to a single extinction session facilitates conditioned fear extinction as measured by fear-potentiated startle but this effect is only partially attenuated by ERK1/2 inhibitor injection and does not reach a significant level (Shen et al., 2011).

The role of ERK in contextual fear extinction was confirmed using transgenic animals. Rap2V12 transgenic mice express constitutively active Rap 2 (a Rap GTPase of the Ras family) in postnatal forebrain including the hippocampus. These animals exhibit normal conditioned fear acquisition, but impaired contextual fear extinction associated with decreased hippocampal ERK activity after the second and third extinction sessions compared to wild-type controls. This effect may be ascribed to active Rap2 repressing ERK signaling (Ryu et al., 2008). The hippocampus appears to be a major site of Rap2 action because Rap2V12 mice show normal extinction of auditory fear memory and normal amygdaloid and cortical ERK activation (Ryu et al., 2008).

ERK-1 knockout mice are characterized by stimulus-dependent overactivation of the ERK2 isoform and therefore have been used to study the selective role of this ERK isoform. These mice exhibit enhanced contextual fear extinction accompanied by faster and stronger activation of ERK2 than their wild-type littermates (Tronson et al., 2008). According to the authors, these findings support the idea that ERK2 compensates for the lack of ERK1 and shows stronger biological activity in the absence of ERK1 (Tronson et al., 2008). Moreover, intra-hippocampal infusion of a MEK inhibitor after each daily extinction session reduces ERK phosphorylation in both ERK-1 deficient mice and wild-type mice, whereas intra-DHC administration of a PKA or PKC inhibitor does not affect pERK level. Thus, these results indicate a key role of MEK, but not PKA nor PKC, in hippocampal ERK regulation during extinction (Tronson et al., 2008).

Transgenic mice have also been employed to further clarify the PKA role in contextual fear memory extinction. TetO-R(AB) transgenic mice with reduced PKA activity in the forebrain exhibit facilitated contextual fear extinction retention compared with wild-type controls (Isiegas et al., 2006) suggesting an inhibitory role of PKA in this mnemonic phase. PKA signaling is partly controlled by association of the enzyme with A-kinase anchoring proteins (AKAPs). Nijholt et al. (2008) found that inhibition of hippocampal PKA anchoring AKAPs after each extinction session facilitates contextual fear memory extinction, confirming that PKA activity inhibits extinction process.

Extinction process also seems to require downregulation of PKC signaling. In fact, intra-DHC post-extinction administration of PKC inhibitor facilitates conditioned contextual freezing extinction. However, this treatment does not affect ERK activity suggesting that PKC suppresses fear extinction through an ERK-independent mechanism (Tronson et al., 2008).

It was recently shown that contextual fear extinction involves hippocampal PI-3K (Chen et al., 2005) and cyclin-dependent kinase 5 (CdK5) (Sananbenesi et al., 2007) pathways. Animals infused with PI-3K inhibitor into the DHC immediately after repeated tests do not exhibit decrease in the contextual conditioned freezing (Chen et al., 2005). On the other hand, inhibition of hippocampal CdK5 facilitates extinction of this fear response (Sananbenesi et al., 2007). Similar results were obtained by intra-hippocampal injections of upstream regulator GTPase Rac-1 (guanosine triphosphatase Rac-1) inhibitor. Thus, Rac-1 and CdK5 activity seems to inhibit contextual fear extinction. Furthermore, it was reported that downstream target PAK-1 (p21 activated kinase-1) is also involved in this memory phase because its inhibition within DHC after extinction training impairs contextual conditioned freezing response extinction (Sananbenesi et al., 2007). Therefore, the hippocampal Rac-1/CdK5/PAK-1 pathway is important for contextual fear extinction. This pathway appears to affect the dynamics of the actin cytoskeleton, whose rearrangement in the DHC is required for extinction process. Indeed, post-extinction training administration of actin dynamics inhibitors impairs contextual conditioned freezing extinction (Fischer et al., 2004).

Several members of the Src-family tyrosine kinases (SFKs) in the hippocampus are involved in extinction of fear-motivated memories as well. Using the inhibitory avoidance paradigm Bevilaqua et al. (2005) found that hippocampal infusion of a specific SFKs inhibitor performed immediately after the first of four extinction sessions blocks memory extinction and they suggested that SFKs play a role in consolidation of inhibitory avoidance extinction. Other authors have reported that pre-extinction inhibition of this kinases family within DHC facilitates extinction of contextual conditioned freezing; the facilitated extinction is related to downregulation of hippocampal Fyn activity, a member of SFKs (Isosaka et al., 2009). Moreover, hippocampal pre-extinction training administration of protein tyrosine phosphatases inhibitor impairs extinction of contextual fear memory (Isosaka and Yuasa, 2010). The authors speculated that during extinction training an increased activity of the protein tyrosine phosphatases might

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occur and these phosphatases should directly or indirectly dephosphorylate Fyn. On the other hand, hippocampal phosphatases involvement in contextual fear memory extinction was reported also by De la Fuente et al. (2011). Intra-DHC inhibition of calcineurin performed before extinction training is related to high levels of contextual freezing response indicating impaired extinction.

3.2.3. Gene expression and protein synthesis

As previously stated, there is evidence supporting the role of gene transcription during contextual long-term memory extinction in amygdala and prefrontal cortex (Mamiya et al., 2009). Surprisingly, it was demonstrated that CREB is not activated in the hippocampus during contextual fear extinction suggesting that gene expression in this neural site may not be involved (Mamiya et al., 2009; Tronson et al., 2008). Nevertheless, Kirtley and Thomas (2010) showed that intra-DHC infusion of recombinant BDNF protein before contextual extinction training impairs consolidation, but not acquisition, of extinction, whereas antisense oligodeoxynucleotide targeting Zif268 injection does not affect extinction process. Moreover, Peters et al. (2010) reported that rats failing to learn extinction of auditory fear show reduced BDNF in hippocampal inputs to the IL-mPFC and enhancing BDNF in this pathway allows extinction of this memory task. These data are consistent with studies in which genetic knockdown of hippocampal BDNF impairs conditioned fear extinction as measured both with fear potentiated startle and contextual freezing (Heldt et al., 2007).

De la Fuente et al. (2011) studied the role of two related transcription factors, NF-κB and NFAT (nuclear factor of activated T-cells), in the hippocampus in extinction memory formation. These transcription factors have opposite roles; in fact, post-extinction training NF-κB inhibition within DHC enhances contextual fear extinction, whereas NFAT blockade performed before extinction training impairs this memorization phase. The authors proposed that the activation or inhibition of these two transcription factors should be regulated by calcineurin phosphatase; during extinction calcineurin might block NF-κB activation and activate NFAT (De la Fuente et al., 2011).

Recent evidence demonstrated that immediate early genes involved in fear extinction are not the same implicated in fear acquisition. For example, during contextual fear conditioning c-Fos and JunB are upregulated (Huff et al., 2006; Strekalova et al., 2003), whereas their expression decreases during subsequent exposures to the same context (Guedea et al., 2011; Tronson et al., 2009) suggesting that they are not activated by extinction. On the contrary, JunD is activated by contextual fear extinction but is not affected by fear acquisition (Guedea et al., 2011). Thus, the learning processes underlying acquisition and extinction of fear are partially different at a molecular level.

Finally, it was shown that extinction of contextual fear conditioning may be modulated by manipulating HATs and HDACs activity. In particular, an HDAC inhibitor (which blocks histone deacetylases activity and increases histone acetylation) given in the hippocampus immediately before extinction training enhances retention of conditioned freezing extinction (Lattal et al., 2007). This effect is due to enhancement of consolidation as the HDAC inhibitor begins to affect histone acetylation about 30 min after administration.

The role of hippocampal protein synthesis in fear extinction has been widely studied. Using an inhibitory avoidance paradigm it was found that intra-hippocampal (dorsal CA1 region) administration of the protein synthesis inhibitor anisomycin, performed either before (Cammarota et al., 2005; Vianna et al., 2001, 2003) or immediately after (Luft et al., 2006; Power et al., 2006; Vianna et al., 2001) the first extinction session, blocks extinction of this fear memory task. Instead, the treatment is ineffective when given 1 or 3 h after the first extinction session (Vianna et al., 2003). Thus, these findings suggest that extinction learning of inhibitory avoidance engages a hippocampus-dependent consolidation process. Regarding contextual fear extinction, inconsistent results were reported. Fischer et al. (2004) showed that intra-hippocampus anisomycin injection immediately after extinction training improves contextual fear extinction without affecting auditory fear extinction. Mamiya et al. (2009) reported that this treatment does not alter the contextual freezing response extinction, whereas De Carvalho Myskiw et al. (2014) demonstrated that this inhibitor impairs extinction consolidation of the conditioned response.

The hippocampal protein synthesis that occurs during extinction of inhibitory avoidance seems to depend on gene expression triggered by the extinction process. It is blocked by pre-extinction training inhibition of hippocampal transcription whereas, as reported above, this inhibition does not affect the extinction when induced 1 or 3 h after extinction training (Vianna et al., 2003). These findings contribute to demonstrate that extinction is indeed a form of associative learning and that it relies upon a single peak of transcription at the time of its acquisition. A recent report has also shown non-ribosomal protein synthesis involvement in the consolidation of contextual fear extinction. Non-ribosomal protein synthesis inhibitor rapamycin blocks fear extinction when given in the hippocampus after an extinction training session. This effect is not blocked by the co-administration of proteasome inhibitor β-lac which by itself is ineffective on extinction consolidation (De Carvalho Myskiw et al., 2014). However, Lee et al. (2008) reported that infusions of β-lac into the hippocampal CA1 region immediately after each extinction session suppress the extinction of this fear memory. They support the idea that extinction also involves some unlearning (or forgetting) process of the pre-existing context-shock association.

3.3. Cortex and other neural sites

In addition to the amygdala and hippocampus, the mPFC plays a crucial role in fear extinction (Tables 6 and 9). Lesion and inactivation studies of mPFC reported contradictory results regarding its role in fear extinction (Akirav et al., 2006; Garcia et al., 2006; Laurent and Westbrook, 2008; Quirk et al., 2000; Sierra-Mercado et al., 2006). Such conflicting findings may be due to the fact that these studies have not distinguished between mPFC subregions. More recently, it was shown that the infralimbic cortex (IL), but not the prelimbic cortex (PL), is the subregion of the mPFC involved in fear extinction. Pre-extinction intra-IL, but not intra-PL, infusion of muscimol impaired extinction of auditory (Sierra-Mercado et al., 2011) and contextual fear (Laurent and Westbrook, 2009). The IL appears to play different roles in two conditioned fear responses. It is implicated in extinction acquisition of freezing to an auditory CS, but not in its consolidation (Sierra-Mercado et al., 2011), whereas in contextual freezing extinction it is critical for consolidation and retrieval of this inhibitory learning (Laurent and Westbrook, 2009). Experiments performed on mPFC slices including IL from previously extinguished animals revealed that extinction training is associated with an increase of IL neurons excitability (Santini et al., 2008). This effect is modulated by M-type potassium channels that contribute to the after-hyperpolarization that occurs after single action potential (Santini and Porter, 2010). In fact, the blockade of M-type K^+ channels in the IL before, but not after, extinction training facilitates auditory fear extinction, whereas activation of these channels before extinction training inhibits fear extinction (Santini and Porter, 2010).

The role of other neural sites, both cortical and subcortical, in fear extinction was studied (Tables 6 and 9). The entorhinal cortex seems to be involved in this process. In our laboratory, it was shown that post-extinction training TTX blockade of ENT activity induces an impaired extinction retention of conditioned

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contextual freezing response, supporting the idea that ENT constitutes a critical component of neuronal network underlying fear extinction (Baldi and Bucherelli, 2014). Among the subcortical sites, we investigated the role of NBM and Substantia Nigra (SN) in contextual fear extinction. TTX inactivation of these neural sites immediately after extinction training does not affect subsequent extinction retention of conditioned freezing response (Baldi and Bucherelli, 2010). Thus, neither the NBM nor the SN are involved in extinction consolidation of fear memory. Little information is available regarding the role of sensory afferents to the forebrain, such as the thalamic nuclei, in the fear extinction. It was shown that the dorsal part of the midline thalamus containing mediodorsal, paraventricular and paratenial nuclei, is not necessary for auditory fear extinction because its muscimol-induced inactivation before extinction training does not affect acquisition of extinction nor retention (Padilla-Coreano et al., 2012).

Expression of conditioned freezing is controlled by the midbrain periaqueductal gray (PAG) (LeDoux, 2000). This neural site was also implicated in extinction of freezing response to an auditory CS (McNally et al., 2004, 2005).

3.3.1. Neurotransmission systems

As in the amygdala, glutamatergic synaptic transmission within the mPFC contributes to fear extinction. Injection of intra-mPFC NMDA receptor antagonists performed pre- or post-extinction training impairs retention of fear conditioned responses extinction (Burgos-Robles et al., 2007; Fiorenza et al., 2012; Holmes et al., 2012), providing evidence that mPFC NMDA receptors are involved in fear extinction consolidation. Further support was obtained in experiments employing selective antagonist of NR2B-containing NMDA receptors. Pre-extinction administration of ifenprodil within the mPFC had no effect on fear conditioned responses (Laurent and Westbrook, 2008; Sotres-Bayon et al., 2009), whereas the same treatment applied immediately after extinction training impaired extinction retention (Laurent and Westbrook, 2008; Sotres-Bayon et al., 2009). To our knowledge there are few works investigating the effect of NMDA agonists directly injected into the mPFC. Fiorenza et al. (2012) reported that post-extinction administration of D-serine into the mPFC enhanced extinction retention of contextual fear and inhibitory avoidance responses. On the other hand, Chang and Maren (2011) found that pre-extinction training DCS infusion in this neural site does not facilitate auditory fear extinction, but enhances the subsequent re-extinction fear. There are a few works analyzing the role of mPFC AMPA receptors. Zushida et al. (2007) observed extinction facilitation of contextual freezing response after pre-extinction injection of an AMPA "potentiator" in this cortical site. This effect is much more potent than that due to the intra-amygdala injection. Thus, the mPFC appears to be a major site in which AMPA "potentiator" acts enhancing fear extinction.

Recently it was proposed that in the mPFC NMDA receptor signaling is regulated by the voltage-gated calcium channels Cav2.1; this regulation is important for fear extinction. Using a contextual fear conditioning paradigm, Niimi et al. (2014) found that mice subjected to intracerebroventricular injections of Cav2.1 channels inhibitor after extinction training exhibit impaired extinction consolidation. This impairment is related to reduced Arc (CREB-dependent gene activity-regulated cytoskeleton-associated protein) expression in mPFC regions. Furthermore, transgenic mice carrying Cav2.1 gene mutation do not exhibit contextual freezing extinction when subjected to intra-mPFC injections of NMDA receptor antagonist (Niimi et al., 2014). Together these findings suggest that Cav2.1-mediated NMDA receptor signaling in the mPFC is involved in fear extinction consolidation.

Glutamatergic transmission within other cerebral sites appears to be involved in the fear extinction. The blockade of ENT NMDA receptors is followed by impaired extinction retention of the inhibitory avoidance response (Bevilaqua et al., 2006). Conversely, the same treatment administered in parietal and cingulate cortices or in the cerebellar nucleus interpositus does not affect extinction of inhibitory avoidance and fear-potentiated startle response, respectively (Falls et al., 1992; Myskiw et al., 2010). These findings confirm that ENT, but neither parietal and cingulate cortices nor cerebellum, are necessary for extinction to occur. Orsini and Maren (2009) reported that administration of NMDA or AMPA antagonists within the thalamic medial geniculate nucleus (MGN) before extinction training prevents extinction of conditioned fear, whereas neither protein synthesis inhibitor nor MAPK inhibitor affect this process. The authors suggested that the MGN is involved in auditory fear extinction as sensory information relay and it does not appear to be a locus of plasticity essential for formation of the extinction memory.

Prefrontal GABAergic transmission is also involved in fear extinction. Local injections of GABAergic agonist muscimol impair fear memory extinction (Laurent and Westbrook, 2008, 2009; Sierra-Mercado et al., 2011, but see Akirav et al., 2006), and intra-mPFC infusion of GABAergic antagonist picrotoxin performed after extinction training facilitates extinction of auditory and contextual freezing response (Chang and Maren, 2011; Thompson et al., 2010). However, this effect is specific to the IL, as it is not observed if picrotoxin is administered into the PL (Thompson et al., 2010). These results further support a role of IL in fear extinction consolidation.

Recent findings indicate that mPFC is a central site for noradrenergic modulation of extinction. Animals infused with the β-AR antagonist propranolol before, but not after, extinction training into the IL, exhibit impaired recall of extinction of auditory fear (Mueller et al., 2008). Similarly, the pre-extinction training administration of α-ARs antagonist into the mPFC impairs acquisition of contextual conditioned fear (Do Monte et al., 2010). However, Fiorenza et al. (2012) showed that intra-mPFC injections of a different β-AR antagonist (timolol) immediately after an extinction session improve extinction retention of contextual fear, and impair that of inhibitory avoidance. In other words, β-AR blockade within mPFC has opposite effects on extinction of the two tasks. Moreover, norepinephrine administration in the same neural site and at the same time point induces impairment of contextual fear extinction, but has no effect on inhibitory avoidance extinction. Thus, modulation of fear extinction by the noradrenergic system into mPFC is complex.

Also, the mPFC expresses many dopaminergic receptors that may be involved in fear extinction modulation (Abraham et al., 2014). Some studies have shown an increase of dopamine in this cortical site following fear extinction (Hugues et al., 2007) and decreased extinction retention after mPFC dopamine depletion (Espejo, 2003). Hikind and Maroun (2008) reported that D1 receptors in the IL are involved in auditory fear extinction consolidation because pre- and post-extinction training injections of D1 antagonist result in an impairment of fear extinction. However, the administration of the same D1 antagonist in mPFC after extinction training of a contextual fear task has no effect on subsequent retention (Fiorenza et al., 2012). On the contrary, in an inhibitory avoidance task D1 antagonism impairs extinction consolidation (Fiorenza et al., 2012). Finally, D1 agonist injections after extinction session in the mPFC do not affect extinction retention of either contextual fear or inhibitory avoidance (Fiorenza et al., 2012). The D2 receptor has also been implicated in the modulation of fear extinction. Recently, it was shown that intra-IL administration of a selective D2 antagonist before extinction training does not affect extinction acquisition of auditory conditioned fear, but impairs extinction retention on the subsequent day, indicating the involvement of IL D2 receptor in extinction consolidation (Mueller et al., 2010). Moreover, this treatment attenuates extinction-evoked firing in IL neurons (Mueller

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et al., 2010). Finally, D4 receptor blockade into the IL performed before auditory fear extinction induces normal extinction acquisition, but impaired extinction retention (Pfeiffer and Fendt, 2006), further suggesting that the dopaminergic activity in this cortical site is crucial for consolidation of fear extinction.

Also dopaminergic activity in the nucleus accumbens is relevant for fear extinction. Intra-accumbens pre-extinction administration of D2 receptors antagonist impairs both extinction acquisition and retention of conditioned freezing response to an auditory CS supporting the hypothesis that "accumbal dopaminergic activity regulates the development and retention of fear inhibition" (Holtzman-Assif et al., 2010).

A critical role in modulating fear extinction consolidation seems to be played by the cholinergic activity in the mPFC. Although, to our knowledge, only one study investigated this neurotransmitter system, it demonstrated that intra-IL blockade of muscarinic receptors before extinction training produces an impairment of auditory fear extinction. Scopolamine-treated animals exhibit normal extinction acquisition, but poor extinction memory retention (Santini et al., 2012). The authors speculated that in the IL a molecular mechanism underlying fear extinction might involve interactions between muscarinic cholinergic receptors and M-type K^+ channels (Santini et al., 2012).

Several studies reported findings supporting the role of CB1 receptors in fear extinction. Pre-extinction infusion of a CB1 antagonist within the IL blocks (Kuhnert et al., 2013; Lin et al., 2009), whereas IL infusion of CB1 agonist has no effect (Kuhnert et al., 2013) or enhances (Lin et al., 2009), extinction of fear-potentiated startle. The IL cannabinoid receptors appear also involved in the extinction of contextual conditioned fear (Do Monte et al., 2013a). The administration of cannabidiol (a non psychotropic phytocannabinoid) within this cortical site performed before each of three extinction sessions facilitates fear extinction. This facilitating effect is probably mediated by activation of IL CB1 receptors because systemic injection of a CB1 antagonist blocks this effect (Do Monte et al., 2013a).

Finally, as shown in the BLA, in the mPFC histaminergic system appears involved in fear memory extinction modulation. Experiments using contextual fear conditioning and the inhibitory avoidance paradigms revealed an extinction deficit in rats treated with the H2 receptors antagonist into the IL (Fiorenza et al., 2012). Because this effect was observed when the injections were performed immediately after extinction training, IL histaminergic receptors appear to modulate extinction consolidation. Conversely, intra-IL post-extinction infusion of histamine N-methyltransferase inhibitor had different effects on extinction of the two fear tasks: improved contextual fear extinction but had no effect on inhibitory avoidance (Fiorenza et al., 2012). Thus, the enhanced levels of histamine in the IL may have different effects on fear extinction consolidation depending on the fear memory task.

McNally and coworkers reported that pre-extinction training infusion into ventro-lateral PAG (vlPAG) of opioid receptors antagonist naloxone impairs auditory freezing response extinction; vlPAG opioid receptors play a specific role in the acquisition but not expression of extinction because the treatment fails to reinstate freezing to an already extinguished CS (McNally et al., 2004). Moreover, this effect is not observed following naloxone injections into dorsal PAG. These authors subsequently showed that vlPAG opioid receptors involved in fear extinction are μ opioid receptors. In fact, intra-vlPAG administration of μ-, but not δ- or κ-opioid receptor antagonist retards auditory fear extinction (McNally et al., 2005). In addition, extinction is also impaired by intra-vlPAG injection of a cAMP analog suggesting that opioid antagonism effect in modulating fear extinction is mediated by cAMP inhibition that would occur with μ-opioid receptor activation (McNally et al., 2005). Instead, administration of PKA activator or MAPK inhibitor within this neural site does not affect fear extinction (McNally et al., 2005). Finally, the authors found that intra-vlPAG pre-extinction training infusions of inhibitor of endogenous opioid catabolizing enzymes facilitate conditioned freezing response extinction to auditory CS (McNally, 2005) confirming a critical role for vlPAG endogenous opioids in fear extinction.

3.3.2. Protein kinases

MAPK, PKA and PI-3K within mPFC are critical for fear extinction, whereas CaMKII is not. It was reported that post-extinction inhibition of MAPK within this cortical site impairs extinction of auditory conditioned fear responses (Hugues et al., 2004). Moreover, phosphorylated MAPK is upregulated (Cannich et al., 2004; Kwapis et al., 2014) and associated with enhanced levels of calcineurin into the IL after extinction training (Cannich et al., 2004). Mueller et al. (2008) found that intra-IL pre-extinction training injection of PKA antagonist, but not of CaMKII inhibitor, impairs subsequent extinction retention of auditory conditioned fear. Thus, PKA activity, but not CaMKII activity, is necessary for extinction consolidation within the IL. Finally, PI-3K inhibition within IL performed after extinction training hinders contextual fear extinction consolidation (Kritman and Maroun, 2013).

Opposite results were obtained in ENT. In fact, intra-ENT infusion of CaMKII inhibitor impairs extinction of the inhibitory avoidance response, whereas the MAPK inhibitor administration has no effect (Bevilaqua et al., 2006). Together these findings confirm a crucial role of IL-mPFC and ENT in extinction consolidation of conditioned fear suggesting that different protein kinases are required in different brain structures.

3.3.3. Gene expression and protein synthesis

Several transcription factors into the mPFC are activated during fear extinction. For example, Mamiya et al. (2009) reported an increased activation of CREB and CREB-dependent gene Arc within this neural site following extinction training of contextual fear paradigm. Herry and Mons (2004) showed that auditory fear extinction is accompanied by an increase in c-fos and zif268 expression into the mPFC; furthermore, resistance to re-extinction learning is associated with an impaired expression of these immediate early genes in the same cortical region. These results were confirmed by other findings showing that rats selectively bred for high anxiety exhibit impaired extinction of auditory conditioned fear response and low levels of c-fos expression within the IL (Muigg et al., 2008). Similarly, mice with specific extinction impairment also show decreased expression of intra-IL immediate early genes (Hefner et al., 2008). The transcription factor BDNF was also implicated in fear memory extinction. Using an auditory fear conditioning task Peters et al. (2010) reported that intra-IL pre-extinction training infusion of BDNF facilitates extinction memory. Further confirmation of BDNF role in the IL in fear extinction was obtained by experiments showing that epigenetic modulation of BDNF genes in the IL is associated with auditory fear extinction (Bredy et al., 2007). The same authors recently reported that the activity of p300/CBP-associated factor within the IL is necessary for auditory fear extinction (Wei et al., 2012).

Long-term memory for fear extinction requires new protein synthesis in the ventral mPFC; rats subjected to pre-extinction training infusion of anisomycin within the IL exhibit normal extinction acquisition of conditioned freezing to an acoustic CS, but are unable to recall extinction the following day (Mueller et al., 2008; Santini et al., 2004). Similar results were obtained using a contextual fear paradigm and immediately post-extinction training administration (Mamiya et al., 2009). Moreover, Mueller et al. (2008) reported that in the IL the fear extinction consolidation-related protein synthesis dependents on new mRNA synthesis, because intra-IL

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pre-extinction training injection of the transcription inhibitor actinomycin impairs extinction retention.

Also protein synthesis in the ENT is important for fear extinction. The administration of anisomycin within ENT after the first extinction session of an inhibitory avoidance paradigm is followed by impaired extinction retention of these fear responses (Bevilaqua et al., 2006).

4. Discussion

The present review is centered on fear memory necessary for the organization of defensive behaviors and the survival of an organism. The role of several cerebral structures involved in fear memory reconsolidation and extinction was analyzed. In recent years there has been a growing interest in these two phases of fear memory processing, both induced by memory retrieval. During non-reinforced retrieval, a consolidated memory re-enters a vulnerable state during which it is again sensitive to disruption and, to persist, must undergo a new stabilization process (reconsolidation). The function of reconsolidation is a matter of debate. Two hypotheses have been proposed: (i) reconsolidation allows memory updating with new information, (ii) through reconsolidation the initial memory becomes stronger and longer lasting (Alberini and LeDoux, 2013; Tronson and Taylor, 2007). As the term reconsolidation is derived from consolidation, the mechanisms that underlie reconsolidation would be identical to those that mediate consolidation (Alberini, 2005; Dudai and Eisenberg, 2004). The two mnemonic processes seem to share some similar molecular mechanisms and pathways, such as protein synthesis, activation of MAPK pathway and the transcription factor CREB (Debiec et al., 2002; Doyere et al., 2007; Mamiya et al., 2009; Nader et al., 2000; Tronson and Taylor, 2007). Nevertheless, it was shown that reconsolidation is not an exact recapitulation of consolidation; the two processes show different time courses (reconsolidation is completed faster than consolidation) and differences at the neural circuits and molecular levels (Alberini and LeDoux, 2013; Mactutus et al., 1979; Tronson and Taylor, 2007). This is not surprising considering the procedural differences involving the two processes. Indeed, consolidation is induced only presenting the CS and US contiguously, whereas reconsolidation is induced presenting either the CS or the US alone.

Reconsolidation would be a behavioral phenomenon opposing extinction, the classical retrieval-induced process caused by changes in the associative relationships that generated the original response. Extinction is not oblivion because the original response recovers spontaneously over time, presenting the CS in a new context (renewal) and upon unpredictable US presentations (reinstatement) (Myers and Davis, 2007; Quirk and Mueller, 2008). These behavioral properties indicate that during extinction a new inhibitory memory trace is formed that competes with the original fear memory (Myers and Davis, 2007; Myskiw et al., 2014; Pape and Pare, 2010; Quirk and Mueller, 2008). Reconsolidation and extinction processes are operationally similar. Both phases are induced by non-reinforced presentation of the CS (Nader and Hardt, 2009; Quirk and Mueller, 2008), but they have opposing actions on the fate of the retrieved memory. Reconsolidation stabilizes or strengthens the memory trace, whereas extinction induces new opposite learning. In other words, reconsolidation and extinction are competing processes. The competition between them seems to depend partly on the length and/or number of memory reactivation sessions. A brief re-exposure, like that caused by a short retrieval session, would induce reconsolidation, whereas longer or repeated reminder trials would result in extinction (Debiec et al., 2002; Eisenberg et al., 2003; Pedreira and Maldonado, 2003). The growing interest about these memory phases is witnessed by the exponential increase in publications related to the two phenomena (Besnard et al., 2012; Delamater and Westbrook, 2014). This is due in part to the fact that understanding the mechanisms of fear memory reconsolidation and extinction may offer new therapeutic interventions for the treatment of human fear and anxiety disorders, such as phobias and post-traumatic stress-disorder (PTSD) characterized by dysregulated fear responses (Alberini, 2005; Auber et al., 2013; Davis et al., 2006; Hartley and Phelps, 2010; Monfils et al., 2009; Nader, 2003; Parsons and Ressler, 2013; Quirk et al., 2010; Rao-Ruiz et al., 2011; Rossato et al., 2010; Schiller et al., 2010; VanElzakker et al., 2014). Thus, the identification of both neural structures and molecular mechanisms underlying the two memory phases appears to be crucial.

4.1. Neural circuit underlying fear memory reconsolidation and/or extinction

Reconsolidation and extinction show different anatomical and biochemical signatures (Mamiya et al., 2009; Merlo and Romano, 2008; Suzuki et al., 2004). Although the experimental results are not always consistent, the amygdala and hippocampus appear to be the neural sites playing a key role in both reconsolidation and extinction of fear memory. Yet, whereas the amygdala is involved in these memorization phases whatever fear memory task is considered (cued and contextual fear conditioning, fear potentiated startle or inhibitory avoidance), the hippocampus is involved when contextual components are implicated. In addition to these brain structures, evidence points to a crucial role of the mPFC in these mnemonic processes. However, fear memory reconsolidation and extinction seem to involve different subregions of this cortical site. Indeed, the PL region appears to be implicated in reconsolidation of conditioned fear responses, whereas the IL region appears to be the candidate to suppress fear responses via extinction learning. Finally, recent results have shown that the ENT as well might be part of a circuit underlying fear memory reconsolidation and extinction. These neural sites are closely interconnected. Anatomical studies revealed that there are reciprocal connections between the amygdala, the hippocampus and the ENT. The hippocampal CA1 field and the ENT are among the prominent sources of amygdalar afferents and project mainly to the BLA (Canteras and Swanson, 1992; Ottersen, 1982; Pitkanen et al., 2000; Wyss, 1981). The BLA in turn projects abundantly to the hippocampus (with dense synapses on the CA1 field) and ENT (Pikkarainen et al., 1999). ENT provides the major gateway for transmission of information between the hippocampus and cortex (Hyman et al., 1990; Maren and Fanselow, 1997). Several lines of evidence suggested that the amygdala modifies the hippocampus and ENT responses and vice versa (Abe, 2001; Maren and Fanselow, 1995; McGaugh, 2000; Packard and Cahill, 2001; Richter-Levin and Akirav, 2000). This seems to be also supported by experimental findings that theta synchrony of hippocampal CA1 and LA increases and decreases during fear memories reconsolidation and extinction, respectively (Narayanan et al., 2007; Sangha et al., 2009). Moreover, it was reported that BLA and ENT neuronal activity oscillates in phase (Pare and Gaudreau, 1996; Paz and Pare, 2013) both structures interacting in the modulation of fear memory consolidation (Roesler et al., 2002). Thus, a dynamic interaction may exist between the amygdala, hippocampus and ENT underlying the dynamic nature of memory processes. The PL and IL are strongly interconnected with each other (Hoover and Vertes, 2007) and with the amygdala, hippocampus and ENT. The PL and IL receive massive afferents from hippocampal CA1 field and ENT, and in turn send projections to these same neural sites (Hoover and Vertes, 2007; Vertes et al., 2007). It was reported that fear extinction is related to LTP-like synaptic changes in DH-mPFC projection; low frequency stimulation of the DH attenuates this synaptic plasticity and impairs extinction retention, whereas high frequency stimulation of the DH has opposite effects (Farinelli

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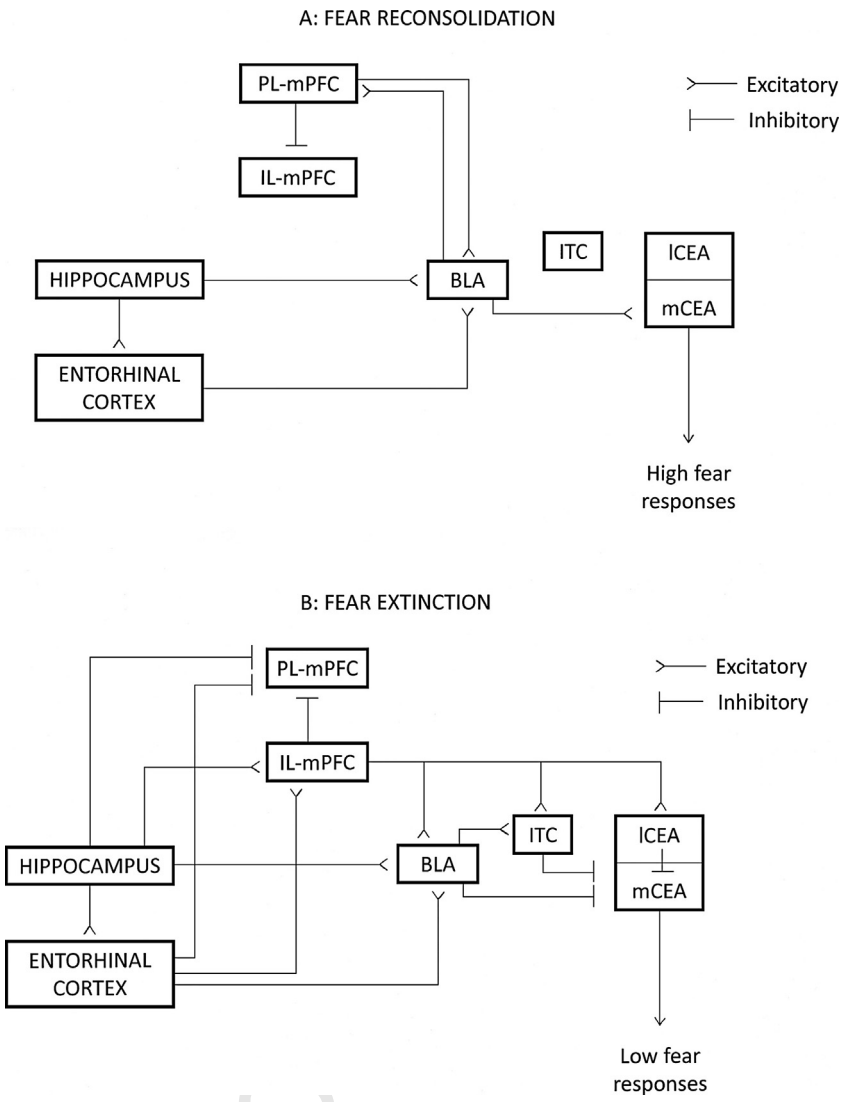

Fig. 1. Proposed neural circuits underlying fear memory reconsolidation and extinction. (A) During fear memory reconsolidation, hippocampal and entorhinal inputs enhance the basolateral amygdala (BLA) activity that excites pyramidal neurons of the prelimbic region within the medial prefrontal cortex (PL-mPFC). In turn, the PL-mPFC input synapses on infralimbic region of the mPFC (IL-mPFC) inhibiting it and on the BLA (probably on "fear neurons") which influences central amygdala activity (CEA), the amygdaloid output nucleus. The result is to rise conditioned fear response. (B) During fear memory extinction, hippocampal and entorhinal inputs inhibit the PL-mPFC, whereas excite the BLA and IL-mPFC. In turn, the IL-mPFC contributes to inhibit PL-mPFC and may act by exciting (i) the BLA "extinction neurons" which inhibit the medial division of CEA (mCEA), directly or indirectly (through intercalated mass cells, ITCs), (ii) GABA-ergic ITCs that inhibit mCEA and (iii) inhibitory interneurons within the lateral division of CEA (lCEA) that, in turn, inhibits mCEA. The result is to lower conditioned fear response.

et al., 2006). Moreover, the IL is the primary site of action for hippocampal BDNF and increasing BDNF in this pathway prevents fear extinction impairment (Peters et al., 2010). Thus, hippocampus-IL projection appears to be a key projection for fear memory extinction. Sotres-Bayon et al. (2012) suggested that following extinction an increased inhibition of PL activity takes place. This might be due partly to the hippocampal inputs that excite local PL interneurons triggering feed-forward inhibition of PL neurons (Sotres-Bayon et al., 2012) and in part to the inhibitory actions of IL on PL (Ji and Neugebauer, 2012). These two regions of the mPFC project differently to the amygdala. Whereas PL fibers selectively target the BLA and CEA, IL fibers are distributed mainly to medial and basomedial nuclei of the amygdala, intercalated cell masses and lateral division of CEA (lCEA) (Vertes, 2004). It is likely that differential activation of the two regions of the mPFC and consequently of their differential connectivity with the amygdalar nuclei orchestrate conditioned fear responses during reconsolidation and extinction processes. Supposedly, during fear reconsolidation enhanced BLA activity driven by hippocampal and entorhinal inputs controls PL activity triggering PL pyramidal neurons. PL input synapse on "fear neurons" within the amygdaloid nuclei, which fire selectively during and after fear conditioning (Herry et al., 2008) (Fig. 1A). These neurons, in turn, may influence CEA activity thus modulating the expression of conditioned fear responses by means of projections to midbrain and hypothalamic sites or the ventrolateral PAG (freezing) (LeDoux, 2000). On the contrary, during fear extinction, PL activity could be inhibited (due to the stimulation of the PL interneurons by hippocampal and IL projections) (Ji and Neugebauer, 2012; Sotres-Bayon et al., 2012;) whereas IL activity is stimulated (Ji and Neugebauer, 2012; Knapska et al., 2012; Milad and Quirk, 2002). IL inputs may synapse on "extinction neurons" within amygdalar nuclei, which fire selectively to an extinguished CS (Herry et al., 2008). Extinction neurons may then inhibit the output of CEA (Fig. 1B). Alternatively, or additionally, IL excitatory output may activate the ITC neurons that in turn inhibit CEA providing a mechanism of extinction (Amano et al., 2010, 2012; Ehrlich et al., 2009; Likhtik et al., 2008; Pape and Pare, 2010; Pare and Duvarci, 2012; Quirk and Mueller, 2008). Moreover, the ITC neurons might

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integrate additional inputs from the BLA to set the level of inhibition of CEA neurons (Amano et al., 2011) (Fig. 1B). Finally, IL-lCEA projections might activate inhibitory interneurons within lCEA which in turn inhibit output neurons of mCEA (Fig. 1B). Thus, although fear reconsolidation and extinction involve the same neural structures, they may take place in distinct neuronal circuits involving different subregions, connections and neuronal populations. This seems to be supported by electrophysiological and immunohistochemical experiments that have identified distinct amygdaloid ("fear neurons" and "extinction neurons") and hippocampal ("cFos$^+$ cells" and "pERK$^+$ cells") neurons activated during conditioning and extinction of fear (Herry et al., 2008; Tronson et al., 2009). Moreover, the two subpopulations of amygdalar neurons have preferential connections either to the PL or the IL; whereas the amygdaloid neurons whose activity is correlated with fear memory are innervated by the PL, those whose activity is correlated with fear extinction receive inputs mainly from the IL (Ji and Neugebauer, 2012; Knapska et al., 2012). Therefore, amygdaloid fear neurons and hippocampal cFos$^+$ cells might be connected with ENT and PL projections that are activated during reconsolidation of conditioned fear responses, whereas amygdaloid extinction neurons and hippocampal pERK$^+$ cells might be connected with ENT and IL projections activated during extinction of these fear responses. Thus, fear memories reconsolidation and extinction are two competing mnemonic phases which require the activation of different neuronal circuits.

4.2. Temporal and biochemical signatures in the neural sites involved in reconsolidation and extinction

The diverse anatomical requirements presumably are related to the distinct temporal and biochemical signatures. Fear memories reconsolidation and extinction have different temporal profiles (Tronson et al., 2012). After retrieval, there is a brief time window for reconsolidation, whereas extinction only takes place after prolonged re-exposure to the CS in absence of the US (Suzuki et al., 2004). At the molecular level, the activity of several molecules is required for both processes, but others are oppositely regulated during the two phases (De la Fuente et al., 2011; Merlo et al., 2005; Merlo and Romano, 2008). For example, both fear memory reconsolidation and extinction are protein synthesis dependent processes, as shown by their disruption when a protein synthesis inhibitor is administered after memory reactivation or extinction training (see Tables 1–3 and 7–9), but the protein synthesis may require different upstream receptors, signaling and transcription factors. For example, increased levels of phosphorylated GluR1 subunit-containing AMPA type glutamate receptor were found in the lateral amygdala after fear memory reactivation, whereas its dephosphorylation was observed after fear memory extinction (Monfils et al., 2009). It was also shown that activation of the endocannabinoid system reduces the reconsolidation of fear memories, whereas its hypo-activation promotes their reconsolidation leading to enduring fear responses (De Oliveira Alvares et al., 2008; Lin et al., 2006). On the contrary, intact CB1 receptor signaling appears to be essential for proper extinction of aversive memories (Abush and Akirav, 2010; De Oliveira Alvares et al., 2008; Ganon-Elazar and Akirav, 2009; Kunhert et al., 2013; Lin et al., 2009). Therefore, it may be postulated that the endocannabinoid system determines the balance between the processes of maintaining or strengthening the original memory (reconsolidation) and the establishment of a new memory (extinction) (De Oliveira Alvares et al., 2008). Both processes require NMDA receptors activation whereas fear extinction, but not reconsolidation, involves L-VGCCs (Davis and Bauer, 2012; De Carvalho Myskiw et al., 2014; Suzuki et al., 2008). Increased intracellular calcium results in the protein kinases activation, such as MAPK, that translocate into the nucleus where they activate (phosphorylate) several transcription factors to promote gene transcription and new protein synthesis. The two isoforms of MAPK, ERK1 and ERK2, seem to be involved in a different manner in the two mnemonic phases (Cestari et al., 2014). Indeed, whereas fear reconsolidation primarily involves ERK2 (Cestari et al., 2006), an increased intranuclear pERK1 has been reported during fear extinction (Fischer et al., 2007). Also PI-3K and its downstream target AKT seem to be recruited in different way in fear memories reconsolidation and extinction: they are reactivated and dephosphorylated, respectively (Lin et al., 2003a). Furthermore, the outcome of retrieval in terms of reconsolidation/extinction may depend on the balance between protein kinases and phosphatases (such as calcineurin) activity. As it has been proposed by Lin et al. (2003a), the stimulation of MAPK may activate several transcriptional factors to reactivate original memory on one hand and promote calcineurin synthesis on the other hand. Calcineurin, in turn, may exerts a negative feedback effect to down-regulate kinases. Therefore, when protein kinases activity dominates the reconsolidation process is triggered, when calcineurin activity dominates the extinction process is triggered. Finally, fear memory reconsolidation and extinction may involve either different transcription factors or the same transcription factors but in different manner. For example, both processes involve NFκB, yet activity of the transcription factor NFAT is engaged by extinction but not reconsolidation (De la Fuente et al., 2011).

As previously mentioned, extinction is a form of new learning and as such it consists of an acquisition and a consolidation phase (Myers and Davis, 2007; Pape and Pare, 2010; Quirk and Mueller, 2008). The two phases are usually studied by means of treatments applied pre- or post-extinction training, respectively. Although it is not completely understood how the several brain sites contribute to each phase of extinction process, the results tend to support the involvement of the BLA in both phases and the mPFC, hippocampus and ENT only in the consolidation phase (Baldi and Bucherelli, 2014; Bevilaqua et al., 2006; Quirk and Mueller, 2008). For example, fear extinction acquisition activates amygdalar NR2B-containing NMDA receptors that induce calcium influx. During extinction consolidation in the same structure L-VGCCs are activated allowing further increase of intracellular calcium concentration, whereas in mPFC the NR2B are activated, perhaps following stimulation by the amygdalar inputs.

4.3. Reconsolidation and extinction in human anxiety disorders

As mentioned above, understanding the biological mechanisms of fear memory reconsolidation and extinction may have clinical relevance in treating human anxiety disorders such as PTSD. PTSD patients show strong traumatic memories that are continuously retrieved in an intrusive manner, causing re-experiencing of the traumatic event and increased arousal and stress response. The persistence of PTSD can be explained in terms of trauma-induced strengthening of the memory trace or failure to extinguish conditioned fear memory (Alberini and LeDoux, 2013; VanElzakker et al., 2014). Thus, the pharmacological interferences effective in disrupting fear memory reconsolidation or enhancing extinction could potentially be useful for reducing expression of fear memory (Fitzgerald et al., 2014; Quirk and Mueller, 2008). Based on results obtained in rodents, translational studies in humans are beginning to be carried out. For example, the β-adrenergic antagonist propranolol and mTOR blocker rapamycin could be promising treatments for targeting the fear memory reconsolidation. The oral administration of propranolol before fear memory reactivation in healthy human subjects reduced significantly fear-potentiated startle response during testing 24 h later and prevented the return of fear (Kindt et al., 2009). Moreover, the same pharmacological treatment in patients suffering from PTSD reduced physiological

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parameters of fear when the subjects again described their traumatic experience a week later (Brunet et al., 2008). Recently, rapamycin combined with reactivation of a traumatic memory was used in a pilot study in male veterans. The results showed that veterans treated with rapamycin (sirolimus) reported significantly fewer and less intense PTSD symptoms 1 month later, although the effects did not persist at 3 months (Suris et al., 2013).

In the treatment of PTSD exposure-based therapy is frequently used. It is conceptually based upon fear extinction. DCS is the best studied extinction enhancer and has been used as an adjunct to psychotherapy in humans (Davis, 2011; Hofmann et al., 2013b). In clinical studies, DCS administered before the exposure sessions improves responses to therapies for acrophobia (fear of heights, Ressler et al., 2004), social anxiety disorder (Hofmann et al., 2013a) and panic disorder (Otto et al., 2010); however, it seems to be less effective in therapeutic treatment of PTSD (De Kleine et al., 2012; Litz et al., 2012). In rodents, other drugs were shown to facilitate extinction and might be useful in humans. These include glucocorticoids and cannabinoid agonists. PTSD patients have reduced circulating levels of cortisol (Yehuda, 2001) and it has been shown that glucocorticoids affect symptoms severity. In fact, hydrocortisone administration enhances exposure therapy in PTSD (Suris et al., 2010; Yehuda and LeDoux, 2007) and low-dose cortisol improves treatment of PTSD symptoms (Aerni et al., 2004). Cannabinoid agonists also facilitated fear extinction memory in healthy humans (Rabinak et al., 2013) and this effect appeared to be due to the modulation of prefrontal-hippocampal circuits (Rabinak et al., 2014). However, these agents are not yet utilized in the treatment of anxiety disorders.

Reconsolidation and extinction might interact at both pharmacological and procedural levels. Their pharmacological interaction may constitute a limit for the use of the reactivation or exposure therapy for the treatment of anxiety disorders in humans. Indeed, the use of exposure to cues to retrieve and extinguish fear memories could, under some circumstances, result in strengthening of fear memory. This is important when extinction-enhancing agents (such as DCS) or reconsolidation-impairing drugs (such propranolol) are used. DCS accelerates and strengthens fear extinction, but it also enhances fear memory reconsolidation (Lee et al., 2006). Similarly, propranolol impairs fear memory reconsolidation but also impairs fear extinction resulting in high fear (Cain et al., 2004). The result might be a potentially strengthening of maladaptive memories after retrieval. Because the duration of the re-exposure to the CS appears to be an important factor, the pharmacological agent used must be coordinated with the exposure duration for targeting the right memory phase. On the other hand, procedural interactions between reconsolidation and extinction might be an alternative to pharmacological intervention for the treatment of anxiety disorders. Recently, several studies demonstrated that fear extinction performed during a reconsolidation window enhances the effects of extinction training preventing the re-expression of fear memory in rodents (Auber et al., 2013; Monfils et al., 2009; Pineyro et al., 2014; Quirk et al., 2010; Rao-Ruiz et al., 2011; Rossato et al., 2010). It was proposed that making the original memory labile through reactivation, extinction learning overwrites the original memory (Monfils et al., 2009). Similar results have been reported in humans. Schiller et al. (2010) showed that post-retrieval extinction may interfere with the fear memory reconsolidation in humans and it selectively blocks the reconsolidation of the retrieved memory but does not affect non-retrieved memories. On the contrary, Soeter and Kindt (2012) failed to replicate these results using different fear memory responses.

In conclusion, although the inconsistent findings indicate the need for further investigation, the improvement of these interventions could lead to new therapeutic treatments of pathological fear memories.

Uncited references

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Acknowledgments

We thank Dr Maria Beatrice Passani for comments on a previous draft of this manuscript and A. Aiazzi, S. Cammarata, C. Pregno, and A. Vannucchi for their technical assistance.

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Please cite this article in press as: Baldi, E., Bucherelli, C., Brain sites involved in fear memory reconsolidation and extinction of rodents. Neurosci. Biobehav. Rev. (2015), http://dx.doi.org/10.1016/j.neubiorev.2015.04.003

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Please cite this article in press as: Baldi, E., Bucherelli, C., Brain sites involved in fear memory reconsolidation and extinction of rodents. Neurosci. Biobehav. Rev. (2015), http://dx.doi.org/10.1016/j.neubiorev.2015.04.003

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Please cite this article in press as: Baldi, E., Bucherelli, C., Brain sites involved in fear memory reconsolidation and extinction of rodents. Neurosci. Biobehav. Rev. (2015), http://dx.doi.org/10.1016/j.neubiorev.2015.04.003

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Please cite this article in press as: Baldi, E., Bucherelli, C., Brain sites involved in fear memory reconsolidation and extinction of rodents. Neurosci. Biobehav. Rev. (2015), http://dx.doi.org/10.1016/j.neubiorev.2015.04.003

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Please cite this article in press as: Baldi, E., Bucherelli, C., Brain sites involved in fear memory reconsolidation and extinction of rodents. Neurosci. Biobehav. Rev. (2015), http://dx.doi.org/10.1016/j.neubiorev.2015.04.003

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Please cite this article in press as: Baldi, E., Bucherelli, C., Brain sites involved in fear memory reconsolidation and extinction of rodents. Neurosci. Biobehav. Rev. (2015), http://dx.doi.org/10.1016/j.neubiorev.2015.04.003