neurobiología
Revista electrónica

Review Article

Molecular and epigenetic mechanisms associated with extinction of fear memory: a systematic review

Mecanismos moleculares y epigeneticos asociados a la extinción de la memoria del miedo: una revisión sistemática

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Received: August, 15, 2019 Accepted August, 21, 2019
Find this paper at: www.uv.mx/eneurobiologia/vols/2019/xx/xx.html

Abstract
Introduction: The present systematic review aims to analyze articles between 2011 and 2017 that describe the involvement of epigenetic and molecular mechanisms associated with extinction of fear memory. Methods: Inclusion and exclusion criteria were considered to filter the final articles extracted from Science Direct, Pubmed and Google Scholar. Results: From a total of 461 articles, 13 attended the criteria and were displayed in a table divided into: Objective, Brain region, techniques and reference. These final articles were critically analyzed and compared between each other. Discussion: Analysis of drug efficiency and molecular mechanisms involved in extinction and/or consolidation of fear memory in mice and rats may elucidate and thus contribute in the treatment of obsessive-compulsive disorder, anxiety, phobia, panic and posttraumatic stress disorder.

Keywords: Memory extinction, Molecular, Epigenetic, Systematic review.

Resumen
Introducción: La presente revisión sistemática tiene como objetivo analizar los artículos entre 2011 y 2017 que describen la participación de los mecanismos epigenéticos y moleculares asociados con la extinción de la memoria del miedo. Método: Se consideraron los criterios de inclusión y exclusión para filtrar los artículos finales extraídos de Science Direct, Pubmed y Google Scholar. Resultados: De un total de 461 artículos, 13 cumplieron con los criterios y se mostraron en una tabla dividida en: Objetivo, Región del cerebro, técnicas y referencia. Estos últimos artículos fueron analizados críticamente y comparados entre si. Discusión: El análisis de la eficacia de los medicamentos y los mecanismos moleculares implicados en la extinción y / o la consolidación de la memoria del miedo en ratones y ratas pueden dilucidar y, por lo tanto, contribuir al tratamiento del trastorno obsesivo-compulsivo, la ansiedad, la fobia, el pánico y el estrés postraumático.

Palabras clave: Extinción de la memoria, Molecular, Epigenética, Revisión sistemática.

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1. Introduction

The brain has the fascinating ability to store long-term memories (LTM). However, some of them may lead to diseases. Accentuated memories of fear may contribute to the development of obsessive-compulsive disorder, anxiety, phobia, panic and posttraumatic stress disorder.[1]

Many molecular neuroscience studies have established that learning-induced molecular changes in genes and proteins expression trigger lasting changes in neuronal plasticity and memory consolidation, but the signaling mechanisms behind it are still poorly understood.[2] Epigenetic mechanisms (e.g acetylation, phosphorylation, methylation, ubiquitination and SUMOylation) influence the accessibility of transcription factor to gene promoters by controlling the conformation of chromatin and thus, facilitating or not gene expression.[3] Targeting these types of mechanism during initial learning or memory retrieval can lead to persistent memory due to plasticity that may result in reconsolidation of the original memory. In this way, molecular events are needed to stabilize the extinction of this consolidated memory.[4]

Classical fear conditioning is the process of making, from an affective neutral stimulus, a conditioned one by pairing it with a noxious aversive stimulus such as foot shock.[5] Experimental extinction is the reduction of a conditioned response following the withdrawal of reinforcement.[6] It does not reflect forgetting, but rather "relearning," in which the perception of the conditioned stimulus without the original reinforcer results in normal behavior.[5,7,8] However, the original response of extinction can be temporarily suppressed and return under conditions that result in reconsolidation of extinction memory.[4] Although extinction learning is a well-established therapeutic intervention, clinicians are aware that patients may re-experience fear after exposure therapy since fear may spontaneously recover over time or be evoked when exposed to a relevant cue in the same or within a new context.[9]

Animal models have proved to be a very useful way of examining the neural and molecular correlates of fear experiences, which has in turn led to the identification of numerous pharmacological adjuncts that can enhance the processes underlying fear inhibition. Several of these drugs have been tested as pharmacological adjuncts in behavioral therapy for a range of anxiety disorders in humans.[10] Studies using fear conditioning and extinction in mammals (e.g rodents and humans) indicate that a neural circuit present in areas such as hippocampus, amygdala and medial prefrontal cortex is responsible for the learning and memory processes that enable context-dependent behavior.

The purpose of this systematic review is to describe the involvement of epigenetic and molecular mechanisms associated with extinction of fear memory, providing an overview of new insights into the potential role of the genes regulation in the pathophysiology of psychiatric disorders.

2. Methodology

This is a systematic review of the literature, based on recommendations described by PRISMA.[11] The research question was based on PICO technique:[12] Could adult male rats and mice have fear memory extinction using epigenetic and molecular approaches compared to negative control groups? This bibliographic research was carried out in the second semester of 2017 and was undertaken by searching in Science Direct, PubMed, Virtual Health Library and Google Scholar electronic databases. The terms and descriptors used in the searching process were selected based on the keywords available in previous studies and via Mesh - Medical Subject Headings or DeCS - Health Sciences Descriptors (Table 1).

The entry terms identified in the literature were described in Table I.

Data extraction and all processes of search, selection and assessment of articles were performed in pairs. The search strategies were customized according to specific tools and indexed terms available in each database (Table 1). Complete studies written in English and published between January, 2000 and November, 2017 were selected according to the following criteria: Major papers and original reports presenting approaches for drug treatment and/or evaluation of the pharmacological adjuncts in obsessive-compulsive disorder and/or anxiety and/or phobia and/or panic and/or posttraumatic stress disorder, highlighting biological, metabolic or epigenetic mechanisms involved. The authors did not include gray literature, editorials, opinions, comments, case report, letters, reviews, encyclopedia and books addressing research questions within only psychotherapeutic or behavioral approaches. Studies published in journals with impact factor less than 2.0, duplicate and presenting only one keyword of the search strategy in their title were also not considered. After the process of collecting the data and identification of the eligible literature, studies were organized by author and year of publication in charts, with the purpose of systematization. Subsequently, they were read in full text for a critical analysis of the content, considering the scientific merit, potential similarities or conflicts between them. Finally, relevant data were extracted and segregated into categories.

ACADEMIC DATABASES	STRATEGY
PubMed	"Fear"[Mesh] AND "Memory"[Mesh] AND "Extinction, Psychological"[Mesh] AND ("Epigenesis, Genetic"[Mesh] OR "Epigenomics"[Mesh] OR "Epigenetic Repression"[Mesh])
Science Direct and Google Scholar	"Fear" AND "Memory" AND "Extinction" AND ("Epigenesis, Genetic" OR "Epigenomics" OR "Epigenetic Repression")
Virtual Health Library	mh:F01.470.361 AND mh:F02.463.425.540 AND mh:F02.463.425.770.232 AND (mh:G05.308.203 OR mh:H01.158.273.180.350.074 OR mh:G05.308.203.311)

Table 1. Search sites and keywords used as an initial strategy to collect and filter articles based on molecular mechanisms involved in extinction of fear memory.

3. Results

Using the full search strategy, 461 papers were initially selected for this systematic review. However, only 13 studies were included in the present analysis after filtering the search by applying the inclusion and exclusion criteria (Figure 1). The final articles were organized in a table containing the following information: author/year, objective, brain region, techniques and model (Table 2). In 2011, Koshibu et al., showed that the nuclear pool of protein phosphatase 1 (PP1) in neurons of the amygdala is involved in the

control of several histone posttranslational modifications (PTMs) and in the expression of memory-associated genes. Inhibiting this pool by conditional transgenesis enhances fear memory and amygdala long-term potentiation (LTP).[13]

In the same year, a study with male Sprague-Dawley rats (Harlan) revealed that the auditory fear conditioning is associated with an increase in histone H3 acetylation and DNA (cytosine-5)-methyltransferase 3A (DNMT3A) expression in the lateral amygdala (LA). Intra-LA infusion of the histone deacetylase (HDAC) inhibitor called TSA increases H3 acetylation and enhances fear memory consolidation, while intra-LA infusion of the DNA methyltransferase (DNMT) inhibitor called 5-AZA impairs fear memory consolidation. Intra-LA infusion of 5-AZA was observed to impair training-related increases in H3 acetylation and pre-treatment with TSA was observed to rescue the memory consolidation deficit induced by 5-AZA.[14]

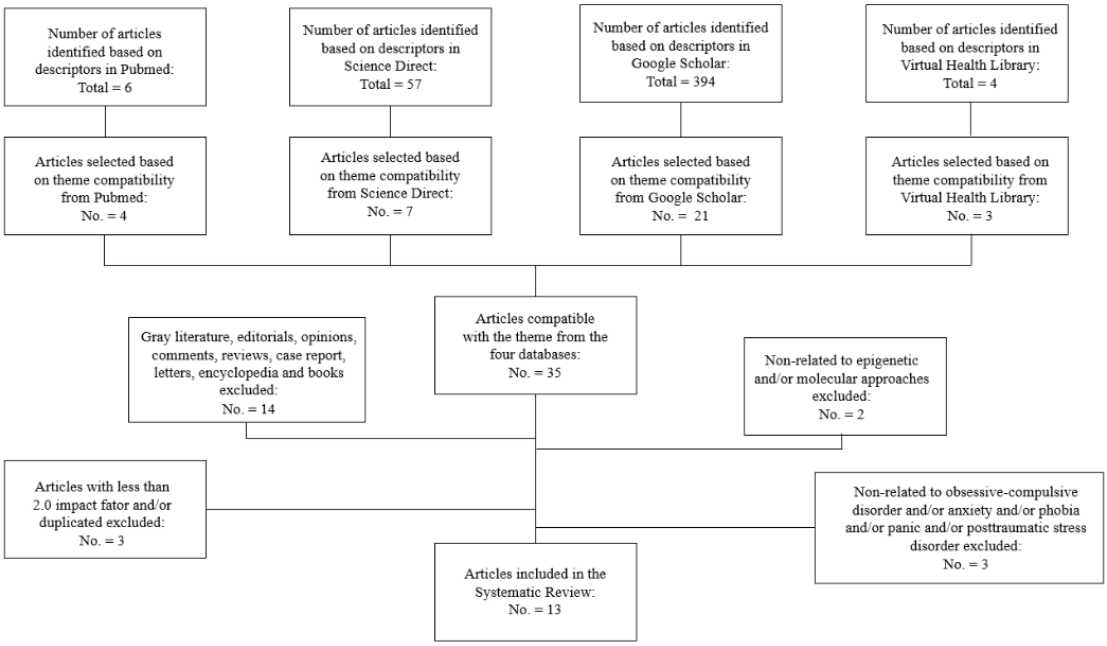

Figure 1. Flowchart of the search and selection process of the articles included in this review.

Brain-derived neurotrophic factor (BDNF) is known to be a crucial regulator of neuroplasticity, learning and memory processes in different brain areas. During an investigation of the role of BDNF in the extinction of amygdala-dependent cued fear memories, Psotta et al.,[15] observed that BDNF KO mice possessed a deficit in the acquisition of extinction memory, while extinction learning remained unaffected in young adult heterozygous BDNF KO mice.

Itzhak et al., (2012) indicated that the sodium butyrate (NaB), a HDAC inhibitor, seems to rescue contextual fear conditioning of nNOS knockout (KO) mice by increasing H3 histone acetylation and had long-term facilitatory effect on the extinction of cued fear memory of wild-type mice by increasing H4 histone acetylation.[16] The same drug promoted fear extinction, infralimbic histone acetylation and c-Fos expression. The involvement of the infralimbic cortex was confirmed as infusions of NaB into the infralimbic, but not prelimbic cortex, induced extinction enhancements.[17]

Author/year	Objective	Brain region	Techniques	Model
DE OLIVEIRA et al., 2016	To analyze the role of flavones on the acquisition and extinction of fear memory and anxiety.	Dorsal hippocampus.	Fear conditioning and extinction training and Quantitative PCR (qPCR) of Gabra5, Htr1a, Grin2a, Grin2b and Mapk1/ Erk2.	Adult male *Wistar* rats.
GALATZER -LEVY et al., 2017	To replicate previous results demonstrating three common trajectories of fear extinction learning in both humans and mice, and to examine the role of genetic and molecular factors associated with FKBP5.	Amygdala.	Fear conditioning and extinction in humans. Immobilization stress, full cued-fear conditioning and extinction and dexamethasone 300 µg/kg administration in C57BL/6J mice.	Human and mouse models.
ITZHAK et al., 2012	To investigate whether increase in histone acetylation rescues the formation of long-term memory of contextual fear conditioning and accelerates the extinction of contextual and cued fear conditioning.	Hippocampus and amygdala.	Fear conditioning and extinction, administration of NaB and sandwich ELISA for histones extraction of nNOS KO mice and the parental strains of their wild type (WT) counterparts.	Adult male homozygous nNOS KO and WT mice.
KOSHIBU et al., 2011	To assess whether PP1-dependent chromatin regulation may underlie disorders affecting emotional memory.	Lateral amygdala.	Fear conditioning and extinction, Western blot, immunohistochemistry, qRT-PCR, colorimetric assay and *in vitro* electrophysiology of coronal slices of brain.	Transgenic mice in C57Bl6/J background carrying a fragment of the nuclear inhibitor of PP1 spanning amino acids 143 to 224 (NIPP1*).
LI et al., 2017	To test the hypothesis that the disruption the interaction between nNOS and PSD-95 may promote neurogenesis in the dentate gyrus followed by the enhancement in retrieval of extinction memory.	Dentate gyrus.	Remote contextual fear conditioning and extinction, immunoprecipitation, western blot, immunohistochemistry and x- ray radiation.	Male C57BL/6 mices and homozygous nNOS-deficient mice.
MAHAN et al, 2012	To examine the mechanisms of transcription during fear conditioning and BDNF induced plasticity of a variant of the Homer1 (Homer1a) gene, which may regulate synaptic plasticity during memory consolidation.	Hippocampus and amygdala.	Fear conditioning, cell culture, chromatin immunoprecipitation and qRT-PCR.	Homer1a wild-type and KO mice.

MONSEY et al., 2011	To verify if the histone acetylation and the DNA methylation are critical for auditory Pavlovian fear conditioning and associated synaptic plasticity in the lateral amygdala.	Lateral amygdala.	Administration of a histone deacetylase inhibitor Trichostatin A (TSA), fear conditioning, western blotting and slice electrophysiology experiments.	Adult male Sprague-Dawley rats.
PSOTTA et al., 2013	To investigate the role of BDNF in the extinction of amygdala-dependent cued fear memories.	Hippocampus, basolateral amygdala and medial and prefrontal córtex.	Fear conditioning and extinction and ELISA.	Wild-type and Young/older-adult heterozygous BDNF knockout mice.
RUDENKO et al., 2013	To study the functions of the neuronal Tet enzymes in brain.	Cortex and hippocampus.	Pavlovian fear conditioning and extinction, knockout of the Tet1 gene (Tet1KO) and analysis of the deregulation in the expression of the Npas4, c-Fos, Arc, Egr2, and Egr4 genes.	Wild-type and Tet1 knockout (Tet1KO) mice.
SIDDIQUI et al, 2017	To explore the hypothesis that differential gene expression in the prefrontal córtex and amygdala, required for the fear and extinction learning, is regulated by the histone H3/H4 acetylation.	Infralimbic, prelimbic and medial prefrontal cortex and basal, lateral, centrolateral and centromedial amygdala.	Fear conditioning and extinction, as well as immunohistochemistry.	12–16 week-old-adult male Sprague–Dawley rats.
STAFFORD et al., 2012	To evaluate the ability of the HDAC inhibitor sodium butyrate (NaB) to produce lasting enhancements in memory following initial learning or extinction.	Intra-hippocampal and intra-medial-prefrontal cortex (mPFC).	Administration of the histone deacetylase (HDAC) inhibitor sodium butyrate (NaB) after contextual fear conditioning and extinction, and immunohistochemistry.	8-12 week-old-adult male C57BL/6 mices.
WHITTLE et al, 2013	To evaluate if the inhibition of histone deacetylases can improve extinction learning in animal models of impaired extinction.	Nucleus accumbens.	Fear conditioning and extinction, deep brain stimulation, administration of valproic acid (VPA), AMN082, PEPA, MS-275 and DCS (NMDA receptor partial agonist)	Male 3-5 month old 129S1/SvImJ (S1) mice.
WHITTLE et al, 2016	To investigate the effect of enhancing dopaminergic signaling and histone acetylation on the rescue of deficient fear extinction.	Medial prefrontal cortex, amygdala, dorsal hippocampus and ventral hippocampus.	Fear conditioning and extinction, dietary ZnR, MS-275 and L-dopa administration, immuno-fluorescence, chromatin immunoprecipitation and qRT-PCR.	Male S1 mice.

Table 2. Description of the selected articles published between January/2011 and November/2017.

Studying epigenetic modulation of Homer1a transcription regulation in amygdala and hippocampus with Pavlovian fear conditioning, Mahan et al., (2012) provided evidences for dynamic epigenetic regulation of Homer1a following BDNF-induced plasticity and during a BDNF-dependent learning process.[18] Homer1a mRNA increases after fear conditioning in vivo within both amygdala and hippocampus of wild-type mice. This mRNA also increases after BDNF application to primary hippocampal and amygdala cultures in vitro and these increases are dependent on transcription and mitogen-activated protein kinase (MAPK) signaling.

Both in vitro and in vivo manipulations resulted in decrease of Homer1 promoter and Histone H3 Lysine 9 (H3K9) methylation in amygdala cells. However, an increase was noticed in Homer1 promoter H3 acetylation in hippocampal cells. No changes were observed in H4 acetylation or Histone H3 Lysine 27 (H3K27) dimethylation. Inhibition of histone deacetylation by NaB enhanced contextual but not cued fear conditioning and enhanced Homer1 H3 acetylation in the hippocampus.

In 2013, Whittle et al.,[19] observed that the rescue of impaired extinction consolidation/retrieval was achieved after extinction training with D-cycloserine (N-methly- D-aspartate partial agonist) or MS-275, a HDAC inhibitor. High frequency stimulation on the nucleus accumbens during extinction training significantly reduced fear during extinction retrieval compared to sham stimulation controls. Rescue of deficient extinction consolidation/ retrieval was achieved with prior extinction training administration of valproic acid or AMN082, a glutamate receptor 7 allosteric agonist. On the other hand, a histone deacetylase-1 inhibitor called MS-275 and a sulfonamide AMPA receptor positive allosteric modulator called PEPA failed to affect extinction acquisition.

In a later study,[20] Whittle et al., revealed that persistent and context-independent rescue of deficient fear extinction was associated with enhanced expression of dopamine-related genes, such as dopamine D1 and D2 receptor genes in the medial prefrontal cortex and amygdala, but not in hippocampus. Moreover, enhanced histone acetylation was observed in the promoter of the extinction-regulated Drd2 gene in the medial prefrontal cortex, revealing a potential gene-regulatory mechanism.

Rudenko et al., show that methyl cytosine dioxygenase 1 (Tet1), a neuronal enzyme, regulates levels of DNA methylation, synaptic plasticity and memory extinction.[21] They propose that it plays an important role in maintaining consistent hypomethylation of specific DNA regions including promoter areas of at least some of the neuronal activity-regulated genes. This, in turn, may promote cognitive flexibility, including memory extinction.

Using adult males Wistar rats, Oliveira et al.,[22] found that the activation of GABAA receptors and inactivation of GluN2B-NMDA receptors are relevant for the acquisition of lick response suppression, which is a conditioned emotional response underlying fear memory. In this case, flavonoid-rich fraction from Erythrina falcata (FfB) reversed the effect of blocking GluN2B-NMDA receptors on the conditioned fear and induced the spontaneous recovery. Thus, FfB represents a potential therapy for preventing or treating memory impairments.

Recently, Siddiqui et al., (2017) highlight that sub-regions of the cortex and the amygdala responded differentially to the fear learning and extinction. Following extinction learning, c-fos and CREB-binding protein expression increased in basal amygdala (BA), lateral amygdala (LA), centrolateral amygdala (CeL) and infralimbic prefrontal cortex (IL-PFC) but not in prelimbic prefrontal cortex (PL-PFC) and centromedial amygdala (CeM)

as compared to the naive control and conditioned group. The acetylation of H3 increased in both IL-PFC and PL-PFC, differently from H4, which increased only in the IL-PFC following extinction learning.[23]

In the same year, Li et al., found that the disruption of the interaction between neuronal nitric oxide synthase and postsynaptic density protein-95 in the remote contextual fear condition promoted neuronal proliferation and survival in the dentate gyrus, contributing to a better recovery of the memory of fear extinction.[24] Finally, Galatzer-Levy et al., revealed that risk alleles of a co-chaperone of hsp90 which regulates glucocorticoid receptor (GR) sensitivity called FKBP5 might contribute to fear extinction deficits. However, the use of dexamethasone may increase FKBP5 mRNA expression in the amygdala during memory consolidation and thus ameliorate the symptoms or development of posttraumatic stress disorder.[25]

4. Discussion

This systematic review suggests that the main areas associated with extinction of fear memory are amygdala, hippocampus, prefrontal cortex and nucleus accumbens. Immunohistochemistry, western blot and qRT-PCR were the methods more frequently used and the animals were mainly adult male Sprague–Dawley rats and C57BL/6J and 129S1/SvImJ mice. Some of the selected studies used pharmacological approaches and some did not, as the case of Whittle (2013) who showed that deep brain stimulation (DBS) may activate NMDA receptors and inhibit HDACs facilitating the recovery of extinction of fear memory. Whittle (2016) and Stafford (2012) also studied HDAC pharmacological inhibitors such as L-dopa, MS-275 and NaB and found the same potential treatment. Additionally, Itzhak (2012) affirmed that NaB may increase H4 acetylation, which is one of the epigenetic events responsible for accelerating the extinction of fear. Galatzer-Levy (2017) also showed that fear extinction can be promoted by injecting high doses of DEX (dexamethasone) in amygdala of rats, since it increases significantly the level of Fkbp5 and single nucleotide polymorphisms in this gene are related to posttraumatic stress disorder.

Li (2017) also found a novel target for the same disorder previously mentioned. This study demonstrated that, by inhibiting nitric oxide synthase and postsynaptic density protein 95 (nNOS-PSD-95) interaction in dentate gyrus, one promotes extinction memory recovery. Furthermore, Oliveira et al., (2016) showed that spontaneous recovery of fear memory might be correlated with the combined activation of GluN2A-containing NMDARs and 5-HT1ARs in the dorsal hippocampus, which, in turn, modulates ERK1/2 activity. Additionally, Monsey (2011) said that DNA methylation and histone acetylation are crucial for fear memory consolidation in lateral amygdala. They discovered that conditioning of auditory fear positively regulates ERK-dependent epigenetic events in neurons of lateral amygdala such as H3 acetylation and DNMT3A expression (an enzyme responsible for DNA methylation/silencing). On the other hand, Siddiqui (2017) found that an increase of histone acetylation in the infralimbic prefrontal cortex is associated with fear extinction and suggested that histone acetylation patterns differ between amygdala and prefrontal cortex after extinction learning.

Mahan (2012) affirmed that Homer1 KO mice had difficulty to assimilate fear conditioning, while the naive group under the same test showed Homer1 mRNA expression increase in hippocampus and amygdala, meaning that a decrease in Homer1 concentration in this brain regions may probably prevent mice of acquiring fear memory. Additionally, PSOTTA (2013) argued that BDNF KO mice have extinction memory deficit, suggesting that the concentration of this molecule play a relevant role on promotion of extinction of

fear memory. Koshibu (2011) also highlighted a powerful suppressor of fear memories: PP1 (phosphatase 1), which acts as a post-translational modifications (PTMs) regulator. However, the author said that the decrease of synaptic plasticity is an important condition for fear extinction, which is the opposite of what Rudenko (2013) affirmed in his paper: Neuronal activity-regulated genes are known to play an important role in processes such as neuronal plasticity and learning. It is through Tet1 activity of keeping promoter areas of some these genes hypomethylated that makes the transcription activation more flexible, promoting events such as memory extinction.

At this point, one could rise some questions: How could non-pharmacological or pharmacological approaches induce extinction of fear memory, which is considered a relearning process by decreasing synaptic plasticity? And how could this treatment not impair other types of memories which may be important for the patient? It seems that the threshold between promoting extinction of fear memories and keeping other important memories is too sharp to lie on damaging or reducing the ability of synaptic plasticity and the best option is to promote fear extinction through a cognitive flexibility/neuroplasticity to overcome this emotion. Overall, the molecular and epigenetic approaches described in the present paper highlight the efforts of modern science to clarify the mechanisms involved in fear extinction in animal model. We hope that these findings will help in integrating the knowledge in this field with studies in humans for the treatment of fear related disorders.

5. Conclusion

This systematic review presents an overview of the current literature on biological mechanisms and brain regions involved in the extinction and consolidation of fear memory in animal models. Generally, nNOS-PSD-95 interaction inhibition, HDACs inhibitors (such as L-dopa, MS-275 and NaB), NMDA activation, and BDNF, PP1 and Fkbp5 expression may contribute to extinction of fear memory. Additionally, histone acetylation patterns differ between amygdala and prefrontal cortex after extinction learning. Enduring epigenetic changes in several genes seems to underlie various neurobiological and behavioral phenotypes in animal models which may aggregate solid information about what may cause, prevent or inhibit fear memory in the field of Psychiatry, Neuroscience and Psychotherapy. However, more studies have to be done to improve the understanding and treatment of fear related disorders such as obsessive-compulsive, panic and posttraumatic stress disorders, anxiety and phobia.

6. Acknowledgements

This work was supported by CAPES foundation and PPGCB-UFRN.

7. Interest conflict

Author declares no conflicts of interest.

8. References

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