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Aversive memory and the role of the mesocorticolimbic system in defensive responses-literature review

K. M. H. Cavalcante

Federal University of Sergipe - Campus Lagarto

Author for correspondence: karenineholanda@gmail.com

Abstract. Evidence from both animal and human research indicates that emotionally significant experiences activate hormonal and brain systems that regulate the consolidation of new memories. Mesocorticolimbic dopamine system has been shown to be critical for many processes that drive learning and memory, including motivation, prediction error, incentive salience, memory consolidation, and response output; and it carries signals of valorization, both for stimuli related to gain, and for aversive stimuli. Literature indicates that dopaminergic system is involved in fear conditioning and extinction. Emotional processes are mainly mediated by the amygdala, and when it becomes active, its anatomical connections with the cortex may facilitate the processing of the presented stimuli. The ventral tegmental area encodes the prediction of errors, and signals are transmitted to regions such as nucleus accumbens, amygdala, hippocampus and prefrontal cortex. Advances in neurobiological research favored the understanding of the mechanisms underlying learning and the evocation of the extinction of aversive memory. We review the behavioral and neurobiological literature showing a role for mesocorticolimbic structures in defensive responses and aversive memory.

Keywords: Memory; Emotion; Fear; Limbic System; Mesencephalon; Prefrontal cortex; Dopamine

Contextualization and analysis

Memory and Emotion

Learning and memory are fundamental to survival independently for both people and animals. Learning corresponds to the change in behavior that results from the acquisition of knowledge about the environment, and memory is the process by which this information is coded, stored, and then evoked. These capabilities have their most developed form in man and most human behaviors depend on learning (KANDEL et.al., 2014). Therefore, memory and learning are the most important mechanisms by which environmental events shape behavior. All behavior is shaped by the interaction of genes with the environment, even more stereotyped behavior is influenced by the environment; as well as highly plastic behavior, such as language, is limited by innate factors (KANDEL; SCHWARTZ; JESSEL, 2000).

Memory processing addresses distinct operations such as encoding, storage, and recall. The first of the mnemonic processes is the encoding, which consists in the input of information in the neural systems related to the memory to be connected with preexisting information. These can originate

from the environment, led to the nervous system through the senses, or from within the person, arising from the thoughts and emotions. As events or stimuli are usually multiple and complex, memory systems perform selection, allowing for the coding of the most relevant aspects of cognition, more emotionally focused, more focused by our attention, or more strongly sensory (McDermott; Roediger, 2017).

After the coding of the selected aspects, the storage happens, which refers to the neural mechanisms that allow the retention of information over time; so the information is available to be remembered. Over time, some aspects or even all of them may be overlooked. Forgetfulness is a normal property of memory and plays an important role as a mechanism of prevention of overload in memory systems dedicated to memory (GLANNON, 2006).

For long-term storage, consolidation should occur, which involves gene expression and protein synthesis that produce structural changes at synapses. Consolidation makes explicit memories independent of the medial temporal lobe (McDermott; Roediger, 2017).

The last of the mnemonic processes is the evocation, through which we have access to the stored information to use it mentally in the cognition

and the emotion, or to externalize it through the behavior (KANDEL et al., 2014).

Memory has different types, and these involve different brain regions or combinations of regions (LENT, 2010). It is known that the hippocampus (HPC) is the region in charge of consolidating explicit memory engrams, either by transferring them to the appropriate cortical regions, or by temporarily storing copies of the cortical engrams (HORNBERG; BURGESS, 2013). In the case of spatial memory, the hippocampus holds a map capable of representing the characteristics of the objects that compose the environment, and their positional relations. There is an important relation between declarative memory and spatial orientation in hippocampal formation; the memory consolidation is guided by a partially pre-configured system related to the outer space representation (BECCHETTI, 2010).

Regarding the formation of long-term implicit memory requires several structures according to their type, for example: the neocortex for priming, the striatum for habits and abilities, the amygdala for conditioned fear, the cerebellum for the learning of motor skills, and some reflex paths for non-associative learning, such as habituation and sensitization (KANDEL et al., 2014). Emotional memory, or emotional associations, is an example of implicit memory that involves behavior change oriented toward a previously neutral stimulus as a result of experience, and this depends on the amygdala (KREBS; WEINBERG; AKESSON, 2013).

Emotion can affect the processes of coding and remembering. Emotion narrows the focus of attention, increasing memory to emotional contents, with a decrease to more peripheral details (PERGHER et al., 2006). In addition, moderate levels of emotions enhance the coding process and, subsequently, memory performance; however, extreme levels of emotions undermine this performance (HEGERL; SANDER; HENSCH, 2016; KRISHNA; STRACK, 2017; YERKES, R.M.; DODSON, 1908).

Emotion can be understood as a generally brief, intense, and circumscribed reaction related to a specific environmental event (PERGHER et al., 2006), or related to a specific stimulus present in the body (e.g., pain), or case of humans, in the mind (e.g., a thought) (KANDEL et al., 2014). The capacity for subjectivation and expression of the emotional response consists in affection; which involves the quality and emotional tone that accompany an idea or mental representation. Studies relating memory and emotion in humans have used the term emotion to refer to an affective state present during memory coding or retrieval; and from the experimental point of view, refers to the affective/physiological state that an individual presents during the validity of a memory test under stress conditions (PERGHER et al., 2006).

In this sense, emotions are automatic, usually unconscious, behavioral and cognitive responses, triggered when the brain detects a significant, positive or negatively charged stimulus. These physio-

logical responses involve encephalic changes in alertness levels and cognitive functions, such as attention, memory processing and decision strategies; and the rest of the body, with endocrine, autonomic and musculoskeletal responses. These autonomic and endocrine changes are part of the mechanisms of homeostatic regulation of the organism, which are mainly mediated by subcortical structures such as amygdala, striatum, hypothalamus and brainstem (NORMAN; BERNTSON; CACIOPPO, 2014; LEVENSON, 2014; MAREN; JIN, 2015).

Evidence from both animal and human research indicates that emotionally significant experiences activate hormonal and brain systems that regulate the consolidation of new memories. Emotional processes are mainly mediated by the amygdala, and when it becomes active, its anatomical connections with the cortex may facilitate the processing of the presented stimuli. Additionally, connections of the amygdala to the hippocampus could directly influence the semantic memory. Thus, the more active the amygdala at the time of learning, the greater the intensity of stored memory for those facts that present emotional content (PARÉ, 2003; MCINTYRE; ROOZENDAALL; MCGAUGH, 2003).

Noradrenergic activation of the basolateral amygdala (BLA) regulates memory consolidation through interactions with many other brain regions involved in consolidating memories from recent experiences. Adrenal medulla (epinephrine) and adrenal cortex hormones (cortisol, corticosterone in rodents) are released during and immediately after emotionally competent stimulation (PARÉ, 2003). Modulator systems not only influence the neurobiological processes underlying the consolidation of new information, but also affect other mnemonic processes, including memory extinction, memory evocation, and working memory. In contrast to its effects of increased consolidation, the adrenal gland's stress hormones impair recovery of memory and working memory (ROOZENDAALL; MCGAUGH, 2011).

Memory extinction involves the learning that clues that previously predicted aversive or appetitive consequences no longer predict such outcomes, and are regulated by the same neuromodulatory systems that regulate original learning. The infusion of the antagonist bicuculin and norepinephrine in the BLA immediately after the extinction training, in the contextual fear conditioning, favors the consolidation of the extinction of the aversive memory in rats (BERLAU; MCGAUGH, 2006). Functional magnetic resonance imaging in humans showed a correlation between the dorsal anterior cingulate cortex, the hippocampus and the amygdala during the extinction of fear conditioned to the context, corroborating with the theoretical model that proposes the inhibitory effect of the medial prefrontal cortex (mPFC) on the amygdala (LANG et al., 2009).

Animal models have allowed meticulous studies of the neural circuits, physiology, and biochemistry of emotional states such as fear. Studies with rodents addressing innate fear and learned fear

have elucidated the neural circuits of fear, highlighting the amygdala and the hypothalamus. These circuits activate the sympathetic nervous system, changing heart rate and blood pressure; stimulate the secretion of stress hormone and evoke species-specific defensive responses such as freezing and flight. In the case of freezing, signaling of the central nucleus occurs to the region of the ventral periaqueductal gray matter. Such basic investigations provide the hypothesis test for studies on fear and anxiety, and their disorders (PHELPS; LEDOUX, 2005).

Fear is the best studied emotion, both because it is so important for survival, and because of the availability of excellent experimental protocols for the study of fear in animals. An important protocol is the Pavlovian conditioning of fear, in which an association is learned between an unconditioned stimulus (US), which is emotionally competent, and thus automatically triggers fear emotions; and conditioned stimuli (CS), which are emotionally neutral. After pairing between stimuli and association memory formation, exposure to conditioned, previously neutral stimulus triggers the emotional responses (TOVOTE; FADOK; LUTHI, 2015).

Lesions in the amygdala prevent the occurrence of Pavlovian fear conditioning. The amygdala consists of approximately 12 nuclei, but the lateral (LA) and central (CeA) nuclei are especially important for conditioned fear, since injury to any of these nuclei, but not others, prevents the onset of conditioned fear. The lateral nucleus is the entrance nucleus, which receives afferents originating from the thalamus about the conditioned stimuli; the CS signs and US converge in the lateral nucleus, where they are paired (PHELPS; LEDOUX, 2005).

In the lateral nucleus of the amygdala there is a competitive transient process that governs the interaction between engrams to integrate memories for events that occur close to time and distinguish memories of events that occur more distant in time. This co-allocation is not limited to relating memories during coding; memory recall may involve a similar process for linking new memories to old memories. The excitatory-inhibitory balance determines whether the memories are linked or, alternatively, segregated in LA. These principles provide a basis for understanding how memories are organized in associative networks (RASHID, et al.; 2016).

The central nucleus of the amygdala is the exit region, neurons from this region project to areas of the brainstem involved in the control of defensive behaviors and endocrine responses and the autonomic nervous system. The lateral and central nuclei are connected to each other and both are sites of synaptic changes in conditioned fear (PHELPS; LEDOUX, 2005).

Fear is a complex psychological behavioral, cognitive, and, in humans, subjective response that occurs to a threatening stimulus. This emotion is usually transient and is characterized as an adaptive response to a real threat. On the other hand, anxiety is a long-term response to the signs of danger that can be signaled by both immediate circumstances,

which have well-defined signs of danger, and by vague indications of ill-defined events in which there are likely to be consequences that harm the individual (TOVOTE; FADOK; LUTHI, 2015).

Anxiety can be highly adaptive; alertness, vigilance and physical preparation increase the chance of survival in dangerous situations. However, when it lasts beyond actual risk, or when it evokes a response exacerbated by a potential threat, it can generate distress and disability. Abnormal regulation of fear generates anxiety disorders (ETKIN; WAGER, 2007).

Post-traumatic stress disorder (PTSD) is an anxiety disorder in which an individual's functional capacity is impaired by emotional responses to memories of a traumatic event or prolonged exposure to a traumatic event (BISSON et al., 201). Growing knowledge about fear circuits has generated testable hypotheses about the pathophysiology of anxiety disorders such as PTSD. The central alteration in this disorder seems to be related to the overconditioning of fear, in which subtle clues are able to evoke fear responses. These deregulated fear responses alter other cognitive, emotional, and physiological responses; leading to changes in baseline alertness, exaggerated startle responses, and sleep disturbances (Milad et al., 2009).

Pavlovian fear conditioning is generally employed to investigate the neurobiology of fear acquisition and its inhibition in rodents, and has also been used in psychophysiological and neuroimaging studies in humans. In this procedure, conditioned responses can then be diminished or extinguished by repeated CS presentation in the absence of the US. The conditioning and extinction of the Pavlovian fear are relevant to the neurobiology of PTSD, since this disorder involves exaggerated expression of the learned fear and that persists prolonged after the exposure to the trauma. Studying them can elucidate the mechanisms by which persistent responses to fear occur. It is also important because the current behavioral treatment of choice, exposure therapy, is based on mechanisms based on extinction. The hypothesis that conditioned fear extinction is deficient in PTSD is supported by new studies of fear conditioning and extinction that have shown impairment in retention of extinction memory (MILAD et al., 2009).

Advances in neurobiological research favored the understanding of the mechanisms underlying learning and the evocation of the extinction of aversive memory. Studies conducted in rodents with pharmacological and molecular manipulations and tools of electrophysiology and microstimulation indicated that the learning and recovery of extinction involve different cellular mechanisms. Studies suggest that, in addition to its role in the acquisition of fear, the amygdala seems to be involved in the learning of extinction, whereas the ventromedial prefrontal cortex-vmPFC (corresponding to the infralimbic cortex in rodents) and the hippocampus appear to be involved in remembering extinction. In contrast, a dorsal region to vmPFC in rats, i.e., the

prelimbic cortex, has been shown to promote expression of conditioned fear (BUKALO et al., 2015).

In addition, the bi-directional modulation of the vmPFC-amygdala circuits is impaired in PTSD patients, resulting in persistent conditioned fear responses even after extinction (PHELPS et al., 2004; PITMAN et al., 2012). Neuroimaging studies show pre-frontal dysregulation of subcortical neural activity in the population genetically vulnerable to the development of anxiety disorders (ADMON; MILAD; HENDLER, 2013).

The role of the mesocorticolimbic system in defensive responses

The sense of reward (pleasure, satisfaction) and punishment (disgust, aversion) are emotions well studied by neurophysiologists. The "reward center" is related mainly to the medial preencephalic bundle (in the lateral and ventromedial nuclei of the hypothalamus), with connections to the septum, amygdala, some areas of the thalamus and the basal ganglia. The "punishment center" is described with location in the central gray area that surrounds the cerebral aqueduct of Sylvius, in the mesencephalon, extending to the periventricular areas of the hypothalamus and thalamus, being related to the amygdala and hippocampus, and also to the portions and the lateral portions of the tegmental area of the midbrain (ESPIRIDÃO-ANTÔNIO et al., 2008).

The medial preencephalic bundle and its integrated regions (ventral tegmental area, hypothalamus, nucleus accumbens (NAcc), anterior cingulate cortex and prefrontal cortex) make up the circuit called the mesocorticolimbic system and demonstrate participation in the appetitive and aversive stimuli. Dopamine neurons project from the ventral tegmental area of the midbrain to many areas of the encephalon through the medial preencephalic bundle. The dopaminergic projections of the ventral tegmental area to the nucleus accumbens strongly influence goal-directed behavior (SALAMONE; CORREA, 2012).

Mesocorticolimbic dopamine neurons and responses to aversive stimuli

Dopamine (DA) has been intensively investigated mainly because of its known involvement in various neurological and psychiatric disorders. In particular, studies on pathological conditions have focused on the roles of dopamine phasic release in regions such as the prefrontal cortex and striatum. However, the release of dopamine may be more complex than just phasic release; because there is also tonic release, and alterations in this release have unique and important functional roles, and may play an important role in psychiatric disorders such as schizophrenia. Therefore, consideration of the bi-directional nature of DA changes is important for the normal functions of brain regions receiving DA innervation, including NAcc and prefrontal cortex (PFC). An abnormal balance of DA release, especially in PFC, may play a significant role in the path-

ophysiology of psychiatric disorders, such as schizophrenia and depression (GOTO; OTANI; GRACE, 2007).

The effects of dopamine are far more complex than previously thought. Dopamine can be released by stressful stimuli, as well as by rewarding stimuli. In addition, DA neurons present a complex and challenging pattern of responses to rewards during learning. The release of DA from the forebrain functions not as a sign of pleasure, but as a prediction-error signal. A dopamine salvo would mean a reward or reward-related stimulus that was not predicted, pauses, or decreases in firing would mean that the reward was less than expected or absent. If a reward is exactly what is expected based on environmental cues, dopamine neurons maintain their tonic firing rate. Changes in dopamine release are believed to modify future responses to stimuli, aiming to maximize the likelihood of rewards, and to minimize unsuccessful attempts (GU et al., 2016; NASSER et al., 2017).

Many researchers have emphasized the involvement of mesocorticolimbic and nigrostriatal dopamine neurons in reinforcing learning and habit formation (Yin; Ostlund; Balaline, 2008, Belin et al., 2009, SALAMONE; CORREA, 2012). Feedback is essential for proper adaptation to the environment. Feedback-related negativity, a negative deflection at fronto-central after feedback, has been found in worse-than-expected outcomes, and reflects a reward prediction error derived from dopaminergic projections of the brain in the anterior cingulate cortex (ACC), as stated in the theory of reinforcement of learning. Additionally, it has been identified that some regions underlying the feedback may signal a prediction error of salience rather than a prediction error of reward (Gu et al., 2016).

By means of electrophysiology, studies show that dopamine neurons of the ventral tegmentar area are responsive to aversive stimuli (BRISCHOUX et al., 2009; SCHULTZ, 2010). Punitive stimuli have motivational effects that are opposed to rewards; produce withdrawal behaviors, are negative outcomes, serve as negative reinforcers in aversive conditioning, reduce behavior leading to punishment, and increase behavior leading to avoidance, and producing aversive predictions for decision-making in behavior choice situations (SCHULTZ, 2007).

Depending on the nature of the stimulus, the responses generally begin slowly and last for several seconds, except for rapid depressions after electrical nerve stimulation, which show time courses similar to the depressions observed after negative prediction errors in awake animals (Schultz, 2015). In responding to aversive stimuli, dopamine neurons have few direct activations, multiple recovery activations, and frequent depressions, and as such, neurons clearly distinguish aversive stimuli from reward-related stimuli (Schultz, 2007).

The role of dopamine in the acquisition and extinction of learned fear demonstrates that learning about aversive situations can be modulated by ap-

petitive systems. It is believed that some reward-related processes, which depend on dopamine, may boost the learning of contingencies of fear extinction (ABRAHAM; NEVE; LATTAL, 2014).

One of the challenges in research on the cellular effects of dopamine receptors is to determine the relationship between inhibitory and excitatory processes at molecular and behavioral levels. Dopaminergic signaling involves clear interactions between these processes, revealed in the effects of the activation of the two major dopamine receptor subfamilies. The receptors of the D1 subfamily, composed of dopamine receptors of type D1 and D5, activate the stimulating G proteins, Gas and G α olf; and D2 subfamily receptors, which include the D2, D3 and D4 receptors, activate the inhibitory G proteins, Gai and Gao (BEAULIEU; GAINETDINOV, 2011).

The classical knowledge on dopamine receptor activity focuses on intracellular signaling through the activity of adenylate cyclase and cAMP (adenosine 3', 5'-cyclic monophosphate), which are widely recognized to play central roles in learning. For example, inhibitory interactions between dopamine and cAMP-regulated neuronal phosphoprotein (DARPP-32) and phosphatase-1 (PP1) protein are important for the intracellular regulation of neural plasticity (GOULD; MANJI, 2005) and DARPP -32 has been considered a critical component in the detection of convergent dopamine and glutamate signals leading to long-term synaptic plasticity (VALJENT et al., 2005). In addition to the modulation of cAMP activity, D1 receptors operate through the activation of phospholipase C (PLC), whose activity has been implicated in the formation of fear memories (OUYANG et al., 2012; BUCKLEY; CALDWELL, 2004).

Several researches on dopamine and fear focus on the potential roles of D1 and D2 receptors in the acquisition, evocation and extinction of fear. Studies with D1 receptor antagonists and knockout animals suggest that dopamine signaling at the D1 receptor contributes directly to the acquisition and extinction of fear (EL-GHUNDI; O'DOWD; GEORGE, 2001; FADOK; DICKERSON; PALMITER, 2009; IKEGAMIL et al., 2014; HEATH et al., 2015; ABRAHAM; NEVE; LATTAL, 2016a; ABRAHAM; NEVE; LATTAL, 2016b).

On the other hand, studies on fear with D2 receptor antagonists presented mixed effects. Rats that do not have D2 receptor show normal fear-enhanced startle performance (FADOK; DICKERSON; PALMITER, 2009), although D3 or D4 receptors can compensate for the loss of D2 receptors to support fear acquisition. Other studies have shown that D2 receptor antagonists, such as raclopride (MUELLER; BRAVO-RIVERA; QUIRK, 2010) and haloperidol (HOLTZMANN-ASSIF, LAURENT; WESTBROOK, 2010) hinder retention of fear extinction. However, improvements in fear extinction have been identified with a systemically administered D2 receptor antagonist, sulpiride (Ponnusamy; Nissim; Barad, 2005). The discrepan-

cies between these studies may be due to the differences in affinity of the antagonists with the D2 receptor, but a contributing factor could be the distribution of the receptors or the different protocols of presentation of the CS used in the experiments (MUELLER; BRAVO-RIVERA; QUIRK, 2010).

Dopaminergic innervation in the brain acts in critical regions for different aspects of learning, and can be divided into four main pathways: the nigrostriatal pathway, which links the substantia nigra (SN) to the striatum and is important for conducting motivated motor responses; the tuberoinfundibular pathway, which connects dopamine neurons from the hypothalamus to the pituitary gland and induces the release of hormones; the mesocortical pathway, which emits dopamine neurons from ventral tegmental area (VTA) to cortical regions; and the mesolimbic pathway, which connects the VTA to the nucleus accumbens, amygdala and hippocampus, and the latter two constitute the mesocorticolimbic pathway, which was well characterized as the region that guides associative learning in instrumental and pavlovian tasks (BEAULIEU; GAINETDINOV, 2011). Many of the regions innervated by VTA and SN were implicated in aspects of fear learning; and suggest an important role of dopamine in the learning and extinction of fear (Pezze; Feldon, 2004, Bromberg-Martin; Matsumoto; Hikosaka, 2010).

Ventral tegmental area and aversive events

The predominant neurobehavioral theory for the dopamine neuronal activity in the ventral tegmental area is the prediction error model, in which, prediction error is a discrepancy between expected and actual results, and this discrepancy is a fundamental element for several models of associative learning (Schultz, 2016). Dopamine neurons fire tonically at basal conditions, but increase the trigger when a reward is greater than predicted or inhibits tonic release when an expected reward is omitted; in addition, after pairings of an CS with a rewarding US, the dopamine neurons of the VTA begin to respond mainly to the CS; suggesting that, rather than just encoding the hedonic value of a UC, they signal expectations corresponding to the previously neutral CS (for review NASSER et al., 2017).

The dopamine neurons of dorsal VTA are excited by rewards or reward-associated stimuli, whereas dopamine neurons of ventral VTA can be activated in response to electrical shock in the legs. Furthermore, the withdrawal of the aversive stimulus increases the firing in certain dopamine neurons, suggesting that the lack of an expected aversive event can trigger dopamine release in a subset of VTA neurons, constituting a continuum between aversion and reward (BRISCHOUX et al., 2009). This observation suggests a mechanism by which VTA encodes the prediction error present during a fear-extinction session, since rewarding stimuli lead to increased firing in the dopamine neurons of the dorsal VTA and the absence of a reward leads to

decreased firing, and an aversive stimulus may reduce firing in the dorsal VTA and the lack of an aversive US may lead to increased activity of these neurons, so there may be effects ventral VTA, with increased activity in response to an aversive stimulus and a reduced response in the absence (ABRAHAM; NEVE; LATTAL, 2014).

The dopamine neurons of the posterior ventromedial portion of the VTA projecting into the prefrontal cortex respond to aversive stimuli, generating modifications in the excitatory synapses (accessed by the AMPA receptor / NMDA receptor ratio) between VTA and PFC (Lammel et al. 2011). It can be said that similar to neurons excited by aversive events, dopamine neurons that are inhibited by aversive events also encode the level of conditioned fear, since the duration of the inhibitions of the dopamine tonic release is related to the acute fear evoked by an CS, which was previously paired with electric shock. After extinction memory formation, the presentation of CS, which previously caused fear due to the association, no longer induces the inhibition of such dopamine neurons. These results suggest that initial signaling of aversive experiences requires coordinated action on subpopulations of VTA neurons, but probably other brain regions maintain storage in the long term of these experiences (MILEYKOVSKIY; MORALES, 2011).

VTA shows neuronal firing according to the prediction error hypothesis, but the expectation of results involves a coordinating activity between different brain regions that measure different aspects of learning. As a modulator of contextual information, the hippocampus plays an important role in facilitating VTA activity, allowing discernment of new stimuli or contexts of previously experienced events. In this sense, Valenti, Lodge and Grace (2011) have shown that inactivation of the ventral hippocampus prevents the increase of the firing in VTA neurons that are activated by electric shock.

This observation suggests a mechanism by which VTA encodes the prediction error present during a fear extinction session. Whereas rewarding stimuli lead to increased firing in the dopamine neurons of the dorsal VTA and the absence of a reward leads to decreased shooting, an aversive stimulus may reduce the firing in the dorsal VTA and the lack of an aversive US can lead to increased activity of these neurons. There may be opposite effects on the ventral VTA with increased activity in response to an aversive stimulus and a reduced response in the absence (ABRAHAM; NEVE; LATTAL, 2014).

Amygdala and aversive stimuli

The amygdala is a key structure for inducing, maintaining, and expressing associative learning. Neuronal activity in the amygdala may be induced by aversive or rewarding events, leading to plastic changes in the amygdala itself and in other sites believed to underlie long-term memory formation (MCGAUGH, 2004; MCGAUGH, 2005; CHAVEZ; MCGAUGH; WEINBERGER, 2013;

MCGAUGH, 2013). Three regions of the amygdala are particularly important for fear behavior; the basolateral amygdala (BLA), which integrates sensory information on CS and US; the masses of intercalated cells that inhibit or excite the activity in the BLA and the central amygdala (CeA); and the central nucleus of the amygdala, which sends projections to other regions that translate these signals into behavioral responses to aversive or appetitive stimuli. In the context of aversive learning, BLA integrates particular sensory stimuli with unconditioned nociceptive stimuli and the central amygdala encodes attention and general affective states that can alter motivated behavior. Together, these regions can generate appropriate fear responses based on specific sensory stimuli and general affective states (MOUSTAFA et al., 2013).

CeA neurons mainly express dopaminergic D2 receptors (WEINER et al., 1991; LEE; LEE; KIN, 2016), and blockade of these receptors may impair fear conditioning or prevent the animal from generating appropriate behaviors related to fear or the reward (GUARACI; FROHARDT; KAPP, 2000; DUVARCI; PARE, 2014). The central amygdala receives glutamatergic afferents from the basolateral amygdala. The BLA coordinates the activity of the nucleus accumbens, the prefrontal cortex and other regions to generate and recover CS-US associations (DUVARCI; PARE, 2014).

The dopamine receptors expressed in the BLA and intercalated amygdala cells (ITC) are mainly D1-type (WEINER et al., 1991; LEE; LEE; KIN, 2016). In addition to high D1 receptor expression, ITCs express D2 receptors at lower levels (WEINER et al., 1991). D1 receptor antagonism in the basolateral amygdala impairs the acquisition of fear extinction (HIKIND; MAROUN, 2008). The neurons glutamatergic enzymes of the BLA project to the neurons of the ITCs and the GABAergic of the ITCs inhibit the activity of CeA. The activation of GABAergic neurons of ITC mediated by the basolateral amygdala and the infralimbic region of the prefrontal cortex is fundamental for the extinction of fear behaviors and inhibitory control of the central amygdala (BUSTI et al., 2011; LEE; LEE; KIN, 2016).

Signaling of dopamine in the amygdala is important for the acquisition and extinction of fear, however, these signals are integrated with other structures to result in memory. Concomitant activation of dopaminergic signals in the nucleus accumbens and basolateral amygdala contributes to the formation of long-term memory. This indicates that NAcc and the amygdala may be regions that integrate dopaminergic signaling to generate appropriate behavioral responses for new contingencies. In an inhibitory avoidance task, the modulation of consolidation is directly influenced by dopaminergic activation in both regions (LaLumiere; Nawar; McGaugh, 2005). Additionally, the restoration of dopaminergic function, both in the BLA and in the NAcc in dopamine deficient mice, is sufficient for the

formation of long-term memory in fear conditioning (FADOK et al., 2010).

The Nucleus Accumbens and defensive behavior

The glutamatergic block of the medial NAcc shell in its rostral portion enhances defensive behaviors, and local dopamine is required for this increase in motivation, since in the presence of AMPA receptor antagonist in the medial portion of the NAcc shell, blockade of D1 and D2, in the same region, interrupts the behavior of fear (Richard; Berridge, 2011). This role is altered by environmental stress (Reynolds; Berridge, 2008) and prolonged stress can deregulate the control that the corticotropin release factor exerts on the release of dopamine in the NAcc (LEMOS et al., 2012).

Blocking of D2 dopamine receptors, such as haloperidol, in the NAcc impairs the consolidation and retention of fear extinction (HOLTZMANN-ASSIF, LAURENT; WESTBROOK, 2010). In addition, evaluating separately the effects of contextual and auditory conditioning, it can be seen that the core and shell portions of NAcc encode different aspects of fear conditioning (PEZZE et al., 2001). Rodriguez-Romaguera, Do Monte and Quirk (2012) showed that deep brain stimulation in the dorsomedial region of NAcc favors the extinction of auditory conditioned fear in rodents.

During the evocation of fear, by the presentation of the CS, the release of dopamine in the NAcc core decreases and, conversely, increases in the NAcc shell (BADRINARAYAN et al., 2012). However, the extinction of aversive memory, through the presentation of the CS, decrease the probability of phasic release of DA in the NAcc core, increasing the amplitude of the release events in the NAcc shell (BADRINARAYAN et al., 2012). The dopamine transmission in the NAcc core is important to encode the overall salience of the environmental stimuli and the activity in the NAcc shell encodes specific predictions of results to guide the motivated behavior (ABRAHAM; NEVE; LATTAL, 2014).

The amygdala can coordinate reward and fear search behaviors by regulating NAcc projections. Additionally, the ventral subiculum of the hippocampus is required for the activation of NAcc by BLA (GILL; GRACE, 2011). Increased activity in the basolateral amygdala and the ventral subiculum leads to activation of the rostral nucleus of the NAcc, leading to behaviors related to fear and avoidance, and the activation of D2 receptors in NAcc is necessary for NAcc responsiveness to BLA (BELUJON; GRACE, 2015).

The hippocampus and aversive memory

The interactions between the hippocampus and the VTA are important for transmitting contextual information in the learning of fear and reward. VTA provides a coordinated signaling to generate specific patterns of an activity in terminal dopaminergic regions based on environmental stimuli and previous experiments. In this sense, research pro-

poses that the VTA forms a loop with the hippocampus, in which the HPC controls the activity of the VTA and, in turn, VTA mediates hippocampal activity through DA release, and is also involved with synaptic plasticity in the HPC (HAGENA; MANAHAN-VAUGHAN, 2016; NOBILI et al., 2017).

D1 receptor antagonists and agonists in the dorsal hippocampus impair and promote, respectively, long-term aversive memory (ROSSATO et al., 200). In addition, when D1 receptors are eliminated or reduced, it results in significant impairment in the acquisition of associative learning, in the increase of the synaptic force between CA3-CA1 and in the induction of Egr1 in the HPC (Ortiz et al., 2010). Interestingly, a brief exposure to a new environment may increase fear extinction in contextual conditioning and inhibitory avoidance, and this effect is dependent on dopaminergic D1-type receptors in the hippocampus (MENEZES et al., 2015).

The hippocampus is considered a modulator of contextual information that is coded during extinction, and the prefrontal cortex (PFC) is more directly involved in the inhibitory learning that develops during extinction (QUIRK; MUELLER, 2008).

The prefrontal cortex and the defensive behavior

The sub-regions of the prefrontal cortex are important for the consolidation and recovery of the extinction of fear (QUIRK; MUELLER, 2008). Vincent, Khan and Benes (1995) state that PFC expresses dopaminergic D1-type receptors on non-pyramidal neurons and D2-type receptors on small pyramidal cells and large interneurons. Furthermore, in this area, dopamine activity is important for working memory, expression of conditioned fear, and the extinction of fear.

By microdialysis, it was identified that the release of dopamine in mPFC increases during and after the evocation of conditioned fear/conditioned fear extinction training (HUGUES; GARCIA; LENA, 2007). Dopamine depletion in mPFC increases the expression of conditioned fear, impairing the acquisition and retention of fear extinction (ESPEJO, 2003).

The supranormal activation of selective agonist D1 receptors in the pre-limbic region (PL) of the prefrontal cortex blocks the expression of conditioned fear; and cyclic AMP activity is important for the expression of aversive memories because the effects are recovered by coadministration of an inhibitor of cAMP signaling (Lauzon et al., 2013).

Nonspecific dopamine blockade with cis-flupenthixol or amphetamine activation in mPFC in the dorsal PL and IL regions lead to decreased freezing during the conditioned fear evocation session when the drugs are infused immediately prior to this session but not when they are infused prior to conditioning, indicating that dopaminergic transmission in mPFC is important for the recovery/expression of conditioned fear rather than for training (PEZZE; BAST; FELDON, 2003). D4R antagonism in PL decreases the expression of innate fear behavior, indicating that the activation of D4R in

PL is necessary for the expression of innate fear behavior (VERGARA, 2017).

In the IL, D1-type dopamine receptors are necessary for the consolidation of the extinction of fear (HIKIND; MAROUN, 2008). Administration of a D2 receptor antagonist in the IL immediately prior to extinction training causes no effects on the acquisition of fear extinction but increases fear on the day of the extinction test and may indicate involvement in the consolidation of fear extinction and in memory recovery (MUELLER; BRAVO-RIVERA; QUIRK, 2010).

A mechanism by which D1 and D2 receptors can interact in the PFC was shown by showing that D2 receptors suppress inhibitory interneurons GABA and D1 receptors increase excitatory activity, leading to a coordinated activity between receptors that induces long-term potentiation (XU; YAO, 2010). Other receptors must also interact with D1 receptors for the long-term storage of aversive or extinction memory, whereas activation of the D1 receptor leads to increased NMDA receptor NR2B subunit expression (HU et al., 2010).

IL exerts bidirectional control over VTA dopamine neurons, being differently modulated through the ventral subiculum of the HPC and the basolateral amygdala. Activation or inactivation of IL attenuates or activates, respectively, the activity of the dopamine neuron population. On the other hand, only the inactivation of PL changes the activity of the dopamine neurons in VTA (PATTON; BIZUP; GRACE, 2013).

The hippocampus is considered a modulator of the contextual information that is coded during extinction, and the IL-PFC is more directly involved in the inhibitory learning that develops during extinction (QUIRK; MUELLER, 2008); while the PL promotes the expression of conditioned fear (BUKALO et al., 2015).

Final considerations

The dopaminergic mesocorticolimbic system carries signals of valorization, both for stimuli related to gain, and for aversive stimuli. The VTA encodes the prediction of errors, and signals are transmitted to regions such as nucleus accumbens, amygdala, hippocampus and prefrontal cortex, constituting the mesocorticolimbic pathway. Interactions between HPC and VTA are important for transmitting contextual information in fear, and in the IL-PFC, dopamine receptors are required to consolidate the extinction of aversive memories.

The interaction between the PFC and the amygdala is particularly relevant for the expression of conditioned fear and its extinction. PFC modulates the responses of the basolateral amygdala through inhibitory interneurons that result in decreased activity of the BLA (ROSENKRANZ; GRACE, 2002). Patients with PTSD are able to acquire fear extinction normally in a laboratory setting, but the evocation of fear extinction is compromised (MILAD et al., 2009) and the increase

in PTSD severity is correlated with the decrease of the activity of the prefrontal cortex and the increase of the activity of the amygdala (SHIN; RAUCH; PITMAN, 2006).

Interestingly the dopaminergic system controls the fear response and its extinction, so it may provide a valuable pharmacological target for altering long-established behaviors such as those seen in PTSD. Possibly, technological innovations will provide a way to fully explore and understand dopamine signaling in the defensive response, aversive memory and its extinction.

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