Progress in Neuropsychopharmacology & Biological Psychiatry 88 (2019) 327–338

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

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

The opioid system in stress-induced memory disorders: From basic mechanisms to clinical implications in post-traumatic stress disorder and Alzheimer's disease

Angélica Torres-Berrio[a,1,2], Mauricio O. Nava-Mesa[b,*,2]

[a] Integrated Program in Neuroscience, McGill University, Montréal, Québec, Canada
[b] Neuroscience Research Group (NEUROS), School of Medicine, Universidad del Rosario, Bogotá, Colombia

ARTICLE INFO

Key Words:
Stress
Memory
Opioid System
Neuropsychiatric stress disorders

ABSTRACT

Cognitive and emotional impairment are a serious consequence of stress exposure and are core features of neurological and psychiatric conditions that involve memory disorders. Indeed, acute and chronic stress are high-risk factors for the onset of post-traumatic stress disorder (PTSD) and Alzheimer's disease (AD), two devastating brain disorders associated with memory dysfunction. Besides the sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis, stress response also involves the activation of the opioid system in brain regions associated with stress regulation and memory processing. In this context, it is possible that stress-induced memory disorders may be attributed to alterations in the interaction between the neuroendocrine stress system and the opioid system. In this review, we: (1) describe the effects of acute and chronic stress on memory, and the modulatory role of the opioid system, (2) discuss the contribution of the opioid system to the pathophysiology of PTSD and AD, and (3) present evidence of current and potential therapies that target the opioid receptors to treat PTSD- and AD-associated symptoms.

1. Introduction

Stress is an adaptive response that allows organisms to cope with environmental challenges that threaten their physiological or psychological homeostasis (Gold, 2015). This process involves the rapid and coordinated activation of the autonomic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis, and facilitates the secretion of stress-related hormones, including corticotrophin releasing factor (CRF), adrenocorticotropic hormone (ACTH), epinephrine, and corticoids (cortisol in humans and corticosterone in rodents) to prepare an organism for fight-or-flight or freeze responses (Gold, 2015). Single, acute, stress is essential to initiate an alarm response and focalize attention towards sources of potential threat. In contrast, prolonged or chronic activation of the stress system stimulates a permanent state of alertness that can result in long-lasting neurophysiological alterations and increased risk for the onset of several neuropsychiatric, and neurodegenerative disorders (McEwen, 2007).

Cognitive and emotional alterations are a serious consequence of stress exposure and are core features of neurological and psychiatric conditions that involve memory disorders. For example, chronic stress impairs working and episodic memories and accelerates the onset of Alzheimer's disease (AD) (McEwen, 2007; Wilson et al., 2003); whereas acute, but intense, stress can facilitate the acquisition of negative emotional memories (de Quervain et al., 2016), and heighten the vulnerability to develop post-traumatic stress disorder (PTSD) (Horn et al., 2016). Indeed, the cognitive and emotional alterations observed in AD and PTSD comprise morphological and functional changes in the limbic system, including areas such as the prefrontal cortex (PFC), hippocampus (HPC) and amygdala (AMYG) (Bailey et al., 2013; Karl et al., 2006; Sørensen et al., 2017). Remarkably, these brain structures do not only control multiple memory systems and higher cognitive functions, but also regulate the response to stress due to the high expression of glucocorticoid receptor and other stress-related receptors (McEwen et al., 2015).

The endogenous opioid system is activated by acute and chronic stress (Akil et al., 1986; Bodnar, 2017; Chen et al., 2004; Yilmaz et al.,

* Corresponding author at: Neuroscience Research Group (NEUROS), School of Medicine, Universidad del Rosario, Kra 24 No. 63C-69, Bogotá, Colombia
E-mail address: monavam@usal.es (M.O. Nava-Mesa).
[1] Present address: Fishberg Department of Neuroscience, Friedman Brain Institute, Icahn School of Medicine at Mount Sinai. 1425 Madison Avenue, 10-26, New York, NY 10029, USA.
[2] The authors contributed equally to this paper.

https://doi.org/10.1016/j.pnpbp.2018.08.011
Received 13 March 2018; Received in revised form 25 July 2018; Accepted 13 August 2018
Available online 15 August 2018
0278-5846/

2010) and its alterations seem to be a shared mechanism between PTSD and AD (Bailey et al., 2013; Mathieu-Kia et al., 2001). The opioid system consists of the G protein-coupled receptors mu (μ), kappa (κ), delta (δ) and the Opioid receptor-like ORL (also known as nociceptin/orphanin FQ receptor-NOP), as well as the diverse opioid families: endorphins, enkephalins, and dynorphin (Bodnar, 2017). In general, β-endorphin binds to μ and δ opioid receptors, whereas dynorphin binds preferentially to κ receptors, and met- and leu-enkephalin bind to δ and μ receptors (Benarroch, 2012). Additional opioid peptides, such as nociceptin/orphanin FQ (N/OFQ) and endomorphin, which have respective affinities for ORL and μ receptors, have been also described (Chu et al., 1999; Horvath, 2000; Meunier, 1997).

The opioid receptors are localized in regions of the central nervous system (CNS) that regulate the response to stress, including the hypothalamus, as well as in brain structures associated with emotional response, learning and memory (Contet et al., 2006). Indeed, a variety of stressors increase the release of endogenous opioid peptides and induce a differential activation of opioid-associated receptors in the HPC, AMYG and PFC in humans and rodents (Love et al., 2009; Tejeda et al., 2015). This evidence suggests that the interaction between the stress and opioid systems play an important role in mediating memory processing under stress, and in the pathogenesis of stress-induced memory disorders. Moreover, the development of specific opioid receptor agonists and antagonists and the increasing use of gene delivery techniques highlight the potential of the opioid system as a therapeutic approach to treat cognitive dysfunction induced by stress (Bodnar, 2017; Lutz et al., 2014; Mercadante et al., 2014; Xu et al., 2003). In this review, we describe the role of the opioid system in (a) memory processes during stress response, and (b) the pathophysiology of psychiatric and neurological memory disorders associated with stress, with special focus on PTSD and AD. We also discuss therapies for these disorders based on the specific modulation of the opioid receptors.

2. Activation of the opioid system during stress

The stress response is mediated by the HPA axis and results in the release of stress hormones and endogenous opioid peptides. The HPA axis integrates responses of the paraventricular nucleus of the hypothalamus (PVN), adenohypophysis, neurohypophysis and adrenal gland (Gold, 2015). During stress, the PVN secretes corticotrophin-releasing hormone (CRH, also known as CRF), which acts on corticotropic cells of the adenohypophysis to release adrenocorticotropin (ACTH). ACTH induces glucocorticoid release by the zona fasciculata of the adrenal cortex. Later, corticoids modulate the activation of the HPA axis to suppress CRH and ACTH production and initiate a mechanism of negative feedback to cease the response to stress (Carrasco and Van de Kar, 2003).

Proopiomelanocortin (POMC) is a precursor polypeptide of ACTH and β-endorphin. Once the HPA axis is activated, POMC is cleaved in the pars intermedia and the pars distalis of the pituitary to release other stress-hormones such as alpha-MSH and Beta-lipotropin (Eipper and Mains, 1980; Rousseau et al., 2007). POMC is also synthesized by multiple neuronal groups of the arcuate nucleus (ArN) of the hypothalamus and the nucleus of the solitary tract, which project to limbic forebrain and midbrain areas, as well as the brainstem and spinal cord (Benarroch, 2012). Furthermore, neurons that express opioid precursors, peptides and receptors are located in brain structures involved in the stress response, such as the HPC, PVN, PFC, AMYG and locus coeruleus (LC) (Drolet et al., 2001; Tejeda et al., 2015). These regions directly regulate the HPA axis and the sympathetic nervous system through the differential activation of opioid receptors (Fig. 1).

The relationship between stress and the opioid system was described for the first time in a phenomenon known as *stress-induced analgesia* (SIA), which refers to the anti-nociceptive response observed after stress exposure (Yilmaz et al., 2010; Butler and Finn, 2009). SIA has been described in several mammalian species, including rodents,

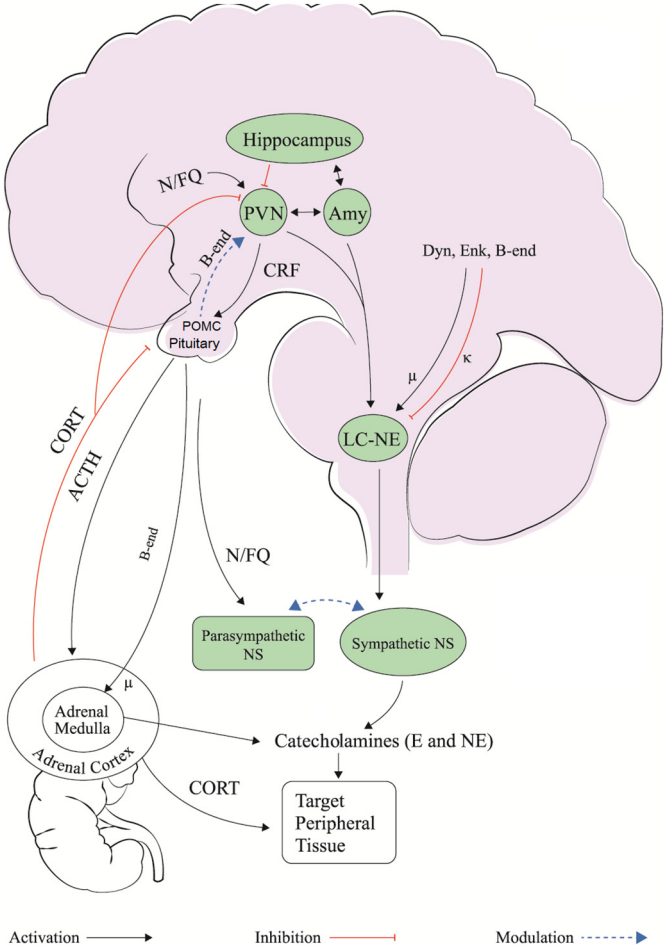

Fig. 1. Schematic representation of the HPA axis and autonomic nervous system in response to stress, and their regulation by the opioid system. Stressors initiate the activation of the HPA axis and induce the release of ACTH by the anterior pituitary gland and CORT by the adrenal gland. Neuroendocrine response to stress is reduced by corticoid-mediated negative feedback and the release of endogenous opioid peptides (red arrows). B-endorphins and N/FQ peptides respond to mild and acute stressors by increasing the activity of the PVN and the sympathetic nervous system. Activation of the μ receptor leads to increased secretion of catecholamine by the adrenal medulla at baseline and in response to mild acute stressors (black arrows). During states of high stress, the opioid system induces a negative feedback to modulate central sympathetic outflow, limit catecholamine release (red arrows) or activate the parasympathetic nervous system as a regulatory mechanism (dashed arrows). B-endorphin modulates the activation of the HPA axis in response to stressors of high intensity or chronic stressors acting on CRF neurons (dashed arrows).
Abbreviations: Amy (Amygdala), B-end (Beta-endorphin), CRF (Corticotropin-Releasing Factor), CORT (glucocorticoids), Dyn (dynorphin), E (epinephrine), Enk (enkephalin), LC (locus coeruleus), NE (norepinephrine), N/FQ (nociceptin/orphanin), NS (Nervous System), POMC (Proopiomelanocortin), PVN (paraventricular nucleus of the hypothalamus).

rhesus monkeys and humans, and following different experimental models, such as electrical and thermal stressors (Butler and Finn, 2009). For example, restraint stress induces analgesia to painful stimuli in rats. Interestingly, this effect is potentiated by the μ receptor agonist, morphine (Calcagnetti and Holtzman, 1990). Naltrexone, a non-specific competitive opioid antagonist, reduces antinociceptive effects of stress by exposure to cold water (Łapo et al., 2003). Importantly, SIA has been also observed in several neuropsychiatric conditions, including PTSD or pain disorders (Fareed et al., 2013; Ibarra et al., 1994; Sher, 2004), thus, understanding its mechanisms may have important clinical implications.

Different stressors induce the release of endogenous opioids in areas

of the CNS involved in emotional response, learning and memory, and systemic physiological functions (i.e. energy homeostasis) (Henry et al., 2017). For example, acute immobilization increases immunoreactivity for dynorphins A and B in the nucleus accumbens (NAc) and HPC (Shirayama et al., 2004), whereas chronic immobilization increases the expression of enkephalins and dynorphin mRNA in the HPC (Chen et al., 2004). Acute stress induced by tail compression increases the release of β-endorphin in the ArN and NAc in rats (Marinelli et al., 2004), and exposure to the odors of predators increases the release of β-endorphin in the ArN and the expression of enkephalins in the AMYG (Hebb et al., 2004). Acute restraint stress enhances the expression of N/OFQ peptides in the hypothalamus, mediodorsal forebrain regions and limbic structures, especially the HPC by inducing corticosterone signaling through glucocorticoid receptors (GRs) in CA3, CA1 and dentate gyrus neurons (Nativio et al., 2012). In addition to the central effects, acute restraint stress also increases plasma levels of β-endorphin, which acts on peripheral tissues (i.e. gastrointestinal, cardiovascular and immune) (Coventry et al., 2001; Veening and Barendregt, 2015). In contrast, neither restraint stress nor chronic inflammatory stress influence the plasma levels of endomorphins in rats (Coventry et al., 2001).

In summary, stress increases dynorphin, endorphin, enkephalin and N/FQ peptides and later stimulates μ, k, δ and ORL receptors in different brain structures. This pattern of activation is determined by (i) the duration of the stressor (acute versus chronic) and (ii) the type of stressor. In general, opioid system activation may both initiate and subsequently modulate the magnitude of the HPA axis and sympathetic response to stress. In the following sections, we describe the effects of stress on memory and how activation of the opioid system modulates cognitive functioning, and discuss the implications for memory-related disorders.

3. Effects of stress on memory processing

Memory is a complex process that involves different phases, including acquisition, retrieval, consolidation and reconsolidation (Abel and Lattal, 2001). Memory *acquisition* refers to the initial learning of information, in which organisms begin to establish novel associations between environmental stimuli, physiological or behavioral responses and/or consequences (Kandel, 2001). Once this information is acquired, it can be stabilized for long-term recall during a *consolidation* process that involves synthesis of proteins and plastic changes at the synapses (Abel and Lattal, 2001; de Quervain et al., 2016; Lee et al., 2004). Memory *retrieval* refers to the process by which organisms recall previously learned information and provide an appropriate behavioral output. *Reconsolidation* is a process in which previously stored information is sensitive to disruption or modification (Nader et al., 2000b; Nader et al., 2000a).

The effects of stress on memory are mediated by different variables, including the phase of memory at which the stressor is applied (acquisition, retrieval and consolidation), the intensity of the stressor (low, moderate and high), the duration (acute versus chronic), and the type of memory that is being evaluated (hippocampal-dependent or hippocampal-independent) (Pinelo-Nava and Sandi, 2007). In general, information is remembered or becomes long-lasting when stress hormones, including glucocorticoids, are released at moderate levels. In contrast, very low or very high levels of stress could delay acquisition, impair memory retrieval or affect consolidation (Pinelo-Nava and Sandi, 2007; Sapolsky, 2015). This effect, known as the U-inverted shape effect, is mediated by the differential activation of the high-affinity mineralocorticoid receptors (MRs) and the low-affinity GRs. Indeed, glucocorticoid hormones bind to MRs under basal, non-stress conditions, and to GRs in response to stress (Pacak and Palkovits, 2001; Sapolsky, 2015).

Mild to moderate levels of stress facilitate acquisition of episodic and spatial memories, which are highly associated with hippocampal function (Schwabe and Wolf, 2013). In fact, moderate levels of stress lead to increased expression of markers of synaptic plasticity in the HPC, including the GluA1 AMPA receptor subunit, the brain-derived nerve factor (BDNF) receptor, TrkB, the phosphorylated cAMP response element binding protein (CREB), the activity-regulated cytoskeleton-associated protein (Arc), and the phosphorylated calcium/calmodulin-dependent protein kinase type II alpha (pCAM-kinase II-a)(Conboy and Sandi, 2010; Salehi et al., 2010; Sandi et al., 2005; Yuncai et al., 2016). In contrast, acute administration of high doses of corticosterone or exposure to high intensity stressors prior to retrieval disrupt object recognition, and contextual and spatial memories in rodents (Almaguer-Melian et al., 2012; De Quervain et al., 1998; Sandi et al., 2005; Vargas-Lopez et al., 2015; Wong et al., 2007; Yu et al., 2018). Importantly, the effects of high acute stress correlate with rapid loss of dendritic spine in hippocampal neurons (Chen et al., 2010), decreased expression of neural cell adhesion molecule (NCAM) in the HPC and PFC (Sandi et al., 2005) and altered connectivity between pyramidal cells and interneurons in the CA1 region of the HPC (Yu et al., 2018). Moreover, acute exposure to stress inhibit long-term potentiation (LTP) and lead to long-term depression (LTD) in the HPC (Howland and Cazakoff, 2010; Wong et al., 2007), further demonstrating the deleterious effects of stress on memory retrieval and HPC function.

Acute stress facilitates the acquisition or retrieval of emotional memories in humans and rodents (Aubry et al., 2016). For example, exposure to psychosocial stress promotes long-term retention of negative memories (Payne et al., 2007; Tollenaar et al., 2009), whereas administration of metyrapone, a corticoid inhibitor, impairs long-lasting retrieval of negative information in humans (Marin et al., 2011). Similarly, acute injection of corticoids or acute restraint stress enhance acquisition and retention of auditory fear conditioning in rodents (Cordero et al., 2003; Hui et al., 2004; Zorawski and Killcross, 2002). This effect is mediated by stress-induced activation of GRs and release of norepinephrine in the basolateral nucleus (BLA) of the AMYG (Roozendaal et al., 2006). Indeed, infusion of β-adrenergic receptor antagonists in the BLA disrupts acquisition and retrieval of fear conditioning (Bush et al., 2010) and prevents corticoid-induced memory enhancement of inhibitory avoidance in rats (Roozendaal et al., 2002). Likewise, acute stress induces delayed spinogenesis (Mitra et al., 2005) and strengthens synaptic plasticity in BLA (Yasmin et al., 2016). For example, single exposure to stress by immobilization enhances synaptic response to excitatory inputs in BLA and increases the number of dendritic spines in BLA principal neurons (Yasmin et al., 2016). Together, these findings demonstrate that acute stress leads to changes of synaptic plasticity in both the HPC and AMYG that result in contrasting effects on memory function.

Chronic exposure to stress, on the other hand, impairs different stages of hippocampal-dependent memories, and induces structural and functional alterations in the HPC (Conrad et al., 1996; Kleen et al., 2006; Lemaire et al., 2000; Magarinos et al., 1997). For example, chronic stress reduces neurogenesis in the dentate gyrus and induces atrophy of the apical dendrites in the hippocampal CA3 region (McEwen, 2016). Interestingly, repeated or chronic exposure to stress facilitates encoding and retention of rigid and inflexible forms of memory (i.e. stimulus-response), which are dependent on the dorsal striatum (Atsak et al., 2016; Medina et al., 2007; Schwabe et al., 2007; Schwabe and Wolf, 2010). In this perspective, we recently showed that chronic stress by elevated platform reduced retrieval of spatial memory, but enhanced the use of stimulus-response memories (Fig. 2) (Torres-Berrio and Nava-Mesa, 2018). This finding further supports previous evidence showing that post-training administration of corticosterone in the dorsolateral striatum accelerates the consolidation of procedural learning, and therefore, determines the switch between the use of spatial vs. stimulus-response strategies in rats (Siller-Pérez et al., 2017).

Further studies are required to identify the factors that protect individuals against the effects of stress on memory dysfunction and cognitive decline. Such studies are urgently needed given the strong association between stress exposure and neuropsychiatric and

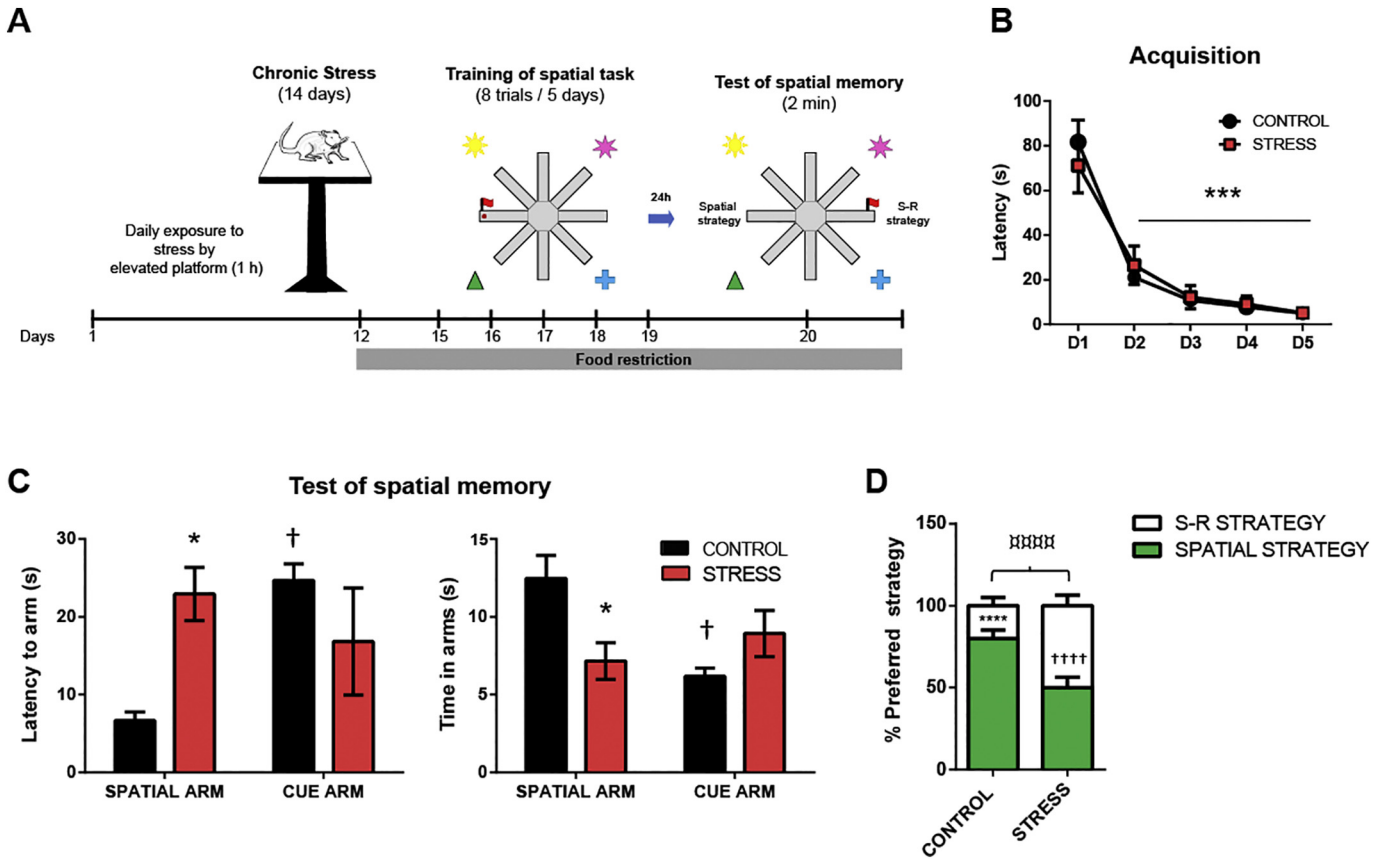

Fig. 2. Chronic stress impairs spatial memory and facilitates stimulus-response memory in a radial arm maze dissociation task. (A) Timeline of experimental procedure and diagram of the radial arm dissociation task (RADT), adapted from (Schwabe et al., 2008). (B) Chronic stress prior to training did not affect acquisition of the RADT. Latency: one-way ANOVA for repeated measures: Training session: [$F_{(4,70)} = 41.71$; $p < 0.0001$]; Tukey test: ***$p < 0.001$, different from D2). (C) Chronic stress increased latency to enter (left panel) and reduced time spent (right panel) in the spatial arm. Latency: two-way ANOVA (stress by arm interaction: [$F_{(1,20)} = 9.05$; $p = 0.0069$]; Tukey test: $p < 0.05$). Time spent in arms: two-way ANOVA (stress by arm interaction: [$F_{(1,20)} = 10.65$; $p = 0.0039$]; Tukey test: $p < 0.05$). $p < 0.05$: * and †, spatial arm vs. control. (D) Reduced preference for spatial strategies and enhanced preference for stimulus-response strategies in rats exposed to chronic stress. Preferred strategy: stress by arm interaction: [$F_{(1,20)} = 30.86$; $p < 0.0001$]; stress [$F_{(1,20)} = 30.86$; $p < 0.0001$]; arm [$F_{(1,20)} = 0.0$; $p = 0.99$]; Tukey test: $p < 0.0001$: ****, spatial strategy; † † † †, spatial strategy vs. control; ¤¤¤¤, control. $N = 6$/group.

neurodegenerative disorders. Indeed, impairment of HPC-dependent memory vs. enhancing of AMYG-dependent and striatum-dependent memories may account for the differential effects of acute and chronic stress on disorders such as AD, and PTSD. Strong evidence demonstrates that the opioid system regulates memories that are associated with HPC, striatal and AMYG function (Le Merrer et al., 2013; Knoll et al., 2011). Furthermore, susceptible mice to chronic stress exhibit decreased levels of ENK mRNA in the BLA and of δ opioid receptor in the ventral HPC (Henry et al., 2018); whereas low levels of μ opioid receptor are associated with reduced vulnerability to stress (Komatsu et al., 2011). In this context, the actions of the opioid system on specific brain circuits during stress response may be at play in the differential susceptibility to those memory alterations observed in neuropsychiatric disorders.

4. Stress-induced activation of the opioid system and memory processing

Animal models and clinical case reports provide evidence that opioid agonists have amnesic properties (Daumas et al., 2007; McGaugh, 1983; Chavant et al., 2011), whereas opioid antagonists exhibit more complex actions, depending on the receptor specificity, dose (U-inverted pattern) and emotional state of the subject (Aigner and Mishkin, 1988; Bodnar, 2017; Katzen-Perez et al., 2001). Many of the effects of opioids drugs on memory are either direct or mediated by other neurotransmitter systems, including the dopaminergic system (Ukai and Lin, 2002).

The interaction between opioid system and stress during memory has been studied by pharmacological, behavioral and electrophysiological approaches. For example, naloxone prevents acute stress- or dexamethasone-induced impairment of memory retrieval in passive avoidance (Rashidy-Pour et al., 2004) or object recognition memory (ORM) tasks (Liu et al., 2016), most likely by acting on the μ opioid receptor (Liu et al., 2016). Moreover, transgenic mice lacking *dynorphin* gene do not display impaired ORM induced by stress (Carey et al., 2009), suggesting that dynorphin/κ opioid receptor signaling may also mediate the effects of stress on memory. In our laboratory, we evaluated the effects of systemic administration of naltrexone during the pre-training of an object recognition memory task (ORM) in rats subjected to acute restraint stress. We found that acute stress impaired short-term object recognition, but this effect was prevented by naltrexone treatment. Interestingly, acute stress enhanced long-term object recognition, however, high doses of naltrexone impaired stress-induced long-term memory facilitation, suggesting differential effects of the opioid system at short and long terms following stress exposure (Nava-Mesa et al., 2013b).

Enhanced activation of endogenous opioids in the HPC may account for the deleterious effects of acute stress on memory. Indeed, acute exposure to immobilization induces a significant increase in dynorphins A and B, while chronic stress increases prodynorphin and enkephalin levels in the HPC (Chen et al., 2004; Shirayama et al., 2004). The following activation of the respective opioid receptors in CA1 and CA3

hippocampal pyramidal neurons affect neuronal excitability (Madamba et al., 1999), presynaptic neurotransmitter release and interneurons activity (Klenowski et al., 2015). In this context, intrahippocampal administration of opioid agonists impairs spatial memory (Daumas et al., 2007; Sandin et al., 1998), whereas intrahippocampal injection of naltrexone blocks impairment of spatial memory induced by glucocorticoids (Sajadi et al., 2007). Together, these findings suggest that increased activation of the opioid system induced by stress have amnesic effects, which can be prevented by naltrexone or naloxone.

Opioid receptors, including μ, κ, and δ are highly expressed in the AMYG and are activated during stress and emotional memory (Mansour et al., 1995, Mansour et al., 1988, Hebb et al., 2004). Indeed, fear conditioning increases the expression of κ opioid receptor mRNA in the BLA, whereas the κ opioid receptor antagonist, JDTic, decreases conditioned fear in rats (Knoll et al., 2011). In addition, several studies indicate that opioid system of the AMY influences noradrenergic and GABAergic systems during memory consolidation and emotional responses (Ferry and McGaugh, 2000; Klenowski et al., 2015; Liberzon et al., 2002). However, the deleterious effects of stress on contextual memory retrieval seem to be independent on the activation of opioid receptors in the AMYG. For example, systemic administration of naltrexone prevents stress-induced memory impairment in a step-through passive-avoidance task. In contrast, microinjection of naltrexone into the basolateral (BLA) AMYG or the CA1 region of the HPC has no protective effects (Rezvanfard et al., 2011). This evidence suggests the involvement of several brain structures, circuits and neurotransmitter systems, as well as complex interactions between stress and opioid system pathways associated with contextual memory. Below, we present three different models that might explain the actions of these antagonists on memory.

(A) Antagonism of opioid receptors may reverse plastic alterations in memory brain circuits induced by acute stress. For example, it has been reported that naltrexone blocks the inhibition of LTP induced by acute stress (Shors et al., 1990). Likewise, Naloxone enhances LTP at Schaffer collateral–CA1 synapses (Zhao et al., 2004), and might counteract LTP inhibition and LTD induction by stress. However, the effects of opioid blockers may be variable and dependent on the specific afferent projection activated. For example, naloxone may block the induction of lateral perforant path–CA3 LTP, unless is induced by strong coactivation of the medial perforant pathway (Martinez et al., 2011). This result indicates that the projections of the perforant path to the hippocampal CA3 region have different mechanisms of LTP induction (opioid and non-opioid).

(B) Opioid antagonists might affect the activity of the HPA axis during stress, and therefore, modify plasma corticosterone levels. For instance, naloxone or naltrexone can enhance or reduce corticosterone release after acute stress depending on the type of stressor (i.e. forced swimming, cold water, acute motion stress) (Douglas et al., 1998; Odio and Brodish, 1990; Retana-Márquez et al., 2009). Moreover, the highly selective k receptor agonist, U-50488H, but not μ and δ agonists, stimulates ACTH and cortisol release in rhesus monkeys, an effect that is blocked by the k antagonist, nor-Binaltorphimine (Pascoe et al., 2008). These divergent effects of opioid antagonists on the HPA axis could be due to differences in the role of the opioid system during each type of stress, as well as pharmacodynamic diversity among the various opioid drugs. However, some other studies involving acute immobilization and restraint found that naltrexone did not impact corticosterone levels (Trudeau et al., 1991; Vazquez-Palacios et al., 2004). Finally, one cannot disregard the fact that opioid drugs modify the levels of other stress-associated hormones (i.e. catecholamine), which may, in turn, affect memory function by acting directly on the CNS or through the peripheral nervous system (Fig. 1). For instance, stress activates two distinct pools of norepinephrine (NE) systems: a central pool associated with the LC in the brainstem, and a peripheral pool, associated with the sympathetic nervous system (Atzori et al., 2016). Central activation of adrenergic receptors (α_1, α_2 and β) modulates working and fear memories (Atzori et al., 2016; Zhang et al., 2013; Zhou et al., 2015), whereas, peripheral catecholamines, which cannot cross the blood–brain barrier, may alter memory via the afferent sensory nerves (Tank and Wong, 2015).

(C) Although less probable, there is a possibility that opioid antagonists compete with corticoids hormones for receptor binding during stress. This concept is based on the description of a corticoid membrane receptor in the amphibian *Taricha granulosa* (Evans et al., 1998) that exhibits binding affinity for naloxone (Evans et al., 2000). In rodents, the glucocorticoid membrane receptors (GMRs) have rapid and non-genomic effects in response to stress (Dorey et al., 2011; Sajadi et al., 2006), however, the binding of opioid antagonists to GMRs remains unclear.

Opioid agonists have been also studied in the context of stress and memory. In a classic report, parallel exposure to stress by immobilization and morphine administration impaired memory consolidation of a passive avoidance task. Indeed, acute stress exacerbated morphine-induced memory impairment (Castellano et al., 1984). This effect indicates that μ receptors and stress hormones interact in a synergistic manner during memory consolidation. Interestingly, selective dopaminergic agonists of D1 and D2 receptors antagonized the effects of the opiate on memory consolidation (Castellano et al., 1994). Therefore, it is possible that the effects of the opioid system on memory during stress require other neurotransmitter systems and specific intracellular pathways. For example, the opioid system and stress may interact through CREB signaling, GRs, norepinephrine and GABA neurotransmitter systems (Bali et al., 2015).

Although ORL-1 and μ receptors share some common intracellular signaling pathways, differential physiological effects have been reported (Bodnar, 2017; Hawes et al., 1998; Wallington et al., 2002). As mentioned previously, acute stress increases N/OFQ peptide levels in the HPC (Nativio et al., 2012). Accordingly, stress intensity might be related to central N/OFQ peptide levels, thereby possibly underlying the U-inverted effect on memory. However, recent explanations for the inverted-U-shaped relationship between stress intensity and memory consider the differential activation of corticoid and opioid receptors, the type of information that is learned, inter-individual characteristics and emotional factors (Katzen-Perez et al., 2001; Luksys and Sandi, 2011; Salehi et al., 2010).

Some studies have suggested an anti-stress effect of the N/OFQ system in anxiety-like behavior and SIA (Bali et al., 2015; Ciccocioppo et al., 2014; Gerashchenko et al., 2011). Furthermore, systemic and central AMYG infusion of ORL-1 receptor agonist (SR-8993), in a rodent model, prevents consolidation of fear memory of an aversive event (Andero et al., 2013). In addition, ORL antagonists (i.e. [Nphe1]-Nociceptin and NC-NH2) reverse N/OFQ-induced impairment of consolidation of passive avoidance task and spatial memory (Andero, 2015), whereas OFQ/N receptor antagonist (Nphe(1)]nociceptin(1-13) NH(2) enhances retention of inhibitory avoidance (Roozendaal et al., 2007). However, the role of N/OFQ on memory acquisition and retrieval during stress remains unclear.

In summary, opioid antagonists could prevent the deleterious effects of stress on memory retrieval by acting preferentially on κ and μ receptors in the HPC. Facilitation effects of stress on memory consolidation may involve opioid peptides on AMY. Moreover, the U-inverted shape effect of glucocorticoids on memory displays similar characteristics to the effects mediated by the opioids peptides released by stress. In the following section, we will discuss the clinical implications of the modulation of the opioid system in stress-induced memory disorders.

5. Clinical implications

The opioid system plays a dual modulatory role in neuropsychiatric disorders induced by stress where memory dysfunction is a hallmark (Fig. 3). PTSD and AD are two debilitating conditions characterized by severe alterations in emotional and episodic memories, respectively

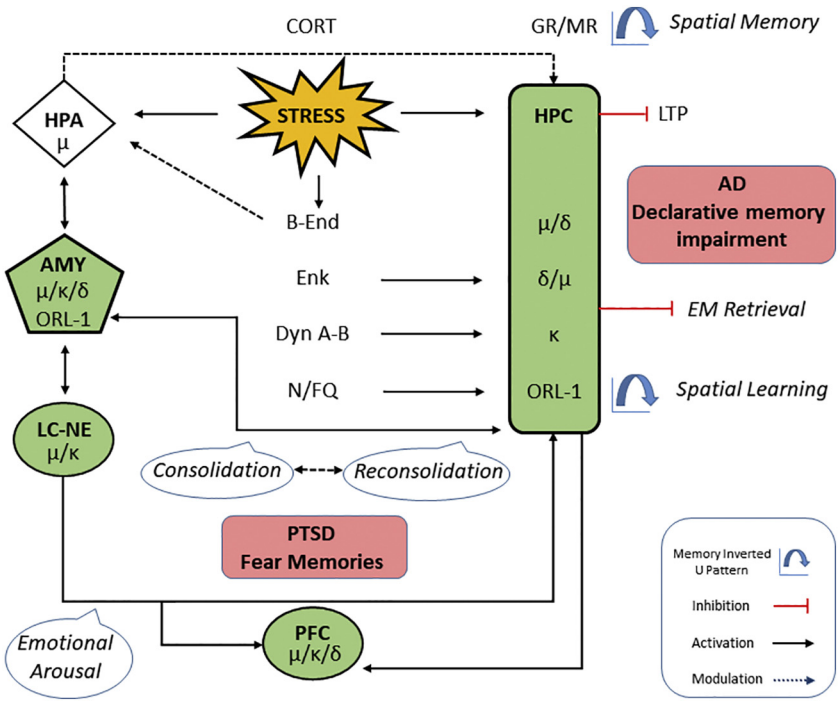

Fig. 3. Role of the opioid system in the pathophysiology of AD and PTSD. Interaction between major brain structures and specific opioid receptors are represented. The effects of stress on memory depend on the specific memory phase (i.e. acquisition, retrieval and consolidation), the differential activation of the opioid receptors and the brain circuits involved. Release of opioid peptides induced by chronic stress, such as enkephalins and dynorphins, impact preferentially the HPC during AD progression. The hippocampal-amygdala–prefrontal cortex circuit, involved in consolidation and reconsolidation processes, has a main role in PTSD. Likewise, norepinephrine-mediated emotional arousal may enhance traumatic and fear memories.
Abbreviations: AD (Alzheimer´s disease), AMY (amygdala), B-end (Beta-endorphin), CORT (corticosteroids), Dyn (dynorphin), Enk (enkephalin), EM (episodic memory), GR (glucocorticoid receptor), HPC (hippocampus), HPA (hypothalamic–pituitary–adrenal axis), LC-NE (Locus Coeruleus/Norepinephrine system), LTP (long-term potentiation), MR (mineralocorticoid receptor), N/FQ (nociceptin/orphanin), PFC (prefrontal cortex), PTSD (Post-traumatic stress disorder).

(Gold and Budson, 2008; Guina et al., 2016). In the following section, we will discuss the role of opioid system in the pathophysiology of PTSD and AD. Furthermore, we will describe and propose some therapeutic approaches to treat these disorders based on the pharmacological modulation of μ, κ, δ and ORL-1 opioid receptors and neurobiological mechanisms.

5.1. PTSD

PTSD is a devastating mental health disorder triggered by a severe life-threatening experience or a situation that involves feelings of helplessness or intense fear. This psychiatric disorder is characterized by nightmares, unwanted memories and intrusive flashbacks of the traumatic event (Guina et al., 2016). These symptoms are caused by the perturbation in acquisition, consolidation and reconsolidation of emotional memories during stressful situations. For instance, exposure to a traumatic trigger results in a fragmented and involuntary retrieved memory trace (intrusion) associated with autonomic responses and fear symptoms (Brewin, 2011). According to Van Marle (2015), the lack of appropriate consolidation of traumatic experiences within a cortical network containing an autobiographical context induces reactivation of traumatic memory traces, which are reexperienced as if they were happening in the present (van Marle, 2015).

The pathophysiology of PTSD involves the dysfunction of the AMYG-PFC pathway (Mahabir et al., 2016, Mahabir et al., 2015) as well as increased sensitivity of the HPA axis to negative glucocorticoid feedback (Nijdam et al., 2015; Yehuda, 2006) and noreadrenergic hyperactivity (Strawn and Geracioti, 2008). There are also alterations in the expression of neuropeptides, hormones and neurotransmitters such as CRF, serotonin, glutamate/GABA, catecholamine, neuropeptide Y and opioids in brain areas involved in cognitive function such as the anterior cingulate cortex (ACC), insular cortex (IC), and HPC (Sherin and Nemeroff, 2011).

The endogenous opioid system participates directly in the pathophysiology of PTSD and other stress-induced psychiatric disorders (Henry et al., 2017). For example, imaging studies have shown that PTSD patients exhibit diminished μ opioid receptor binding potential in the ACC, in comparison to healthy controls, whereas trauma exposure, with or without PTSD, was associated with reduced μ opioid receptor binding potential in the extended AMYG, nucleus accumbens and IC (Liberzon et al., 2007). Furthermore, individuals suffering from PTSD exhibit reduced plasma levels of β-endorphin at baseline (Hoffman et al., 1989), but increased levels immediately after exercise as compared to controls (Hamner and Hitri, 1992). Likewise, high levels of β-endorphin in the cerebrospinal fluid (CSF) of patients with PTSD correlate with intrusive and avoidant symptoms (Baker et al., 1997), suggesting that alterations in the opioid system may readily detected in peripheral and central fluids in vulnerable individuals to stress. Evidence from preclinical models demonstrate that opioid receptors mediate extinction of fear conditioning in rats (Cole et al., 2011; McNally and Westbrook, 2003), whereas altered expression of enkephalin and δ opioid receptor are observed in susceptible mice to chronic stress (Henry et al., 2018).

The relationship between SIA, the opioid system and PTSD has been previously studied (Ibarra et al., 1994; Sher, 2004). For example, war veterans with PTSD exposed to a traumatic stressor (combat videotape) display reduced pain sensitivity in comparison to PTSD patients treated with naloxone or control patients (Van der Kolk et al., 1989; Pitman et al., 1990). This indicates that PTSD patients may exhibit higher activation of the endogenous opioid system during re-exposure to traumatic events. Similarly, repeated stress may lead to opioid abuse in PTSD-susceptible patients through mechanisms of opioid tolerance and dependence. Indeed, there is a high comorbidity of opioid abuse and PTSD (Clark et al., 2001; Fareed et al., 2013).

Because the opioid system modulates stress-induced memory consolidation, opioid receptor agonists and antagonists may have therapeutic potential for PTSD. In fact, naltrexone has been used as a coadjutant drug in the treatment of patients with long-lasting traumatic memories and comorbid alcohol dependence (Lubin et al., 2002; Petrakis et al., 2012, Petrakis et al., 2006). Furthermore, naltrexone decreases the frequency of flashbacks and other dissociative phenomena in patients with borderline personality disorders (Bohus et al., 1999). These dissociative symptoms are also observed in patients with PTSD. In addition to μ, κ and δ opioid receptor blockade, the modulation of nociceptin (ORL-1) receptors reduces consolidation of fear-related memories without affecting other memory stages (i.e. acquisition or extinction) in mice (Sartor et al., 2016), and may therefore serve as a therapeutic target for memory adjustment in PTSD.

Rodent models of PTSD, such as single-prolonged stress (SPS), leads to increased levels of N/OFQ peptides in CSF and serum, as well as anxiety-like behavior and long-lasting hyperalgesia (Zhang et al., 2012a). Indeed, the N/OFQ receptor antagonist, JTC-801, ameliorates anxiety- and pain-like behaviors in the SPS models (Zhang et al., 2015a), suggesting that modulators of N/OFQ may be promising for the treatment of emotional symptoms and for co-morbid PTSD and pain. For example, immobilization-fear conditioning (a PTSD-like mouse model) induces high expression of the *Oprl1* mRNA, which encodes for ORL-1 receptor, in the AMYG, whereas systemic and AMYG infusion of the highly-selective ORL-1 agonist, SR-8993, interferes with consolidation of fear memory (Andero et al., 2013). Importantly, single nucleotide polymorphisms in the *OPRL1* gene has been associated with self-reported history of childhood trauma and PTSD symptoms (Andero et al., 2013), further highlighting the importance of ORL-1 as therapeutic target of PTSD.

Accumulating evidence indicates the potential role of opioid agonists in the treatment of PTSD. For instance, administration of systemic morphine after training disrupts persistence of contextual fear memory in rats (Porto et al., 2015). In adult humans, acute administration of morphine blocks fear conditioning and the risk of PTSD after a traumatic injury (Bryant et al., 2009; Stoddard et al., 2009; Holbrook et al., 2010; Melcer et al., 2014), whereas in children this effect seems to occur in a dose-dependent manner (Nixon et al., 2010; Stoddard et al., 2009).

Because opioid receptor agonists and antagonists have differential actions and windows of administration, opioid agonists might have therapeutic effect during acute traumatic painful events in PTSD, while opioid antagonists might have efficacy once the traumatic long-lasting memory and dissociative symptoms have been consolidated and established. Interestingly, other studies show that repeated administration of morphine may interrupt memory consolidation and the associated fear learning which generate PTSD (Szczytkowski-Thomson et al., 2013). A recent observational study in war veterans with PTSD reported that buprenorphine improves PTSD symptoms compared with other opioid medications (Seal et al., 2016). In fact, buprenorphine is an opioid with mixed agonist (ORL-1 receptor) and antagonist (κ and δ receptors) effects, with a complex pharmacodynamics for μ receptors (partial agonist and antagonist according to dosage level) (Lutfy and Cowan, 2004).

Some reports indicate that the antinociceptive effects of the opioid agonist methadone is potentiated by an ultralow dose of the opioid antagonist naltrexone (Chindalore et al., 2005; Cruciani et al., 2003). Therefore, this synergistic drug combination may have substantial therapeutic potential for treating painful traumatic experiences. However, more clinical trials are needed to optimize the ratio of opioid agonist/antagonist and to identify the opioids involved in PTSD pathophysiology, as well as opioid receptors susceptible to pharmacological modulation.

5.2. Alzheimer's disease (AD)

AD is the most common progressive neurodegenerative disorder worldwide. It is characterized by cognitive decline, brain atrophy due to specific neuronal loss, and presence of two neuropathological features: extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (Goedert and Spillantini, 2006). Although reduced exposure to stress does not prevent dementia (Tsolaki et al., 2003), susceptibility to psychological stress is a risk factor for AD (Wilson et al., 2003). In fact, several epidemiologic and clinical studies have shown that chronic stress early in life increases the risk of AD (Johansson et al., 2010; Tsolaki et al., 2010; Wilson et al., 2003). Animal models indicate that chronic stress leads to inflammatory processes and metabolic dysfunction in the HPC, PFC and AMYG (Machado et al., 2014). Oxidative stress, excitotoxicity and synaptic plasticity impairment are part of the pathophysiology of AD induced by stress (Gonzalez-Reyes et al., 2017; Rothman and Mattson, 2010). Indeed, human brain-imaging studies have shown hippocampal atrophy in patients subjected to repetitive traumatic stress experiences (McEwen, 2000) and functional imaging studies have shown that AD patients have metabolic alterations on hippocampal subregions (Moreno et al., 2007; Wu and Small, 2006). This regional susceptibility is associated with aging prior to dementia, PTSD and depression (McEwen, 2000).

Two of the most characteristic symptoms of AD, which are part of the initial cognitive decline, are impairments in declarative memory and disorientation (Gold and Budson, 2008). This is caused by hippocampal and entorhinal cortical dysfunction. Several studies have shown that opioid system dysfunction (hyper- or hypo-activation) is associated with the pathogenesis of AD, including increased Aβ generation (Sarajärvi et al., 2011; Teng et al., 2010), hyperphosphorylation of tau protein (Anthony et al., 2010) and neuroinflammation (Cai and Ratka, 2012; Liang et al., 2016). Changes in opioid peptide levels in the CSF of patients with AD, as well as changes in opioid receptor binding and distribution, found in postmortem brains, suggest that opioid system dysfunction is associated with cognitive impairment in AD (Cai and Ratka, 2012). However, despite the large amount of experimental evidence, it is not clear if these changes are part of the cascade that causes the cognitive deficit, or if this effect is a compensatory mechanism against neurodegeneration.

There is evidence showing that soluble and aggregated forms of Aβ1-40 or 1-42 compromises G protein-coupled receptors function on AD models *in vivo* and *in vitro* (Janickova et al., 2013; Thathiah and De Strooper, 2011). Indeed, opioid receptors are G-protein coupled receptors linked to G protein-coupled inwardly-rectifying potassium channels (GirK) channels (Mitrovic et al., 2003), which mediate hyperpolarization and synaptic inhibition. Accordingly, we showed for the first time that Aβ (25-35) decreased inhibitory currents in CA3 pyramidal neurons, likely by decreasing GirK channels activity, and leading to hippocampal hyperexcitability *in vitro* (Nava-Mesa et al., 2013a; Nava-Mesa et al., 2014). Similarly, Aβ 25-35 can reduce GirK channels expression (GirK2, 3, and 4 subunits) (Mayordomo-Cava et al., 2015), whereas GirK agonist (ML297) reduce synaptic, network, and cognitive deficits observed in a mouse model of early AD (Sanchez-Rodriguez et al., 2017). Although the role of GirK channels in the pathophysiology of AD remained to be characterized, it is plausible that Aβ-induced intracellular signaling dysfunction in the opioid system as well as opioid effectors (i.e. calcium and potassium channels).

The endogenous opioid system influences the presynaptic and postsynaptic activity of many transmitter systems in cognitive function (Mizuno and Kimura, 1996; Shen and Johnson, 2002). In this regard, altered protein levels of AMPA and NMDA receptors in the HPC are observed in aged prodynorphin KO mice (Menard et al., 2014). Correspondingly, increased expression of dynorphin and polymorphisms in the *PRODYNORPHIN* gene have been associated with memory impairment during aging and in AD patients (Kölsch et al., 2009; Yakovleva et al., 2007). As we mentioned before, increased activation of κ-opioid receptors by dynorphins may explain stress-related memory impairment. Therefore, the opioid system is a promising therapeutic target for age-related cognitive decline and AD progression.

At an intracellular level, chronic opiate administration activates components of the cyclic AMP pathway in a manner similar to chronic stress (Valentino and Van Bockstaele, 2001). Furthermore, higher methadone doses increase proinflammatory cytokines and contribute to neuroinflammation (Chan et al., 2015). Also, OFQ/N system mediate inflammatory events during stress (Mallimo and Kusnecov, 2013). Therefore, abnormal opioid system activation induced by chronic stress may be related to the pathophysiology of AD and cognitive deficit. For example, Meilandt and colleagues (Meilandt et al., 2008), found overexpression of enkephalin in brain tissue derived from patients with AD. Furthermore, they reported that high expression of the opioid precursor preproenkephalin and met-enkephalin was related to the cognitive and behavioral alterations in the transgenic animal model of AD.

Different neurotransmitters systems (i.e. GABA) and ion channels can be targeted by drugs to attenuate the cognitive symptoms in early-stages of AD and rapid progressive dementia, as well as patients with mild cognitive impairment (MCI), a prodromal stage of AD (Mutis et al., 2017; Nava-Mesa et al., 2014). New perspectives in the pathophysiology of AD suggest that synaptic dysfunction precedes neurodegeneration and is the primary event in early memory impairment (Palop and Mucke, 2010; Selkoe, 2002). Similarly, excitatory and inhibitory imbalance in several neurotransmitter systems (i.e. glutamatergic, cholinergic and GABAergic) underlie synaptic dysfunction in the HPC and AMYG during AD progression (Nava-Mesa et al., 2014; Palop et al., 2007; Verret et al., 2012). In this context, current treatments for AD symptoms include the NMDA receptor blocker, memantine, and cholinesterase inhibitors (Gold and Budson, 2008). However, to date there are no effective pharmacological interventions to treat AD.

Considering that dysregulation of endogenous opioid peptides is observed in AD, novel therapeutic approaches could target opioid receptors to potentially induce clinical benefits. In this regard, inactivation of the enkephalin receptor with the irreversible μ receptor antagonist β-funaltrexamine can ameliorate cognitive impairment in a mouse model of AD (Meilandt et al., 2008). Furthermore, transgenic animals overexpressing the mutant human amyloid precursor protein (hAPP-J20 mouse model) exhibit elevated levels of enkephalin in the HPC (Diez et al., 2003; Diez et al., 2000). Likewise, it has been suggested that κ antagonists prevent neurodegeneration (Leung, 2013), and that the selective δ opioid receptor antagonist, naltridole, attenuates the cognitive deficit in mouse models of AD (AβPP/PS1) (Zhang et al., 2012b). However, clinical studies using the non-specific opioid antagonist naltrexone have showed no significant clinical improvement in AD patients (Henderson et al., 1989; Hyman et al., 1985). Therefore, drugs with higher selectivity for opioid receptors might be required to reduce memory impairment in AD.

In addition to subtype-specific opioid receptor modulation, brain-specific aminopeptidases that hydrolyze endogenous opioid peptides (i.e. enkephalinase) could provide neuroprotective effect in AD (Hui, 2007). In a recent study, endomorphin-1 was shown to block Aβ aggregation *in vitro* and reduce impairment in episodic memory induced by Aβ42 in mice. Intriguingly, this effect was independent of the μ opioid receptor (Zhang et al., 2015b). Overall, these studies suggest that endogenous opioid peptides, as well as opioid receptor antagonists, might be effective for treating some aspects of memory decline and preventing further neurodegeneration in AD.

6. Conclusions

Acute and chronic stress exert opposite effects on episodic, emotional, and stimulus-response memories. In general, acute stress impairs episodic, HPC-dependent memories, but enhances emotional, AMYG-dependent memories. Chronic stress, on the other hand, facilitates retrieval of rigid, stimulus-response memories, which are associated with striatal function. These effects reflect the differential susceptibility of brain structures such as the HPC, AMYG, and PFC to stress. Here, we described evidence indicating that both beneficial and deleterious effects of stress on different stages of memory are controlled by activation of the opioid system in the HPC and AMYG. Furthermore, we reported that the opioid system modulates the levels of stress hormones, which in turn have an impact on memory function.

Although it is still not clear which factors determine individual susceptibility to neuropsychiatric disorders induced by stress, the evidence points towards an important role of endogenous opioids in the limbic system as a critical neural substrate in the pathophysiology of AD and PTSD. Preclinical findings indicate that drugs with high selectivity for enkephalin (μ and δ) and dynorphin/k receptors, might alleviate memory impairment in AD and HPC-related memory disorders. Likewise, we highlighted the potential therapeutic actions of combined μ/ORL agonists and non-specific opioid antagonists in PTSD. However, considering a possible downregulation of opioid receptors in chronic disorders where opioid peptides are released at sustained high levels, opioid modulators must be differentially used under acute, subacute and chronic stress conditions. Finally, it is important to clarify the molecular and cellular mechanisms underlying the critical modulatory role of the opioid system in stress-related memory disorders and to recognize its therapeutic and neuroprotective potential for the treatment of AD and PTSD, as well as related nervous system disorders.

Acknowledgements

This work was supported by the Colombian Science and Technology Institute (COLCIENCIAS, project code: 122265840550, CT-160-2015) and the Natural Sciences and Engineering Research Council of Canada (NSERC). We thank N. Martinez-Rodriguez for help in fig. design. We thank Barry Patel, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

References

Abel, T., Lattal, K.M., 2001. Review: Molecular mechanisms of memory acquisition, consolidation and retrieval. Curr. Opin. Neurobiol. 11, 180–187. https://doi.org/10.1016/S0959-4388(00)00194-X.

Aigner, T., Mishkin, M., 1988. Improved recognition memory in monkeys following naloxone administration. Psychopharmacology (Berl.) 94, 21–23.

Akil, H., Young, E., Walker, J.M., Watson, S.J., 1986. The many possible roles of opioids and related peptides in stress-induced analgesia. Ann. N. Y. Acad. Sci. 467, 140–153.

Almaguer-Melian, W., Bergado-Rosado, J., Pavón-Fuentes, N., Alberti-Amador, E., Mercerón-Martínez, D., Frey, J.U., 2012. Novelty exposure overcomes foot shock-induced spatial-memory impairment by processes of synaptic-tagging in rats. pp. 953.

Andero, R., 2015. Nociceptin and the nociceptin receptor in learning and memory. Prog. Neuropsychopharmacol. Biol. Psychiatry 62, 45–50. https://doi.org/10.1016/j.pnpbp.2015.02.007.

Andero, R., Brothers, S.P., Jovanovic, T., Chen, Y.T., Salah-Uddin, H., Cameron, M., Bannister, T.D., Almli, L., Stevens, J.S., Bradley, B., 2013. Amygdala-dependent fear is regulated by Oprl1 in mice and humans with PTSD. Sci. Transl. Med. 5, 188ra73.

Anthony, I.C., Norrby, K.E., Dingwall, T., Carnie, F.W., Millar, T., Arango, J.C., Robertson, R., Bell, J.E., 2010. Predisposition to accelerated Alzheimer-related changes in the brains of human immunodeficiency virus negative opiate abusers. Brain 133, 3685–3698.

Atsak, P., Guenzel, F.M., Kantar-Gok, D., Zalachoras, I., Yargicoglu, P., Meijer, O.C., Quirarte, G.L., Wolf, O.T., Schwabe, L., Roozendaal, B., 2016. Glucocorticoids mediate stress-induced impairment of retrieval of stimulus-response memory. Psychoneuroendocrinology 67, 207–215. https://doi.org/10.1016/j.psyneuen.2016.02.006.

Atzori, M., Cuevas-Olguin, R., Esquivel-Rendon, E., Salgado-Delgado, R.C., Saderi, N., Miranda-Morales, M., Garcia-Oscos, F., Treviño, M., Pineda, J.C., Salgado, H., 2016. Locus ceruleus norepinephrine release: A central regulator of cns spatio-temporal activation? Front. Synaptic Neurosci. 8. https://doi.org/10.3389/fnsyn.2016.00025.

Aubry, A.V., Serrano, P.A., Burghardt, N.S., 2016. Molecular Mechanisms of Stress-Induced Increases in Fear Memory Consolidation within the Amygdala. Front. Behav. Neurosci. 10, 191. https://doi.org/10.3389/fnbeh.2016.00191.

Bailey, C.R., Cordell, E., Sobin, S.M., Neumeister, A., 2013. Recent progress in understanding the pathophysiology of post-traumatic stress disorder. CNS Drugs 27, 221–232.

Baker, D.G., West, S.A., Orth, D.N., Hill, K.K., Nicholson, W.E., Ekhator, N.N., Bruce, A.B., Wortman, M.D., Keck, P.E., Geracioti, T.D., 1997. Cerebrospinal fluid and plasma β-endorphin in combat veterans with post-traumatic stress disorder. Psychoneuroendocrinology 22, 517–529.

Bali, A., Randhawa, P.K., Jaggi, A.S., 2015. Review: Stress and opioids: Role of opioids in modulating stress-related behavior and effect of stress on morphine conditioned place preference. Neurosci. Biobehav. Rev. 51, 138–150. https://doi.org/10.1016/j.neubiorev.2014.12.018.

Benarroch, E.E., 2012. Endogenous opioid systems: current concepts and clinical correlations. Neurology 79, 807–814. https://doi.org/10.1212/WNL.0b013e3182662098.

Bodnar, R.J., 2017. Endogenous Opiates and Behavior: 2015. Peptides 88, 126–188. https://doi.org/10.1016/j.peptides.2016.12.004.

Bohus, M.J., Landwehrmeyer, G.B., Stiglmayr, C.E., Limberger, M.F., Böhme, R., Schmahl, C.G., 1999. Naltrexone in the treatment of dissociative symptoms in patients with borderline personality disorder: an open-label trial. J. Clin. Psychiatry 60, 598.

Brewin, C.R., 2011. The nature and significance of memory disturbance in posttraumatic stress disorder. Annual Review of Clinical Psychology. https://doi.org/10.1146/annurev-clinpsy-032210-104544.

Bryant, R.A., Creamer, M., O'Donnell, M., Silove, D., McFarlane, A.C., 2009. A study of the protective function of acute morphine administration on subsequent posttraumatic stress disorder. Biol. Psychiatry 65, 438–440.

Bush, D.E.A., Caparosa, E.M., Gekker, A., Ledoux, J., 2010. Beta-adrenergic receptors in the lateral nucleus of the amygdala contribute to the acquisition but not the consolidation of auditory fear conditioning. Front. Behav. Neurosci. 4, 154. https://doi.org/10.3389/fnbeh.2010.00154.

Butler, R.K., Finn, D.P., 2009. Stress-induced analgesia. Prog. Neurobiol. 88, 184–202.
Cai, Z., Ratka, A., 2012. Opioid system and Alzheimer's disease. Neuromolecular Med. 14, 91–111.
Calcagnetti, D.J., Holtzman, S.G., 1990. Factors affecting restraint stress-induced potentiation of morphine analgesia. Brain Res. 537, 157–162.
Carey, A.N., Lyons, A.M., Shay, C.F., Dunton, O., McLaughlin, J.P., 2009. Endogenous kappa Opioid Activation Mediates Stress-Induced Deficits in Learning and Memory. J. Neurosci. 29, 4293–4300.
Carrasco, G.A., Van de Kar, L.D., 2003. Neuroendocrine pharmacology of stress. Eur. J. Pharmacol. 463, 235–272.
Castellano, C., Pavone, F., Allegra, S.P., 1984. Morphine and memory in DBA/2 mice: Effects of stress and of prior experience. Behav. Brain Res. 11, 3–10. https://doi.org/10.1016/0166-4328(84)90003-2.
Castellano, C., Cestari, V., Cabib, S., Puglisi-Allegra, S., 1994. The effects of morphine on memory consolidation in mice involve both D1 and D2 dopamine receptors. Behav. Neural Biol. 61, 156–161.
Chan, Y.-Y., Yang, S.-N., Lin, J.-C., Chang, J.-L., Lin, J.-G., Lo, W.-Y., 2015. Inflammatory response in heroin addicts undergoing methadone maintenance treatment. Psychiatry Res. 226, 230–234. https://doi.org/10.1016/j.psychres.2014.12.053.
Chavant, F., Favreliere, S., Lafay-Chebassier, C., Plazanet, C., Perault-Pochat, M.-C., 2011. Memory disorders associated with consumption of drugs: updating through a case/noncase study in the French PharmacoVigilance Database. Br. J. Clin. Pharmacol. 72, 898–904. https://doi.org/10.1111/j.1365-2125.2011.04009.x.
Chen, J.X., Li, W., Zhao, X., Yang, J.X., Xu, H.Y., Wang, Z.F., Yue, G.X., 2004. Changes of mRNA expression of enkephalin and prodynorphin in hippocampus of rats with chronic immobilization stress. World J. Gastroenterol. 10, 2547–2549.
Chen, Y., Rex, C.S., Rice, C.J., Dubé, C.M., Gall, C.M., Lynch, G., Baram, T.Z., 2010. Correlated memory defects and hippocampal dendritic spine loss after acute stress involve corticotropin-releasing hormone signaling. Proc. Natl. Acad. Sci. 107, 13123–13128.
Chindalore, V.L., Craven, R.A., Yu, K.P., Butera, P.G., Burns, L.H., Friedmann, N., 2005. Adding ultralow-dose naltrexone to oxycodone enhances and prolongs analgesia: A randomized, controlled trial of oxytrex. J. PAIN 6, 392–399.
Chu, X.P., Xu, N.S., Li, P., Wang, J.Q., 1999. Endomorphin-1 and endomorphin-2, endogenous ligands for the mu-opioid receptor, inhibit electrical activity of rat rostral ventrolateral medulla neurons in vitro. Neuroscience 93, 681–686.
Ciccocioppo, R., de Guglielmo, G., Hansson, A.C., Ubaldi, M., Kallupi, M., Cruz, M.T., Oleata, C.S., Heilig, M., Roberto, M., 2014. Restraint Stress Alters Nociceptin/Orphanin FQ and CRF Systems in the Rat Central Amygdala: Significance for Anxiety-Like Behaviors. J. Neurosci. 34, 363–372.
Clark, H.W., Masson, C.L., Delucchi, K.L., Hall, S.M., Sees, K.L., 2001. Violent traumatic events and drug abuse severity. J. Subst. Abuse Treat. 20, 121–127.
Cole, S., Richardson, R., McNally, G.P., 2011. Kappa opioid receptors mediate where fear is expressed following extinction training. Learn. Mem. Cold Spring Harb. N 18, 88–95. https://doi.org/10.1101/lm.2049511.
Conboy, L., Sandi, C., 2010. Stress at learning facilitates memory formation by regulating AMPA receptor trafficking through a glucocorticoid action. Neuropsychopharmacology 35, 674.
Conrad, C.D., Galea, L.A.M., Kuroda, Y., McEwen, B.S., 1996. Chronic stress impairs rat spatial memory on the Y maze, and this effect is blocked by tianeptine pretreatment. Behav. Neurosci. 110, 1321–1334. https://doi.org/10.1037/0735-7044.110.6.1321.
Contet, C., Gavériaux-Ruff, C., Matifas, A., Kieffer, B.L., Caradec, C., Champy, M.F., 2006. Dissociation of analgesic and hormonal responses to forced swim stress using opioid receptor knockout mice. Neuropsychopharmacology 31, 1733–1744. https://doi.org/10.1038/sj.npp.1300934.
Cordero, M.I., Venero, C., Kruyt, N.D., Sandi, C., 2003. Prior exposure to a single stress session facilitates subsequent contextual fear conditioning in rats. Evidence for a role of corticosterone. Horm. Behav. 44, 338–345.
Coventry, T.L., Jessop, D.S., Fin, D.P., Crabb, M.D., Kinoshita, H., Harbuz, M.S., 2001. Endomorphins and activation of the hypothalamo-pituitary-adrenal axis. J. Endocrinol. 169, 185–193. https://doi.org/10.1677/joe.0.1690185.
Cruciani, R.A., Lussier, D., Miller-Saultz, D., Arbuck, D.M., 2003. Ultra-low dose oral naltrexone decreases side effects and potentiates the effect of methadone. J. Pain Symptom Manage. 25, 491–494.
Daumas, S., Betourne, A., Halley, H., Wolfer, D.P., Lipp, H.-P., Lassalle, J.-M., Francés, B., 2007. Transient activation of the CA3 Kappa opioid system in the dorsal hippocampus modulates complex memory processing in mice. Neurobiol. Learn. Mem. 88, 94–103. https://doi.org/10.1016/j.nlm.2007.02.001.
De Quervain, D.J.F., Roozendaal, B., McGaugh, J.L., 1998. Stress and glucocorticoids impair retrieval of long-term spatial memory. Nature 394, 787.
de Quervain, D., Schwabe, L., Roozendaal, B., 2016. Stress, glucocorticoids and memory: implications for treating fear-related disorders. Nat. Rev. Neurosci. https://doi.org/10.1038/nrn.2016.155.
Diez, M., Koistinaho, J., Kahn, K., Games, D., Hökfelt, T., 2000. Neuropeptides in hippocampus and cortex in transgenic mice overexpressing V717F beta-amyloid precursor protein–initial observations. Neuroscience 100, 259–286.
Diez, M., Danner, S., Frey, P., Sommer, B., Staufenbiel, M., Wiederhold, K.-H., Hökfelt, T., 2003. Neuropeptide alterations in the hippocampal formation and cortex of transgenic mice overexpressing β-amyloid precursor protein (APP) with the Swedish double mutation (APP23). Neurobiol. Dis. 14, 579–594.
Dorey, R., Piérard, C., Shinkaruk, S., Tronche, C., Chauveau, F., Baudonnat, M., Béracochéa, D., 2011. Membrane mineralocorticoid but not glucocorticoid receptors of the dorsal hippocampus mediate the rapid effects of corticosterone on memory retrieval. Neuropsychopharmacology 36, 2639.
Douglas, A.J., Johnstone, H.A., Wigger, A., Landgraf, R., Russell, J.A., Neumann, I.D., 1998. The role of endogenous opioids in neurohypophysial and hypothalamo-pituitary-adrenal axis hormone secretory responses to stress in pregnant rats. J. Endocrinol. 158, 285–293.
Drolet, G., Dumont, É.C., Gosselin, I., Kinkead, R., Laforest, S., Trottier, J.-F., 2001. Role of endogenous opioid system in the regulation of the stress response. Prog. Neuropsychopharmacol. Biol. Psychiatry 25, 729–741. https://doi.org/10.1016/S0278-5846(01)00161-0.
Eipper, B.A., Mains, R.E., 1980. Structure and biosynthesis of pro-adrenocorticotropin/endorphin and related peptides. Endocr. Rev. 1, 1–27.
Evans, S.J., Moore, F.L., Murray, T.F., 1998. Solubilization and pharmacological characterization of a glucocorticoid membrane receptor from an amphibian brain. J. Steroid Biochem. Mol. Biol. 67, 1–8.
Evans, S.J., Searcy, B.T., Moore, F.L., 2000. A subset of kappa opioid ligands bind to the membrane glucocorticoid receptor in an amphibian brain. Endocrinology 141, 2294–2300.
Fareed, A., Eilender, P., Haber, M., Bremner, J., Whitfield, N., Drexler, K., 2013. Comorbid posttraumatic stress disorder and opiate addiction: a literature review. J. Addict. Dis. 32, 168–179.
Ferry, B., McGaugh, J.L., 2000. Role of amygdala norepinephrine in mediating stress hormone regulation of memory storage. Acta Pharmacol Sin. 21, 481–493.
Gerashchenko, D., Horvath, T.L., Xie, X., 2011. Direct inhibition of hypocretin/orexin neurons in the lateral hypothalamus by nociceptin/orphanin FQ blocks stress-induced analgesia in rats. Neuropharmacology 60, 543–549. https://doi.org/10.1016/j.neuropharm.2010.12.026.
Goedert, M., Spillantini, M.G., 2006. A century of Alzheimer's disease. science 314, 777–781.
Gold, P., 2015. The organization of the stress system and its dysregulation in depressive illness. Mol. Psychiatry 20, 32.
Gold, C.A., Budson, A.E., 2008. Memory loss in Alzheimer's disease: implications for development of therapeutics. Expert Rev Neurother. 8, 1879–1891. https://doi.org/10.1586/14737175.8.12.1879.
Gonzalez-Reyes, R., Nava-Mesa, M., Vargas-Sanchez, K., Ariza-Salamanca, D., Mora-Muñoz, L., 2017. Involvement of astrocytes in Alzheimer´s disease from a neuroinflammatory and oxidative stress perspective. Front. Mol. Neurosci. 10, 427.
Guina, J., Welton, R.S., Broderick, P.J., Correll, T.L., Peirson, R.P., 2016. DSM-5 Criteria and Its Implications for Diagnosing PTSD in Military Service Members and Veterans. Curr. Psychiatry Rep. 18, 43. https://doi.org/10.1007/s11920-016-0686-1.
Hamner, M.B., Hitri, A., 1992. Plasma beta-endorphin levels in post-traumatic stress disorder: a preliminary report on response to exercise-induced stress. J. Neuropsychiatry Clin. Neurosci. 4 (1), 59–63.
Hawes, B.E., Fried, S., Yao, X., Weig, B., Graziano, M.P., 1998. Nociceptin (ORL-1) and mu-opioid receptors mediate mitogen-activated protein kinase activation in CHO cells through a Gi-coupled signaling pathway: evidence for distinct mechanisms of agonist-mediated desensitization. J. Neurochem. 71, 1024–1033.
Hebb, A.L.O., Zacharko, R.M., Gauthier, M., Trudel, F., Laforest, S., Drolet, G., 2004. Brief exposure to predator odor and resultant anxiety enhances mesocorticolimbic activity and enkephalin expression in CD-1 mice. Eur. J. Neurosci. 20, 2415–2429. https://doi.org/10.1111/j.1460-9568.2004.03704.x.
Henderson, V.W., Roberts, E., Wimer, C., Bardolph, E.L., Chui, H.C., Damasio, A.R., Eslinger, P.J., Folstein, M.F., Schneider, L.S., Teng, E.L., 1989. Multicenter trial of naloxone in Alzheimer's disease. Ann. Neurol. 25, 404–406.
Henry, M.S., Gendron, L., Tremblay, M.-E., Drolet, G., 2017. Enkephalins: Endogenous Analgesics with an Emerging Role in Stress Resilience. Neural Plast. 2017.
Henry, M.S., Bisht, K., Vernoux, N., Gendron, L., Torres-Berrio, A., Drolet, G., Tremblay, M.-E., 2018. Delta Opioid Receptor Signaling Promotes Resilience to Stress Under the Repeated Social Defeat Paradigm in Mice. Front. Mol. Neurosci. 11, 100. https://doi.org/10.3389/fnmol.2018.00100.
Hoffman, L., Watson, P.B., Wilson, G., Montgomery, J., 1989. Low plasma β-endorphin in post-traumatic stress disorder. Aust. N. Z. J. Psychiatry 23, 269–273.
Holbrook, T.L., Galarneau, M.R., Dye, J.L., Quinn, K., Dougherty, A.L., 2010. Morphine use after combat injury in Iraq and post-traumatic stress disorder. N. Engl. J. Med. 362, 110–117. https://doi.org/10.1056/NEJMoa0903326.
Horn, S.R., Charney, D.S., Feder, A., 2016. Understanding resilience: New approaches for preventing and treating PTSD. Exp. Neurol. 284, 119–132. https://doi.org/10.1016/j.expneurol.2016.07.002.
Horvath, G., 2000. Endomorphin-1 and endomorphin-2: pharmacology of the selective endogenous mu-opioid receptor agonists. Pharmacol. Ther. 88, 437–463.
Howland, J.G., Cazakoff, B.N., 2010. Effects of acute stress and GluN2B-containing NMDA receptor antagonism on object and object–place recognition memory. Neurobiol. Learn. Mem. 93, 261–267. https://doi.org/10.1016/j.nlm.2009.10.006.
Hui, K.S., 2007. Brain-specific aminopeptidase: From enkephalinase to protector against neurodegeneration. Neurochem. Res. 32, 2062–2071.
Hui, G.K., Figueroa, I.R., Poytress, B.S., Roozendaal, B., McGaugh, J.L., Weinberger, N.M., 2004. Memory enhancement of classical fear conditioning by post-training injections of corticosterone in rats. Neurobiol. Learn. Mem. 81, 67–74.
Hyman, B.T., Eslinger, P.J., Damasio, A.R., 1985. Effect of naltrexone on senile dementia of the Alzheimer type. J. Neurol. Neurosurg. Psychiatry 48, 1169–1171. https://doi.org/10.1136/jnnp.48.11.1169.
Ibarra, P., Bruehl, S.P., McCubbin, J.A., Carlson, C.R., Wilson, J.F., Norton, J.A., Montgomery, T.B., 1994. An unusual reaction to opioid blockade with naltrexone in a case of post-traumatic stress disorder. J. Trauma. Stress 7, 303–309.
Janickova, H., Rudajev, V., Zimcik, P., Jakubik, J., Tanila, H., El-Fakahany, E.E., Dolezal, V., 2013. Uncoupling of M1 muscarinic receptor/G-protein interaction by amyloid beta(1-42). Neuropharmacology 67, 272–283.
Johansson, L., Guo, X.X., Waern, M., Ostling, S., Gustafson, D., Bengtsson, C., Skoog, I., 2010. Midlife psychological stress and risk of dementia: a 35-year longitudinal population study. Brain 133, 2217–2224.

Kandel, E.R., 2001. The molecular biology of memory storage: a dialogue between genes and synapses. Science 294, 1030–1038.
Karl, A., Schaefer, M., Malta, L.S., Dörfel, D., Rohleder, N., Werner, A., 2006. A meta-analysis of structural brain abnormalities in PTSD. Neurosci. Biobehav. Rev. 30, 1004–1031.
Katzen-Perez, K.R., Jacobs, D.W., Lincoln, A., Ellis, R.J., 2001. Opioid blockade improves human recognition memory following physiological arousal. Pharmacol. Biochem. Behav. 70, 77–84.
Kleen, J.K., Sitorner, M.T., Killeen, P.R., Conrad, C.D., 2006. Chronic stress impairs spatial memory and motivation for reward without disrupting motor ability and motivation to explore. Behav. Neurosci. 120, 842–851.
Klenowski, P., Morgan, M., Bartlett, S.E., 2015. The role of δ-opioid receptors in learning and memory underlying the development of addiction. Br J Pharmacol. 172, 297–310. https://doi.org/10.1111/bph.12618.
Knoll, A.T., Muschamp, J.W., Sillivan, S.E., Ferguson, D., Dietz, D.M., Meloni, E.G., Carroll, F.I., Nestler, E.J., Konradi, C., Carlezon, W.A.J., 2011. Kappa opioid receptor signaling in the basolateral amygdala regulates conditioned fear and anxiety in rats. Biol. Psychiatry 70, 425–433. https://doi.org/10.1016/j.biopsych.2011.03.017.
Kölsch, H., Wagner, M., Bilkei-Gorzó, A., Toliat, M.R., Pentzek, M., Fuchs, A., Kaduszkiewicz, H., Van den Bussche, H., Riedel-Heller, S.G., Angermeyer, M.C., 2009. Gene polymorphisms in prodynorphin (PDYN) are associated with episodic memory in the elderly. J. Neural Transm. 116, 897–903.
Komatsu, H., Ohara, A., Sasaki, K., Abe, H., Hattori, H., Hall, F.S., Uhl, G.R., Sora, I., 2011. Decreased response to social defeat stress in mu-opioid-receptor knockout mice. Pharmacol. Biochem. Behav. 99, 676–682. https://doi.org/10.1016/j.pbb.2011.06.008.
Łapo, I.B., Konarzewski, M., Sadowski, B., 2003. Effect of cold acclimation and repeated swimming on opioid and nonopioid swim stress-induced analgesia in selectively bred mice. Physiol Behav. 78, 345–350.
Le Merrer, J., Rezai, X., Scherrer, G., Becker, J.A., Kieffer, B.L., 2013. Impaired hippocampus-dependent and facilitated striatum-dependent behaviors in mice lacking the delta opioid receptor. Neuropsychopharmacology 38, 1050.
Lee, J.L., Everitt, B.J., Thomas, K.L., 2004. Independent cellular processes for hippocampal memory consolidation and reconsolidation. Science 304, 839–843.
Lemaire, V., Koehl, M., Le Moal, M., Abrous, D.N., 2000. Prenatal Stress Produces Learning Deficits Associated with an Inhibition of Neurogenesis in the Hippocampus 11032.
Leung, K., 2013. [Carbonyl-11C](S)-3-chloro-4-(4-((2-(pyridine-3-yl) pyrrolidin-1-yl) methyl) phenoxy) benzamide. http://www.ncbi.nlm.nih.gov/books/NBK138311/.
Liang, X., Liu, R., Chen, C., Ji, F., Li, T., 2016. Opioid system modulates the immune function: a review. Transl. Perioper. Pain Med. 1, 5.
Liberzon, I., Zubieta, J.K., Fig, L.M., Phan, K.L., Koeppe, R.A., Taylor, S.F., 2002. mu-Opioid receptors and limbic responses to aversive emotional stimuli. Proc Natl Acad Sci U S A. 99, 7084–7089.
Liberzon, I., Taylor, S.F., Phan, K.L., Britton, J.C., Fig, L.M., Bueller, J.A., Koeppe, R.A., Zubieta, J.-K., 2007. Altered central micro-opioid receptor binding after psychological trauma. Biol. Psychiatry 61, 1030–1038. https://doi.org/10.1016/j.biopsych.2006.06.021.
Liu, Y., Wu, Y., Qian, Z., Yan, C., Fan, K., Xu, J., Li, X., Liu, Z., 2016. Effect of opioid receptors on acute stress-induced changes in recognition memory. Sheng Li Xue BaoActa Physiol. Sin. 68, 757–766.
Love, T.M., Stohler, C.S., Zubieta, J.-K., 2009. Positron emission tomography measures of endogenous opioid neurotransmission and impulsiveness traits in humans. Arch. Gen. Psychiatry 66, 1124–1134.
Lubin, G., Weizman, A., Shmushkevitz, M., Valevski, A., 2002. Short-term treatment of post-traumatic stress disorder with naltrexone: an open-label preliminary study. Hum. Psychopharmacol. Clin. Exp. 17, 181–185.
Luksys, G., Sandi, C., 2011. Neural mechanisms and computations underlying stress effects on learning and memory. Curr. Opin. Neurobiol. 21, 502–508. https://doi.org/10.1016/j.conb.2011.03.003.
Lutfy, K., Cowan, A., 2004. Buprenorphine: a unique drug with complex pharmacology. Curr. Neuropharmacol. 2, 395–402.
Lutz, P.-E., Ayranci, G., Chu-Sin-Chung, P., Matifas, A., Koebel, P., Filliol, D., Befort, K., Ouagazzal, A.-M., Kieffer, B.L., 2014. Distinct mu, delta, and kappa opioid receptor mechanisms underlie low sociability and depressive-like behaviors during heroin abstinence. Neuropsychopharmacology 39, 2694.
Machado, A., Herrera, A.J., de Pablos, R.M., Espinosa-Oliva, A.M., Sarmiento, M., Ayala, A., Venero, J.L., Santiago, M., Villaran, R.F., Delgado-Cortes, M.J., Arguelles, S., Cano, J., 2014. Chronic stress as a risk factor for Alzheimer's disease. Rev. Neurosci. 25, 785–804.
Madamba, S.G., Schweitzer, P., Siggins, G.R., 1999. Dynorphin selectively augments the M-current in hippocampal CA1 neurons by an opiate receptor mechanism. J. Neurophysiol. 82, 1768–1775.
Magarinos, A.M., Jose, M.G.V., McEwen, B.S., 1997. Chronic Stress Alters Synaptic Terminal Structure in Hippocampus. pp. 14002.
Mahabir, M., Tucholka, A., Shin, L.M., Etienne, P., Brunet, A., 2015. Emotional face processing in post-traumatic stress disorder after reconsolidation impairment using propranolol: A pilot fMRI study. J. Anxiety Disord. 36, 127–133. https://doi.org/10.1016/j.janxdis.2015.10.004.
Mahabir, M., Ashbaugh, A.R., Saumier, D., Tremblay, J., 2016. Propranolol's impact on cognitive performance in post-traumatic stress disorder. J. Affect. Disord. 192, 98–103. https://doi.org/10.1016/j.jad.2015.11.051.
Mallimo, E.M., Kusnecov, A.W., 2013. The role of orphanin FQ/nociceptin in neuroplasticity: relationship to stress, anxiety and neuroinflammation. Front. Cell. Neurosci. 7.
Mansour, A., Khachaturian, H., Lewis, M.E., Akil, H., Watson, S.J., 1988. Anatomy of CNS opioid receptors. Trends Neurosci. 11, 308–314.
Mansour, A., Fox, C.A., Akil, H., Watson, S.J., 1995. Opioid-receptor mRNA expression in the rat CNS: anatomical and functional implications. Trends Neurosci. 18, 22–29.
Marin, M.-F., Hupbach, A., Maheu, F.S., Nader, K., Lupien, S.J., 2011. Metyrapone administration reduces the strength of an emotional memory trace in a long-lasting manner. J. Clin. Endocrinol. Metab. 96, E1221–E1227. https://doi.org/10.1210/jc.2011-0226.
Marinelli, P., Quirion, R., Gianoulakis, C., 2004. An in vivo profile of β-endorphin release in the arcuate nucleus and nucleus accumbens following exposure to stress or alcohol. Neuroscience 127, 777–784.
Martinez, C.O., Do, V.H., Derrick, B.E., 2011. Endogenous opioid peptides contribute to associative LTP in the hippocampal CA3 region. Neurobiol. Learn. Mem. 96, 207–217.
Mathieu-Kia, A.-M., Fan, L.-Q., Kreek, M.J., Simon, E.J., Hiller, J.M., 2001. μ-, δ-and κ-opioid receptor populations are differentially altered in distinct areas of postmortem brains of Alzheimer's disease patients. Brain Res. 893, 121–134.
Mayordomo-Cava, J., Yajeya, J., Navarro-López, J.D., Jiménez-Díaz, L., 2015. Amyloid-β(25-35) Modulates the Expression of GirK and KCNQ Channel Genes in the Hippocampus. PLoS ONE 10, 1–18. https://doi.org/10.1371/journal.pone.0134385.
McEwen, B.S., 2000. The neurobiology of stress: from serendipity to clinical relevance. Brain Res. 886, 172–189.
McEwen, B.S., 2007. Physiology and neurobiology of stress and adaptation: Central role of the brain. Physiol. Rev. 87, 873–904.
McEwen, B.S., 2016. Review: Stress-induced remodeling of hippocampal CA3 pyramidal neurons. Brain Res. 1645, 50–54. https://doi.org/10.1016/j.brainres.2015.12.043.
McEwen, B.S., Bowles, N.P., Gray, J.D., Hill, M.N., Hunter, R.G., Karatsoreos, I.N., Nasca, C., 2015. Mechanisms of stress in the brain. Nat. Neurosci. 18, 1353–1363. https://doi.org/10.1038/nn.4086.
McGaugh, J.L., 1983. Hormonal influences on memory. Annu. Rev. Psychol. 34, 297.
McNally, G.P., Westbrook, R.F., 2003. Opioid receptors regulate the extinction of Pavlovian fear conditioning. Behav. Neurosci. 117, 1292–1301. https://doi.org/10.1037/0735-7044.117.6.1292.
Medina, A.C., Charles, J.R., Espinoza-González, V., Sánchez-Resendis, O., Prado-Alcalá, R.A., Quirarte, G.L., Roozendaal, B., 2007. Glucocorticoid administration into the dorsal stratium facilitates memory consolidation of inhibitory avoidance training but not of the context or footshock components. Learn. Mem. 14, 673–677. https://doi.org/10.1101/lm.654407.
Meilandt, W.J., Yu, G.-Q., Chin, J., Roberson, E.D., Palop, J.J., Wu, T., Scearce-Levie, K., Mucke, L., 2008. Enkephalin elevations contribute to neuronal and behavioral impairments in a transgenic mouse model of Alzheimer's disease. J. Neurosci. Off. J. Soc. Neurosci. 28, 5007–5017. https://doi.org/10.1523/JNEUROSCI.0590-08.2008.
Melcer, T., Walker, J., Sechriest, V.F., Lebedda, M., Quinn, K., Galarneau, M., 2014. Glasgow Coma Scores, early opioids, and posttraumatic stress disorder among combat amputees. J. Trauma. Stress 27, 152–159. https://doi.org/10.1002/jts.21909.
Menard, C., Herzog, H., Schwarzer, C., Quirion, R., 2014. Possible Role of Dynorphins in Alzheimer's Disease and Age-Related Cognitive Deficits. Neurodegener. Dis. 13, 82–85.
Mercadante, S., Porzio, G., Gebbia, V., 2014. New Opioids. J. Clin. Oncol. 32, 1671–1676.
Meunier, J.C., 1997. Nociceptin/orphanin FQ and the opioid receptor-like ORL1 receptor. Eur. J. Pharmacol. 340, 1–15.
Mitra, R., Jadhav, S., McEwen, B.S., Vyas, A., Chattarji, S., 2005. Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. Proc Natl Acad Sci U S A. 102, 9371–9376.
Mitrovic, I., Margeta-Mitrovic, M., Bader, S., Stoffel, M., Jan, L.Y., Basbaum, A.I., 2003. Contribution of GIRK2-Mediated Postsynaptic Signaling to Opiate and α 2 -Adrenergic Analgesia and Analgesic Sex Differences 271.
Mizuno, T., Kimura, F., 1996. Research report: Medial septal injection of naloxone elevates acetylcholine release in the hippocampus and induces behavioral seizures in rats. Brain Res. 713, 1–7. https://doi.org/10.1016/0006-8993(95)01287-7.
Moreno, H., Wu, W.E., Lee, T., Brickman, A., Mayeux, R., Brown, T.R., Small, S.A., 2007. Imaging the Abeta-related neurotoxicity of Alzheimer disease. Arch Neurol. 64, 1467–1477.
Mutis, J.A., Rodríguez, J.H., Nava-Mesa, M.O., 2017. Rapidly progressive cognitive impairment with neuropsychiatric symptoms as the initial manifestation of status epilepticus. Epilepsy Behav. Case Rep. 7, 20–23.
Nader, K., Schafe, G.E., Le Doux, J.E., 2000a. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature 406, 722.
Nader, K., Schafe, G.E., LeDoux, J.E., 2000b. The labile nature of consolidation theory. Nat. Rev. Neurosci. 1, 216.
Nativio, P., Pascale, E., Maffei, A., Scaccianoce, S., Passarelli, F., 2012. Effect of stress on hippocampal nociceptin expression in the rat. Stress 15, 378–384.
Nava-Mesa, M.O., Jiménez-Díaz, L., Yajeya, J., Navarro-Lopez, J.D., 2013a. Amyloid-β induces synaptic dysfunction through G protein-gated inwardly rectifying potassium channels in the fimbria-CA3 hippocampal synapse. Front. Cell. Neurosci. 7.
Nava-Mesa, M.O., Lamprea, M.R., Múnera, A., 2013b. Divergent short-and long-term effects of acute stress in object recognition memory are mediated by endogenous opioid system activation. Neurobiol. Learn. Mem. 106, 185–192.
Nava-Mesa, M.O., Jiménez-Díaz, L., Yajeya, J., Navarro-Lopez, J.D., 2014. GABAergic neurotransmission and new strategies of neuromodulation to compensate synaptic dysfunction in early stages of Alzheimer's disease. Front. Cell. Neurosci. 8.
Nijdam, M.J., Van Amsterdam, J.G.C., Gersons, B.P.R., Olff, M., 2015. Dexamethasone-suppressed cortisol awakening response predicts treatment outcome in posttraumatic stress disorder. J. Affect. Disord. 184, 205–208. https://doi.org/10.1016/j.jad.2015.05.058.
Nixon, R.D., Nehmy, T.J., Ellis, A.A., Ball, S.-A., Menne, A., McKinnon, A.C., 2010. Predictors of posttraumatic stress in children following injury: The influence of

appraisals, heart rate, and morphine use. Behav. Res. Ther. 48, 810–815.
Odio, M., Brodish, A., 1990. Central but not peripheral opiate receptor blockade prolonged pituitary-adrenal responses to stress. Pharmacol. Biochem. Behav. 35, 963–969.
Pacak, K., Palkovits, M., 2001. Stressor specificity of central neuroendocrine responses: Implications for stress-related disorders. Endocr. Rev. 22, 502–548.
Palop, J.J., Mucke, L., 2010. Amyloid-[beta]-induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. Nat. Neurosci. 13, 812–818.
Palop, J.J., Chin, J., Roberson, E.D., Wang, J., Thwin, M.T., Bien-Ly, N., Yoo, J., Ho, K.O., Yu, G.-Q., Kreitzer, A., 2007. Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. Neuron 55, 697–711.
Pascoe, J.E., Williams, K.L., Mukhopadhyay, P., Rice, K.C., Woods, J.H., Ko, M.-C., 2008. Effects of mu, kappa, and delta opioid receptor agonists on the function of hypothalamic–pituitary–adrenal axis in monkeys. Psychoneuroendocrinology 33, 478–486.
Payne, J.D., Jackson, E.D., Hoscheidt, S., Ryan, L., Jacobs, W.J., Nadel, L., 2007. Stress administered prior to encoding impairs neutral but enhances emotional long-term episodic memories. Learn. Mem. Cold Spring Harb. N 14, 861–868. https://doi.org/10.1101/lm.743507.
Petrakis, I.L., Poling, J., Levinson, C., Nich, C., Carroll, K., Ralevski, E., Rounsaville, B., 2006. Naltrexone and disulfiram in patients with alcohol dependence and comorbid post-traumatic stress disorder. Biol. Psychiatry 60, 777–783.
Petrakis, I.L., Ralevski, E., Desai, N., Trevisan, L., Gueorguieva, R., Rounsaville, B., Krystal, J.H., 2012. Noradrenergic vs serotonergic antidepressant with or without naltrexone for veterans with PTSD and comorbid alcohol dependence. Neuropsychopharmacology 37, 996.
Pinelo-Nava, M.T., Sandi, C., 2007. Stress and Memory: Behavioral Effects and Neurobiological Mechanisms. Neural Plast. 2007, 2007. https://doi.org/10.1155/2007/78970.
Pitman, R.K., Van der Kolk, B.A., Orr, S.P., Greenberg, M.S., 1990. Naloxone-reversible analgesic response to combat-related stimuli in posttraumatic stress disorder: A pilot study. Arch. Gen. Psychiatry 47, 541–544.
Porto, G.P., Milanesi, L.H., Rubin, M.A., Mello, C.F., 2015. Effect of morphine on the persistence of long-term memory in rats. Psychopharmacology (Berl.) 232, 1747–1753.
Rashidy-Pour, A., Sadeghi, H., Taherain, A.A., Vafaei, A.A., Fathollahi, Y., 2004. Research report: The effects of acute restraint stress and dexamethasone on retrieval of long-term memory in rats: an interaction with opiate system. Behav. Brain Res. 154, 193–198. https://doi.org/10.1016/j.bbr.2004.02.007.
Retana-Márquez, S., Bonilla-Jaime, H., Vázquez-Palacios, G., Martínez-García, R., 2009. Naltrexone effects on male sexual behavior, corticosterone, and testosterone in stressed male rats. Physiol. Behav. 96, 333–342. https://doi.org/10.1016/j.physbeh.2008.10.022.
Rezvanfard, M., Zarrindast, M.-R., Ownegh, V., 2011. Systemic opioid receptor antagonism blocks swim stress-induced retention impairment independently from CA1 and BLA opioidergic pathways. Life Sci. 89, 320–326. https://doi.org/10.1016/j.lfs.2011.06.014.
Roozendaal, B., Quirarte, G.L., McGaugh, J.L., 2002. Glucocorticoids interact with the basolateral amygdala beta-adrenoceptor–cAMP/cAMP/PKA system in influencing memory consolidation. Eur. J. Neurosci. 15, 553–560.
Roozendaal, B., Okuda, S., Van der Zee, E.A., McGaugh, J.L., 2006. Glucocorticoid enhancement of memory requires arousal-induced noradrenergic activation in the basolateral amygdala. Proc. Natl. Acad. Sci. U. S. A. 103, 6741–6746. https://doi.org/10.1073/pnas.0601874103.
Roozendaal, B., Lengvilas, R., McGaugh, J.L., Civelli, O., Reinscheid, R.K., 2007. Orphanin FQ/nociceptin interacts with the basolateral amygdala noradrenergic system in memory consolidation. Learn. Mem. 14, 29–35.
Rothman, S.M., Mattson, M.P., 2010. Adverse Stress, Hippocampal Networks, and Alzheimer's Disease. Neuromolecular Med. 12, 56–70.
Rousseau, K., Kauser, S., Pritchard, L.E., Warhurst, A., Oliver, R.L., Slominski, A., Wei, E.T., Thody, A.J., Tobin, D.J., White, A., 2007. Proopiomelanocortin (POMC), the ACTH/melanocortin precursor, is secreted by human epidermal keratinocytes and melanocytes and stimulates melanogenesis. FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 21, 1844–1856. https://doi.org/10.1096/fj.06-7398com.
Sajadi, A.A., Rashidy-Pour, A., Samaei, S.A., 2006. Intra-hippocampal microinjections of anisomycin did not block glucocorticoid-induced impairment of memory retrieval in rats: An evidence for non-genomic effects of glucocorticoids. Behav. Brain Res. 173, 158–162. https://doi.org/10.1016/j.bbr.2006.06.018.
Sajadi, A.A., Samaei, S.A., Rashidy-Pour, A., 2007. Blocking effects of intra-hippocampal naltrexone microinjections on glucocorticoid-induced impairment of spatial memory retrieval in rats. Neuropharmacology 52, 347–354.
Salehi, B., Cordero, M.I., Sandi, C., 2010. Learning Under Stress: The Inverted-U-Shape Function Revisited. Learn. Mem. 17, 522–530.
Sanchez-Rodriguez, I., Temprano-Carazo, S., Najera, A., Djebari, S., Yajeya, J., Gruart, A., Delgado-Garcia, J.M., Jimenez-Diaz, L., Navarro-Lopez, J.D., 2017. Activation of G-protein-gated inwardly rectifying potassium (Kir3/GirK) channels rescues hippocampal functions in a mouse model of early amyloid-beta pathology. Sci. Rep. 7, 14658. https://doi.org/10.1038/s41598-017-15306-8.
Sandi, C., Woodson, J.C., Haynes, V.F., Park, C.R., Touyarot, K., Lopez-Fernandez, M.A., Venero, C., Diamond, D.M., 2005. Acute stress-induced impairment of spatial memory is associated with decreased expression of neural cell adhesion molecule in the hippocampus and prefrontal cortex. Biol. Psychiatry 57, 856–864. https://doi.org/10.1016/j.biopsych.2004.12.034.
Sandin, J., Georgieva, J., Terenius, L., Nylander, I., Schött, P.A., Ögren, S.O., 1998. Hippocampal dynorphin B injections impair spatial learning in rats: A κ-opioid receptor-mediated effect. Neuroscience 85, 375–382. https://doi.org/10.1016/S0306-4522(97)00605-2.
Sapolsky, R.M., 2015. Stress and the brain: individual variability and the inverted-U. Nat. Neurosci. 18, 1344–1346. https://doi.org/10.1038/nn.4109.
Sarajärvi, T., Tuusa, J.T., Haapasalo, A., Lackman, J.J., Sormunen, R., Helisalmi, S., Roehr, J.T., Parrado, A.R., Mäkinen, P., Bertram, L., 2011. Cysteine 27 variant of the δ-opioid receptor affects amyloid precursor protein processing through altered endocytic trafficking. Mol. Cell. Biol. 31, 2326–2340.
Sartor, G.C., Powell, S.K., Wiedner, H.J., Wahlestedt, C., Brothers, S.P., 2016. Nociceptin receptor activation does not alter acquisition, expression, extinction and reinstatement of conditioned cocaine preference in mice. Brain Res. 1632, 34–41. https://doi.org/10.1016/j.brainres.2015.11.044.
Schwabe, L., Wolf, O.T., 2010. Learning under stress impairs memory formation. Neurobiol. Learn. Mem. 93, 183–188. https://doi.org/10.1016/j.nlm.2009.09.009.
Schwabe, L., Wolf, O.T., 2013. Stress and multiple memory systems: from thinking to doing. Trends Cogn. Sci. 17, 60–68. https://doi.org/10.1016/j.tics.2012.12.001.
Schwabe, L., Oitzl, M.S., Philippsen, C., Richter, S., Bohringer, A., Wippich, W., Schachinger, H., 2007. Stress modulates the use of spatial versus stimulus-response learning strategies in humans. Learn. Mem. 14, 109–116.
Schwabe, L., Dalm, S., Schächinger, H., Oitzl, M.S., 2008. Chronic stress modulates the use of spatial and stimulus-response learning strategies in mice and man. Neurobiol Learn Mem. 90, 495–503. https://doi.org/10.1016/j.nlm.2008.07.015.
Seal, K.H., Maguen, S., Bertenthal, D., Batki, S.L., Striebel, J., Stein, M.B., Madden, E., Neylan, T.C., 2016. Observational Evidence for Buprenorphine's Impact on Posttraumatic Stress Symptoms in Veterans With Chronic Pain and Opioid Use Disorder. J. Clin. Psychiatry 77, 1182–1188.
Selkoe, D.J., 2002. Alzheimer's disease is a synaptic failure. Science 298, 789–791.
Shen, K.-Z., Johnson, S.W., 2002. Presynaptic modulation of synaptic transmission by opioid receptor in rat subthalamic nucleus in vitro. J. Physiol. 541, 219–230.
Sher, L., 2004. The role of endogenous opioids in the placebo effect in post-traumatic stress disorder. Forsch. KomplementärmedizinResearch Complement. Med. 11, 354–359.
Sherin, J.E., Nemeroff, C.B., 2011. Post-traumatic stress disorder: The neurobiological impact of psychological trauma. Dialogues Clin. Neurosci. 13, 263–278.
Shirayama, Y., Ishida, H., Iwata, M., Hazama, G.I., Kawahara, R., Duman, R.S., 2004. Stress increases dynorphin immunoreactivity in limbic brain regions and dynorphin antagonism produces antidepressant-like effects. J. Neurochem. 90, 1258–1268. https://doi.org/10.1111/j.1471-4159.2004.02589.x.
Shors, T.J., Levine, S., Thompson, R.F., 1990. Opioid antagonist eliminates the stress-induced impairment of long-term potentiation (LTP). Brain Res. 506, 316–318.
Siller-Pérez, C., Serafín, N., Prado-Alcalá, R.A., Roozendaal, B., Quirarte, G.L., 2017. Glucocorticoid administration into the dorsolateral but not dorsomedial striatum accelerates the shift from a spatial toward procedural memory. Neurobiol. Learn. Mem. 141, 124–133.
Sørensen, L., Igel, C., Pai, A., Balas, I., Anker, C., Lillholm, M., Nielsen, M., Alzheimer's Disease Neuroimaging Initiative, 2017. Differential diagnosis of mild cognitive impairment and Alzheimer's disease using structural MRI cortical thickness, hippocampal shape, hippocampal texture, and volumetry. NeuroImage Clin. 13, 470–482.
Stoddard, F.J., Jr., Sorrentino, E.A., Ceranoglu, T.A., Saxe, G., Murphy, J.M., Drake, J.E., Ronfeldt, H., White, G.W., Kagan, J., Snidman, N., Sheridan, R.L., Tompkins, R.G., 2009. Preliminary evidence for the effects of morphine on posttraumatic stress disorder symptoms in one- to four-year-olds with burns. J. Burn Care Res. Off. Publ. Am. Burn Assoc. 30, 836–843. https://doi.org/10.1097/BCR.0b013e3181b48102
Strawn, J.R., Geracioti, T.D., 2008. Noradrenergic dysfunction and the psychopharmacology of posttraumatic stress disorder. Depress. Anxiety 1091-4269 (25), 260–271. https://doi.org/10.1002/da.20292.
Szczytkowski-Thomson, J.L., Lebonville, C.L., Lysle, D.T., 2013. Morphine prevents the development of stress-enhanced fear learning. Pharmacol. Biochem. Behav. 103, 672–677. https://doi.org/10.1016/j.pbb.2012.10.013.
Tank, W., Wong, L.D., 2015. Peripheral and central effects of circulating catecholamines. Compr. Physiol. 5 (1), 1–15.
Tejeda, H.A., Hanks, A.N., Scott, L., Mejias-Aponte, C., Hughes, Z.A., O'donnell, P., 2015. Prefrontal cortical kappa opioid receptors attenuate responses to amygdala inputs. Neuropsychopharmacology 40, 2856.
Teng, L., Zhao, J., Wang, F., Ma, L., Pei, G., 2010. A gpcr/secretase complex regulates [beta]-and [gamma]-secretase specificity for a [beta] production and contributes to ad pathogenesis. Cell Res. 20, 138.
Thathiah, A., De Strooper, B., 2011. The role of G protein-coupled receptors in the pathology of Alzheimer's disease. Nat. Rev. Neurosci. 12, 73–87.
Tollenaar, M.S., Elzinga, B.M., Spinhoven, P., Everaerd, W., 2009. Psychophysiological responding to emotional memories in healthy young men after cortisol and propranolol administration. Psychopharmacology (Berl.) 203, 793–803. https://doi.org/10.1007/s00213-008-1427-x.
Torres-Berrio, A., Nava-Mesa, M.O., 2018. El estrés crónico facilita la recuperación de memoria tipo estímulo-respuesta y empeora la recuperación de memoria tipo espacial en el laberinto radial. Presented at the Xi Congreso Nacional Xii Seminario internacional de Neurociencias Colegio Colombiano de Neurociencias, Bogotá. pp. 241–242 ISBN: 9789587729160.
Trudeau, L.-E., Aragon, C.M.G., Amit, Z., 1991. Involvement of endogenous opioid mechanisms in the interaction between stress and ethanol. Psychopharmacology (Berl.) 103, 425–429.
Tsolaki, M., Pantazi, C., Stiliou, F., Aminta, M., Diudi, P., Karasoulas Kazis, A., Pollen, D., 2003. Prevalence of dementia in Greek Orthodox Monasteries: the role of diet poor in lipids. Brain Aging 3, 13–17.
Tsolaki, M., Papaliagkas, V., Kounti, F., Messini, C., Boziki, M., Anogianakis, G., Vlaikidis, N., 2010. Severely stressful events and dementia: A study of an elderly Greek

demented population. PSYCHIATRY Res. 176, 51–54.
Ukai, M., Lin, H.P., 2002. Endomorphins 1 and 2 induce amnesia via selective modulation of dopamine receptors in mice. Eur. J. Pharmacol. 446, 97–101.
Valentino, R.J., Van Bockstaele, E., 2001. Opposing regulation of the locus coeruleus by corticotropin-releasing factor and opioids: Potential for reciprocal interactions between stress and opioid sensitivity. Psychopharmacology (Berl.) 158, 331.
Van der Kolk, B.A., Greenberg, M.S., Orr, S. ea, Pitman, R.K., 1989. Endogenous opioids, stress induced analgesia, and posttraumatic stress disorder. Psychopharmacol. Bull. 25, 417–421.
van Marle, H., 2015. PTSD as a memory disorder. Eur. J. Psychotraumatology 6, 27633.
Vargas-Lopez, V., Torres-Berrio, A., Gonzalez-Martinez, L., Munera, A., Lamprea, M.R., 2015. Acute restraint stress and corticosterone transiently disrupts novelty preference in an object recognition task. Behav. Brain Res. 291, 60–66. https://doi.org/10.1016/j.bbr.2015.05.006.
Vazquez-Palacios, G., Retana-Marquez, S., Bonilla-Jaime, H., Velazquez-Moctezuma, J., 2004. Stress-induced REM sleep increase is antagonized by naltrexone in rats. Psychopharmacology (Berl.) 171, 186–190.
Veening, J.G., Barendregt, H.P., 2015. The effects of Beta-Endorphin: State change modification. Fluids Barriers CNS. https://doi.org/10.1186/2045-8118-12-3.
Verret, L., Mann, E.O., Hang, G.B., Barth, A.M., Cobos, I., Ho, K., Devidze, N., Masliah, E., Kreitzer, A.C., Mody, I., 2012. Inhibitory interneuron deficit links altered network activity and cognitive dysfunction in Alzheimer model. Cell 149, 708–721.
Wallington, C.L., Peters, D.M., Gelb, C.R., Peterfreund, R.A., 2002. Orphanin FQ/nociceptin and mu-opioid receptor mRNA levels in human SH-SY5Y neuroblastoma cells: effects of activating the cAMP-PKA signal transduction pathway. BRAIN Res. 944, 73–81.
Wilson, R.S., Evans, D.A., Bienias, J.L., de Leon, C.F.M., Schneider, J.A., Bennett, D.A., 2003. Proneness to psychological distress is associated with risk of Alzheimer's disease. Neurology 61, 1479–1485.
Wong, T.P., Howland, J.G., Robillard, J.M., Ge, Y., Yu, W., Titterness, A.K., Brebner, K., Liu, L., Weinberg, J., Christie, B.R., Phillips, A.G., Wang, Y.T., 2007. Hippocampal Long-Term Depression Mediates Acute Stress-Induced Spatial Memory Retrieval Impairment 11471.
Wu, W., Small, S.A., 2006. Imaging the earliest stages of Alzheimer's disease. Curr Alzheimer Res. 3, 529–539.
Xu, Y., Gu, Y., Xu, G.-Y., Wu, P., Li, G.-W., Huang, L.-Y., 2003. Adeno-associated viral transfer of opioid receptor gene to primary sensory neurons: a strategy to increase opioid antinociception. Proc. Natl. Acad. Sci. 100, 6204–6209.
Yakovleva, T., Marinova, Z., Kuzmin, A., Seidah, N.G., Haroutunian, V., Terenius, L., Bakalkin, G., 2007. Dysregulation of dynorphins in Alzheimer disease. Neurobiol. Aging 28, 1700–1708.
Yasmin, F., Saxena, K., McEwen, B.S., Chattarji, S., 2016. The delayed strengthening of synaptic connectivity in the amygdala depends on NMDA receptor activation during acute stress. Physiol Rep. 4, e13002.
Yehuda, R., 2006. Advances in Understanding Neuroendocrine Alterations in PTSD and Their Therapeutic Implications. Ann. N. Y. Acad. Sci. 1071, 137–166. https://doi.org/10.1196/annals.1364.012.
Yilmaz, P., Diers, M., Diener, S., Rance, M., Wessa, M., Flor, H., 2010. Brain correlates of stress-induced analgesia. Pain 151, 522–529. https://doi.org/10.1016/j.pain.2010.08.016.
Yu, J.-Y., Fang, P., Wang, C., Wang, X.-X., Li, K., Gong, Q., Luo, B.-Y., Wang, X.-D., 2018. Dorsal CA1 interneurons contribute to acute stress-induced spatial memory deficits. Neuropharmacology 135, 474–486. https://doi.org/10.1016/j.neuropharm.2018.04.002.
Yuncai, C., Molet, J., Lauterborn, J.C., Trieu, B.H., Bolton, J.L., Patterson, K.P., Gall, C.M., Lynch, G., Baram, T.Z., 2016. Converging, Synergistic Actions of Multiple Stress Hormones Mediate Enduring Memory Impairments after Acute Simultaneous Stresses. J. Neurosci. 36, 11295–11307. https://doi.org/10.1523/JNEUROSCI.2542-16.2016.
Zhang, R., Xue, G., Wang, S., Zhang, L., Shi, C., Xie, X., 2012a. Novel object recognition as a facile behavior test for evaluating drug effects in AβPP/PS1 Alzheimer's disease mouse model. J. Alzheimers Dis. 31, 801–812.
Zhang, Y., Gandhi, P.R., Standifer, K.M., 2012b. Increased nociceptive sensitivity and nociceptin/orphanin FQ levels in a rat model of PTSD. Mol. Pain 8. https://doi.org/10.1186/1744-8069-8-76.
Zhang, Z., Cordeiro Matos, S., Jego, S., Adamantidis, A., Séguéla, P., 2013. Norepinephrine Drives Persistent Activity in Prefrontal Cortex via Synergistic α1 and α2 Adrenoceptors. PLoS ONE 8, 1–13. https://doi.org/10.1371/journal.pone.0066122.
Zhang, R.S., Xu, H.J., Jiang, J.H., Han, R.W., Chang, M., Peng, Y.L., Wang, Y., Wang, R., 2015a. Endomorphin-1 attenuates Aβ42 induced impairment of novel object and object location recognition tasks in mice. Brain Res. 1629, 210–220. https://doi.org/10.1016/j.brainres.2015.10.028.
Zhang, Y., Simpson-Durand, C.D., Standifer, K.M., 2015b. Nociceptin/orphanin FQ peptide receptor antagonist JTC-801 reverses pain and anxiety symptoms in a rat model of post-traumatic stress disorder. Br. J. Pharmacol. 172, 571–582.
Zhao, H., Xu, H., Xu, X.H., 2004. Effects of naloxone on the long-term potentiation of EPSPs from the pathway of Schaffer collateral to CA1 region of hippocampus in aged rats with declined memory. BRAIN Res. 996, 111–116.
Zhou, J., Luo, Y., Zhang, J.T., Li, M.X., Wang, C.M., Guan, X.L., Wu, P.F., Hu, Z.L., Jin, Y., Ni, L., Wang, F., Chen, J.G., 2015. Propranolol decreases retention of fear memory by modulating the stability of surface glutamate receptor GluA1 subunits in the lateral amygdala. Br. J. Pharmacol. 172, 5068–5082.
Zorawski, M., Killcross, S., 2002. Posttraining glucocorticoid receptor agonist enhances memory in appetitive and aversive Pavlovian discrete-cue conditioning paradigms. Neurobiol. Learn. Mem. 78, 458–464.