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Review

Stress and opioids: Role of opioids in modulating stress-related behavior and effect of stress on morphine conditioned place preference

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ABSTRACT

Research studies have defined the important role of endogenous opioids in modulating stress-associated behavior. The release of β-endorphins in the amygdala in response to stress helps to cope with a stressor by inhibiting the over-activation of HPA axis. Administration of mu opioid agonists reduces the risk of developing post-traumatic stress disorder (PTSD) following a traumatic event by inhibiting fear-related memory consolidation. Similarly, the release of endogenous enkephalin and nociceptin in the basolateral amygdala and the nucleus accumbens tends to produce the anti-stress effects. An increase in dynorphin levels during prolonged exposure to stress may produce learned helplessness, dysphoria and depression. Stress also influences morphine-induced conditioned place preference (CPP) depending upon the intensity and duration of the stressor. Acute stress inhibits morphine CPP, while chronic stress potentiates CPP. The development of dysphoria due to increased dynorphin levels may contribute to chronic stress-induced potentiation of morphine CPP. The activation of ERK/cyclic AMP responsive element-binding (CREB) signaling in the mesocorticolimbic area, glucocorticoid receptors in the basolateral amygdala, and norepinephrine and galanin system in the nucleus accumbens may decrease the acute stress-induced inhibition of morphine CPP. The increase in dopamine levels in the nucleus accumbens and augmentation of GABAergic transmission in the median prefrontal cortex may contribute in potentiating morphine CPP. Stress exposure reinstates the extinct morphine CPP by activating the orexin receptors in the nucleus accumbens, decreasing the oxytocin levels in the lateral septum and amygdala, and altering the GABAergic transmission (activation of $GABA_A$ and inactivation of $GABA_B$ receptors). The present review describes these varied interactions between opioids and stress along with the possible mechanism.

Contents

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1. Introduction

"Stress" is a word derived from the Latin word 'Stringere' meaning to draw tight and was popularly used in the 17th century to mean hardship, strain, adversity or affliction. In modern times, stress is a buzzword used to describe the physical, emotional, cognitive and behavioral response to events that are appraised as threatening and challenging (Cartwright and Cooper, 1997). The term stress was first employed in a biological context by a Canadian endocrinologist Hans Selye in 1930s. He defined "stress as a nonspecific response of the body to any kind of demand made upon it" (Selye, 1998). Stress is a physical or psychological stimulus that can produce mental tension or physiological reactions to produce illness. The changes involved in disturbing the homeostasis of an organism trigger various changes, including an alteration in behavior, autonomic function and over-activation of hypothalamic–pituitary–adrenal (HPA) axis (Bali and Jaggi, 2013, 2014). The ability to cope with a stressor is a crucial determinant of health and the chemical mediators (stress hormones) play an important role in promoting stress adaptation. Stress is a predecessor and is a causative factor for the development of anxiety and depression. Both anxiety and depression are the result of an inappropriate adaptation to stress and these have been termed as 'stress-related disorders', with a causal role of HPA axis (Bali et al., 2014).

The endogenous opioids are derived from three independent genes that give rise to three precursor proteins known as proopiomelanocortin (POMC), proenkephalin (PENK), and prodynorphin, and their appropriate processing yields β-endorphin, met-enkephalin, leu-enkephalin, dynorphin and nociceptin, respectively. These peptides and their derivatives exhibit different affinity and selectivity for the mu-, delta- and kappa-receptors located on the central and the peripheral neurons, neuroendocrine, immune, mucosal cells and on many other organ systems (Fig. 1). Two additional endogenous opioid peptides have been isolated from the bovine brain that includes endomorphin-1 and endomorphin-2. Apart from the analgesic actions of opioids, different opioid agonists and antagonists have shown therapeutic actions in diverse diseases of the central nervous system, including depression, stress, anxiety, epilepsy; gastro-intestinal diseases such as ulceration, irritable bowel syndrome, diarrhea, postoperative ileus; diseases of immune system and related inflammatory disorders such as osteoarthritis and rheumatoid arthritis; and others, including ischemia-reperfusion injury, alcoholism and obesity/binge eating (Sauriyal et al., 2011).

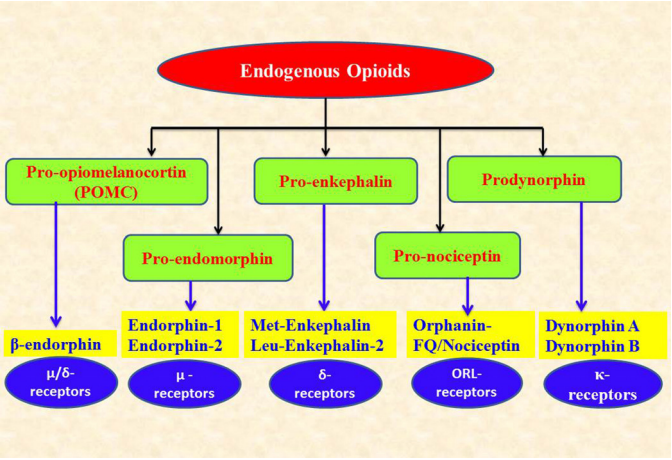

Fig. 1. Endogenous opioids with their precursor molecules and binding receptor sites.

Opioids receptors are widely distributed on different components of the HPA axis such as the hypothalamus, pituitary and adrenal gland. It has been documented that the POMC fibers originating in the arcuate nucleus innervate the stress-responsive hypothalamic nuclei, including the paraventricular nucleus (PVN) of hypothalamus, median eminence and other limbic structures, including the septum, bed nucleus of stria terminalis (BNST) and amygdala (Palkovits, 1987; Steckler et al., 2005; Sauriyal et al., 2011). Numerous research studies and reviews provide evidence for the role of the endogenous opioid system in regulating and modulating the HPA axis, autonomic nervous system and behavioral responses during stress (Valentino and Bockstaele, 2008). Various clinical and preclinical studies have documented the critical role of endogenous as well as exogenous opioids in modulating stress and stress-associated anxiety, posttraumatic stress disorder (PTSD) and depression (Nixon et al., 2010; Szczytkowski-Thomson et al., 2013). Furthermore, stress has also been shown to modulate the response of opioids, including drug craving and reinstatement of drug of abuse (Hays et al., 2012; Haghparast et al., 2013). The present article reviews the role of opioids in modulating stress-associated behavior, and effect of stress on morphine-induced CPP with the possible mechanisms.

2. Effect of endorphin/mu opioid agonists on stress-related behavior

Endorphins (endogenous morphine) are endogenous opioid peptides that function as neurotransmitters by acting on the mu receptors. The possible involvement of β-endorphin in stress-related psychiatric disorders, including depression, PTSD and fear conditioning has been reported (Merenlender-Wagner et al., 2009). Specifically, the central endorphinergic neurons originate from two nuclei, the arcuate nucleus in the posterior hypothalamus and nucleus tractus solitarius in the brain stem. The endorphinergic neurons have extensive projections to other brain areas, including the hippocampus, midbrain and the amygdala, thus, providing a rich network of POMC fibers throughout the brain, particularly to regions associated with stress (Palkovits, 1987; Narita and Tseng, 1998).

2.1. Stress and anxiety

Research evidence suggests the key role of β-endorphin in stress-coping behavior (Grisel et al., 2008; Barfield et al., 2010). Transgenic mice with low β-endorphin exhibit increased anxious behavior and show deficits in coping ability during an inescapable

aversive situation, suggesting the anxiolytic actions of endogenous endorphins (Grisel et al., 2008; Barfield et al., 2010). Mice with low/no β-endorphin have enlarged adrenal glands suggesting that persistent up-regulation of HPA axis may occur with the decreased β-endorphin levels (Rubinstein et al., 1996). The reduction in endogenous opioid tone has been linked with the development of depression (Burnett et al., 1999). Poulin and collaborators demonstrated that the activation of mu-opioid receptors in the intercalated nucleus of amygdala modulates the communication between the basolateral and central amygdala to inhibit stress-induced fear response (Poulin et al., 2006). A very recent study has shown that mice with depleted levels of β-endorphin display a stronger aversion to novelty-feeding in response to stress, suggesting that β-endorphin plays a key role in stress coping behavior (Barfield et al., 2010, 2013). It has been reported that morphine (1 and 5 mg/kg) attenuates acute restraint stress-induced anxiety and potentiates adaptation in response to repeated stress exposure in rats (Joshi et al., 2014; Anand et al., 2012).

Studies have described that genetic differences influence stress coping behavior that is associated with variation in endogenous β-endorphin system (Amir, 1982; Yamada and Nabeshima, 1995; Sarkar et al., 2007). The response of β-endorphin system to acute stress is heritable and the genetic variations in mu-opioid receptors mainly contribute to differential stress coping response (Dai et al., 2005; Schwandt et al., 2011). A recent study examined the anxious behavior of transgenic mice with varying capacities to synthesize β-endorphin in response to stress. The animals with low/no β-endorphin displayed a stronger aversion to novelty-suppressed feeding test following stress exposure. The above findings suggest that stress induces the release of β-endorphin to promote adaptation at the endocrine and behavioral level, and in the absence of β-endorphin, the over-activation of HPA axis may contributes to maladaptive behavior. Therefore, it is proposed that β-endorphins play an important role in stress-coping behavior and that genotypic variability in the β-endorphin system may contribute to the heritable differences in stress reactivity and vulnerability (Barfield et al., 2013).

Stress-induced β-endorphin release may be attributed to increase in CRH secretion that in turn increases the expression of the POMC gene in the anterior pituitary to produce ACTH and β-endorphin (Charmandarie et al., 2005). In turn, β-endorphin attenuates the stress response, including stress-induced nociception by inhibiting the secretion of CRH through a negative feedback mechanism (Nakagawasai et al., 1999) (Fig. 2). Curtis et al. described that both CRH and opioids are involved in fine tuning the LC activity during stressful conditions. The activation of opioid afferents tends to restrain the actions of CRH and facilitates the recovery to pre-stress levels (Curtis et al., 2012).

2.2. Post-traumatic stress disorder (PTSD)

A growing body of literature addresses the important relationship between morphine and post-traumatic stress (Holbrook et al., 2010; Nixon et al., 2010; Szczytkowski-Thomson et al., 2013). Administration of morphine following a traumatic event reduces the severity of symptoms and the risk of PTSD development (Bryant et al., 2009; Stoddard et al., 2009). Bryant and collaborators described that acute administration of morphine inhibits the development of fear conditioning following a traumatic injury, suggesting that morphine may be employed as a preventive strategy to reduce the development of PTSD (Bryant et al., 2009). Nixon and coworkers documented that morphine reduces the development of PTSD in children experiencing a traumatic event and the reduction in PTSD symptoms is positively correlated with morphine dosage (Nixon et al., 2010). Stoddard and coworkers described a correlation between the morphine usage and PTSD development in young children (1–4 years) admitted to pediatric burn center. Treatment with morphine decreased the development of post-traumatic symptoms, assessed 3–6 months after the burn event (Stoddard et al., 2009). A clinical study by Holbrook and collaborators described that the use of morphine (2–20 mg) in the US military personnel after a combat injury reduces the risk of PTSD development (Holbrook et al., 2010). A very recent study has also described a lower prevalence rate of PTSD in patients with traumatic brain injury who received intravenous morphine within hours of injury (Melcer et al., 2014). A recent study documented that the repeated administration of morphine, but not a single dose, inhibits the enhancement of fear learning in PTSD model. The authors proposed that administration of morphine following a traumatic event may obstruct the memory consolidation and associated fear learning that are necessary for the development of PTSD (Szczytkowski-Thomson et al., 2013) (Table 1).

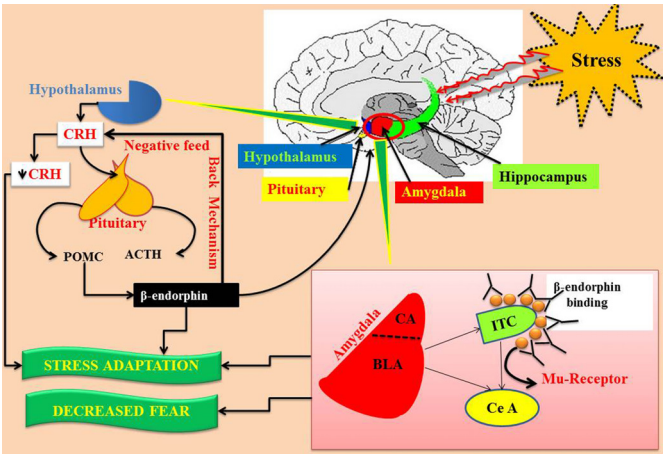

Fig. 2. Role of brain derived β-endorphin (mu receptor agonists) in stress adaptation. Stress enhances the release of CRH from hypothalamus to increase the expression of the POMC gene in the anterior pituitary that in turn is converted to ACTH and β-endorphin. The latter binds to mu-opioid receptors in the intercalated nucleus of amygdala to decrease fear response and produce stress adaptation. β-Endorphin inhibits the CRH release by a negative feedback mechanism, which may also contribute in attenuating stress response.

Table 1
Traumatic stress attenuating effects of morphine in experimental and clinical conditions of PTSD.

Sr. No.	Intervention	Response	Reference
1.	Morphine	Limits fear conditioning after traumatic injury	Bryant et al. (2009)
2.	Morphine	Reduces the development of PTSD in children experiencing a single traumatic event	Nixon et al. (2010)
3.	Morphine	Decreased post-traumatic symptoms assessed 3–6 months after the burn event	Stoddard et al. (2009)
4.	Morphine	Reduces the risk of subsequent PTSD development in US military personnel after combat injury	Holbrook et al. (2010)
5.	Repeated administration of morphine (not with single dose administration)	Inhibits the enhancement in fear learning in another context suggests that morphine's mechanism of action is related to consolidation processes occurring around that time	Szczytkowski-Thomson et al. (2013)

2.3. Learning and memory

Research data demonstrates the interactions between stress and opioids in modulating the learning and memory processes (Homayoun et al., 2003; Yang et al., 2004). Sanders and collaborators demonstrated impairment in stress-induced acquisition of fear learning in mu-opioid receptors deleted mice, suggesting that activation of these receptors is critical in the fear learning process (Sanders et al., 2005). Earlier studies had described that the activation of mu-opioid receptor either by endogenous opioids or exogenous agonists (morphine) enhances the excitability of the hippocampal pyramidal cells and dentate gyrus granule cells by facilitating long term potentiation (LTP) (Simmons and Chavkin, 1996). However, in contrast to these reports, studies have also shown that opioids may impair the memory during stressful conditions. A microinjection of morphine into the amygdala or hippocampus has been shown to impair stress-induced contextual fear conditioning (Westbrook et al., 1997). Furthermore, as described earlier, the ability of morphine to attenuate the development of PTSD following a traumatic event has been attributed to obstruction in memory consolidation and fear learning processes (Bryant et al., 2009; Stoddard et al., 2009; Szczytkowski-Thomson et al., 2013).

3. Effect of dynorphin system on stress-related anxiety and depression

The multiple active forms of dynorphin including dynorphin A, dynorphin B, and α/β-neo-endorphin are produced from the precursor prodynorphin by an enzyme proproteinconvertase. Dynorphin A and B are primarily present in the hypothalamus, medulla, pons, mid-brain, and spinal cord. Dynorphins exert their effects primarily through G-protein-coupled κ-opioid receptors, K_1 and K_2. Although all dynorphin primarily produce their actions by interacting with κ receptors, these peptides also have some affinity for mu- and δ-opioid receptors (DOR) (Valentino and Bockstaele, 2008).

Studies have shown that stress induces dynorphin release, which subsequently activates κ receptors in the central nervous systems to induce anxiety and depression (Hollt et al., 1980; Mague et al., 2003; McLaughlin et al., 2003; Van't Veer and Carlezon, 2013). The literature evidences the association between dynorphin and dysphoria; therefore, the role of dynorphin has also been investigated in the development of depression. The repeated exposure of immobilization stress decreases the motivational behavior in animals and correlate with changes in the dynorphin/κ-opioid receptor system in the different brain regions (Lucas et al., 2011). Shirayama and coworkers documented the importance of both dynorphin A and B in stress-induced depression and reported that during "learned helplessness", the levels of dynorphin A and B are increased in the hippocampus and nucleus accumbens regions. Furthermore, administration of nor BNI (KOR antagonist) was shown to promote recovery from the learned helplessness suggesting that the release of dynorphin is responsible for stress-induced depression (Shirayama et al., 2004). A single (2 h) or repeated exposures (2 h × 10 days) of immobilization stress increases the mRNA levels of κ-opioid receptors in the striatal and nucleus accumbens regions of rats. The κ-opioid receptor related transcriptional changes are diminished only after a longer recovery period (about 9 days) and remain unchanged after a shorter recovery period. Consequently, it is proposed that the prolonged inescapable stress alters the motivational system to produce learned helplessness and dysphoria, which is attributed to an increase in dynorphin in the striatal region (Lucas et al., 2011). Other research studies have also documented that the activation of dynorphin/κ-opioid receptor system may

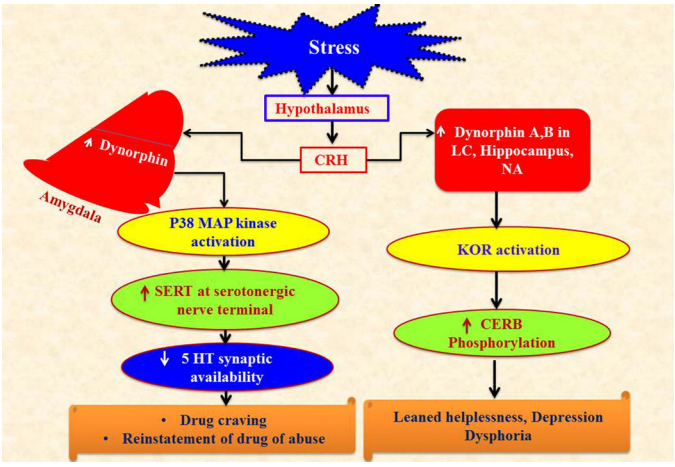

Fig. 3. Role of dynorphin system in stress-induced increase in drug craving, reinstatement of drug of abuse, learned helplessness, dysphoria and depression. Stress enhances the release of CRH from the hypothalamus that increases the levels of dynorphin A and B in the locus coeruleus, hippocampus and nucleus accumbens regions to activate the kappa opioid receptors and trigger the phosphorylation of CREB which in turn produces learned helplessness, dysphoria and depression. In amygdala, increased dynorphin levels stimulate p38α MAPK, which subsequently causes the translocation of the serotonin transporter to the synaptic terminals of serotonergic neurons and decreases the 5HT synaptic availability to produce drug craving and reinstatement of drug of abuse.

be involved in producing prolonged inescapable stress-induced depression-like behavior in rodents (Land et al., 2008). Chartoff and coworkers documented that the antidepressant effects of desipramine in the swim stress test are accompanied by a decrease in dynorphin expression and CREB phosphorylation in the nucleus accumbens, and are independent of the norepinephrine or other monoaminergic inputs (Chartoff et al., 2009). Research evidence suggests that stress activates the dynorphin/κ-opioid receptor system to trigger the intracellular signaling involving the activation of ERK/CREB pathway (Bruchas and Chavkin, 2010) (Fig. 3).

The activation of the κ-opioid receptor system in the LC region is also important in the development of stress-related problems as an increased gene expression of κ-opioid receptors has been documented in this region of Wistar Kyoto rats (a strain particularly useful for studying stress-related behavior) (Pearson et al., 2006). It is also suggested that CRH activates the dynorphin/κ-opioid receptor system in the mouse basolateral amygdala to produce anxiety-like behavior as pretreatment with κ-opioid receptor antagonist (norbinaltorphimine) is reported to block stress/CRH-induced increase in anxiety (Bruchas et al., 2009). Administration of KOR antagonist 2-(3,4-dichlorophenyl)-N-methyl-N-[(1S)-1-(3-isothiocyanatophenyl)-2-(1-pyrrolidinyl) ethyl] acetamide hydrochloride (DIPPA) produces anxiolytic effects in two different strains of rats, Wistar Kyoto and Sprague Dawley (Carr and Lucki, 2010). Furthermore, administration of norbinaltorphimine (a selective KOR antagonist) prevents stress-induced decline in learning and memory. Dynorphin gene-disrupted mice do not show the learning and memory deficits in response to stress exposure, suggesting that stress-induced activation of kappa opioids receptors is critical to produce deficits in a novel object recognition test (Carey et al., 2009).

4. Role of enkephalin in stress and associated behavior

Enkephalin is distributed throughout the limbic system, including the extended amygdala, cingulate cortex, entorhinal cortex, septum, hippocampus, and the hypothalamus (Drolet et al., 2001). The met-enkephalin peptide sequence is coded by the enkephalin gene; while the sequence of leu-enkephalin peptide is coded by

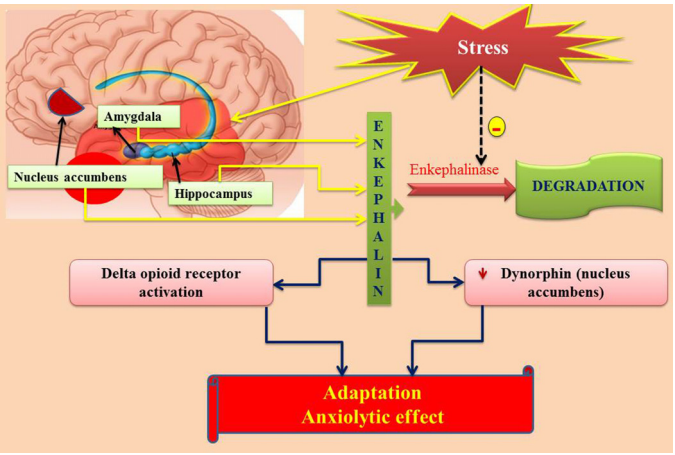

Fig. 4. Adaptogenic and anxiolytic effects of brain-derived enkephalin. Stress induces increased release ofenkephalin in the amygdala, nucleus accumbens and hippocampus to produce delta opioid receptor activation and decrease dynorphin levels in the nucleus accumbens, which are responsible for adaptive and anxiolytic effects.

both enkephalin and dynorphin genes. The POMC also contains met-enkephalin sequence on the N-terminus of β-endorphin, but the endorphin peptide is not processed into enkephalin. The latter demonstrates its action by acting on the delta opioid receptors (Amir, 1982).

Enkephalin system plays an important role in promoting stress adaptation in an organism (Van Loon et al., 1990). The decreased functioning of the enkephalin system produces depression-like symptoms and accordingly, an increase in enkephalin signaling is therapeutically explored in the treatment of depression. Chronic immobilization stress (21 days) has been shown to increase the expression of enkephalin and delta opioid receptors in the hippocampus region of rats (Chen et al., 2004). During acute stress exposure, the reduced activity of soluble enkephalinase in the hippocampus and membrane enkephalinase in the amygdala increases the availability and duration of action of enkephalins to produce anxiolytic actions (Hernández et al., 2009; Kung et al., 2010). Furthermore, preproenkephalin knockout mice are more sensitive to traumatic stimuli, and develop more severe anxiety and depressive symptoms, suggesting the anti-anxiety influence of enkephalin (Lishmanov et al., 2012). In individuals vulnerable to stress, the decreased mRNA expression of enkephalin in the posterior basolateral nucleus of amygdala has been documented. Furthermore, the specific knockout of enkephalin genes in this region increases the anxiety-like behavior. Accordingly, the authors suggested that the enkephalin system in the basolateral nucleus of amygdala is involved in producing specific neuro-adaptation and resilience (Bérubé et al., 2014). In another study, the same group of scientists reported the decrease in mRNA expressions of enkephalin in the basolateral nucleus of amygdala and an increase in mRNA levels of dynorphin in the dorsal and media shell of nucleus accumbens in stress vulnerable rats. It suggests that enkephalin facilitates the behavioral adaptation in chronic social stress model by opposing the actions of dynorphin (Bérubé et al., 2013). A very recent study has documented that the down-regulation of enkephalin in the nucleus accumbens region triggers the development of anhedonia in a chronic stress model. The decrease in preproenkephalin mRNA expression in the nucleus accumbens region is associated with the development of anxiety in restraint stress-subjected rats suggesting that the down-regulation of enkephalin in the nucleus accumbens might underlie the susceptibility to chronic stress (Poulin et al., 2014) (Fig. 4).

5. Role of nociceptin on stress-related behavior

Nociceptin (orphanin FQ), a relatively newly discovered endogenous heptadecapeptide, is a 17-amino acid peptide, which shows structural homology to opioid peptides, particularly to dynorphin A. Nociceptin/orphanin FQ (N/OFQ)-expressing neurons are present in the hypothalamus and limbic system to regulate the HPA axis and stress response (Mollereau et al., 1994; Witkin et al., 2013). Nociceptin binds to the opioid receptor like-1 receptors (ORL1 receptors), also termed as nociceptin receptors (NOP)/orphanin FQ receptors, and these receptors lack affinity toward the traditional opioid receptors (Wick et al., 1994).

Studies have demonstrated the key role of nociceptin in regulating the stress-associated behavioral and psychological alterations (Witkin et al., 2013). N/OFQ is essentially an anxiolytic peptide and plays an important role in stress adaptation. Transgenic mice lacking the OFQ/N precursor proteins exhibit anxiety-like behaviors and do not habituate to repeated exposure to stress (Reinscheid and Civelli, 2002). A number of nociceptin agonists, including N/OFQ and Ro 64-6198 produce anxiolytic-like effects in the preclinical models of anxiety (Goeldner et al., 2012; Delaney et al., 2012). Goeldner and coworkers reported that the N/OFQ peptide receptor agonists produce dose-dependent anxiolytic effects similar to benzodiazepine receptor agonists (Goeldner et al., 2012). Both acute and chronic restraint stress produces time-dependent changes in the preproN/OFQ transcript expression in the hippocampus, medio-dorsal forebrain and hypothalamus. Furthermore, acute and chronic stress induces differential changes in the ppNN/OFQ expression, with their decreased expression in the central amygdala in response to acute stressor and increased expression in the bed nucleus and reticular thalamus in response to a repeated restraint stressor (Delaney et al., 2012). Injection of N/OFQ in the central nucleus of amygdala is shown to significantly and selectively reduce anxiety-like behavior (in the elevated plus maze test) in restraint rats, suggesting that acute stress activates the N/OFQ system in this brain region to produce anti-stress effects (Ciccocioppo et al., 2014). In response to acute restraint stress, the enhanced expression of N/OFQ in the CA1, CA3, and dentate gyrus of the hippocampus and rise in the plasma corticosterone levels has been documented. However, restraint stress failed to increase the N/OFQ expression in adrenalectomized rats, suggesting that the increased expression of N/OFQ may be secondary to an increase in plasma corticosterone in stress-subjected rats (Nativio et al., 2012).

It has been reported that bilateral microinjections of N/OFQ into the rat perifornical area of the lateral hypothalamus abolish stress-induced analgesia and it has been proposed that N/OFQ attenuates immobilization/restraint stress-induced analgesia via inhibition of hypocretin/orexin (Hcrt) neurons in the lateral hypothalamus (Gerashchenko et al., 2011). In response to a single-prolonged stress (an animal model for PTSD), increased levels of N/OFQ in the CSF have been correlated with the development of anxiety, hyperalgesia and allodynia (Zhang et al., 2012). It has been shown that N/OFQ antagonizes a CRH-induced increase in GABAergic transmission in the central amygdala in alcohol-dependent rats. Therefore, it has been hypothesized that nociceptin may produce anxiolytic effects by inhibiting the actions of CRH (Cruz et al., 2012). In contrast, Nazzaro and others demonstrated that the potent inhibitory effects of N/OFQ on the dorsal raphe nuclei are independent of CRH and GABA (Nazzaro et al., 2009) (Fig. 5).

6. Influence of gender on stress modulatory role of opioids

There have been studies suggesting that ovarian hormones alter the levels of enkephalin in hippocampal mossy fiber pathway in

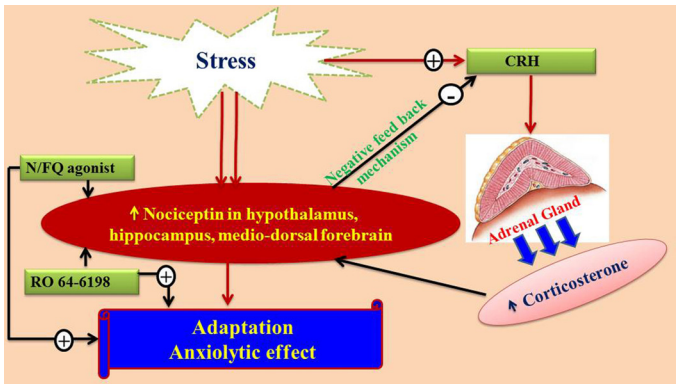

Fig. 5. Adaptogenic and anxiolytic effects of brain-derived nociceptin. Stress increases the nociceptin levels directly in the hypothalamus, hippocampus and medio-dorsal forebrain regions to produce anxiolytic and adaptive effects. The nociceptin levels are also increased indirectly through increased release of CRH and corticosterone, which in turn inhibits the CRH release and prevents HPA axis overactivation by negative feed mechanism. Administration of nociceptin agonists including N/OFQ and Ro 64-6198 produces anxiolytic-like effects.

females (Torres-Reveron et al., 2008) and dynorphin immunoreactivity in the hippocampus (Torres-Reveron et al., 2009). The mossy fiber-CA3 pathway is the most stress vulnerable region in males, and is rich in opioid peptides and receptors as well as gonadal steroid receptors (Drake et al., 2007a,b). Ovarian hormones influence corticotropin releasing factor receptor colocalization with delta opioid receptors in the CA1 pyramidal cell dendrites (Williams et al., 2011). Furthermore, ovarian hormones, particularly estrogens, also alter the mu-opioid receptor binding throughout the hippocampus. It has been shown that prenatal exposure to morphine selectively alters the density of mu-opioid receptors in the hippocampus of adult female (Slamberová et al., 2003). Accordingly, the studies have shown that gender and fluctuations in estrogen levels modulate the effects of opioids on stress-associated behavior. Research data demonstrates that chronic stress differentially alters the cognitive process in male and females. In contrast to the impaired cognition in male rats, females exhibit preserved memory following stress exposure (Bowman et al., 2003; Bowman, 2005). In males, chronic stress impairs learning, decreases LTP, and produces the atrophy of CA3 pyramidal cell dendrites of the hippocampus (Magariños et al., 1997; McEwen and Milner, 2007). Conversely, chronic stress neither impairs spatial learning performance (particularly in the proestrus phase) nor produces deleterious morphological changes in the hippocampus of females (Galea et al., 1997; Luine, 2002; McEwen and Milner, 2007). Milner and collaborators correlated the differential effects of chronic stress on the memory of females and males to the density and trafficking of mu-opioid receptors (availability of opioid receptor pool) in the hippocampal parvalbumin (PARV)-containing GABAergic interneurons in the hilus of the dentate gyrus of hippocampus. Results demonstrated that chronic stress differentially decreases the PARV-labeled cells in males, without any significant effect in females (Milner et al., 2013). Other studies have described that activation of mu-opioid receptors in the hippocampus region inhibits the GABAergic transmission to facilitate LTP and memory formation (Drake et al., 2007a,b). Accordingly, Milner and colleagues proposed that the disruption of PARV neurons (having mu-opioid receptors) following chronic stress may be responsible for memory deterioration in males. Conversely, the maintenance of PARV neurons in females during chronic stress may be responsible for maintenance of LTP and preservation of memory (Milner et al., 2013). In contrast to chronic stress, acute stress is associated with higher immunoreactivity of phosphorylated mu opioid receptors in the dentate gyrus region of hippocampus in males as compared to females at proestrus and estrus stage (high estrogen stages) (Gonzales et al., 2011). Milner et al. also demonstrated the differential effects of acute stress on mu-opioid receptors in males and females. In males, an increase in mu opioid PARV-labeled cells was demonstrated in response to acute stress; however, a decrease in mu opioid PARV-labeled cells was reported in females (Milner et al., 2013). The same group of workers described the increased immunoreactivity of phosphorylated dynorphin receptors in the stratum radiatum of CA2/CA3a of hippocampus in estrus females (elevated estrogen and progesterone) as compared to proestrus and diestrus females and males. However, acute immobilization stress was shown to abolish the increased immunoreactivity of dynorphin receptors in the estrous cycle phase (Burstein et al., 2013).

Numerous research studies have recognized the positive interfacing between the endogenous opioid system and sex hormones on stress reactivity (Allen et al., 2014). Allen and coworkers demonstrated that estrogen modulates the blood pressure through endogenous opioids in stressful conditions. It was shown that stress increases the blood pressure in women taking estrogen with an intact opioid receptor system and blockade of opioid receptors with naltrexone decreases blood pressure, suggesting that estrogen mediates its effects on blood pressure by activating opioid receptors (Allen et al., 2014). In consistent with the studies of premenopausal women, the same group of workers demonstrated the interactions between estrogen and opioids in postmenopausal women. The postmenopausal women on estrogen therapy and with intact opioid receptors showed the largest systolic blood pressure responses to psychological stress, compared with all other conditions. The interaction between estrogen and endogenous opioids may be responsible for the sex differences in opioid effects on stress reactivity in younger premenopausal women (Allen et al., 2014).

The variation in stress-induced analgesia with fluctuations in gender-specific hormones also suggests the significance of opioid-estrogen interactions (Butler and Finn, 2009). The circulating estrogen influences the pain sensitivity response in a cold pressor test (opioid-related behavior) during stressful conditions. Premenopausal women (with higher circulating estrogen) exhibit decreased pain sensitivity following naltrexone administration compared to postmenopausal women (with low estrogen), suggesting that the circulating estrogen influences the actions of opioids to modulate stress-induced analgesia (al'Absi et al., 2004). Other studies have also shown the influence of gender and estrogen on pain-related changes during stress exposure. Stress-induced analgesia is more profound in males than in females suggesting that males are more sensitive to stress than females (Kimoto et al., 2013). It has been reported that kappa opioid receptor-mediated anti-nociceptive and anti-hyperalgesic effects are enhanced by exogenous or endogenous estrogen in the females rats (Lawson et al., 2010). The intensity and unpleasantness of cold-induced pain following a psychological stress was shown to be significantly increased in naltrexone administered women as compared to men (Frew and Drummond, 2007). Larauche et al. demonstrated that acute and repeated water avoidance stress-induced visceral analgesia is naloxone-dependent in females, but naloxone-independent in males (Larauche et al., 2012). In contrast to acute stress-induced analgesia (Carvalho-Costa et al., 2014; Ghasemzadeh and Rezayof, 2015), chronic stresses may contribute to hypersensitivity to pain known as stress-induced hyperalgesia (Dai and Ma, 2014). As in stress-induced analgesia, there is also a significant impact of gender on stress-induced hyperalgesia. Recently, Gamaro et al. studied the influence of gender on chronic variable stress-induced hyperalgesia and reported that male rats show a decrease in tail-flick latency, while females demonstrate an increase in this parameter (Gamaro et al., 2014).

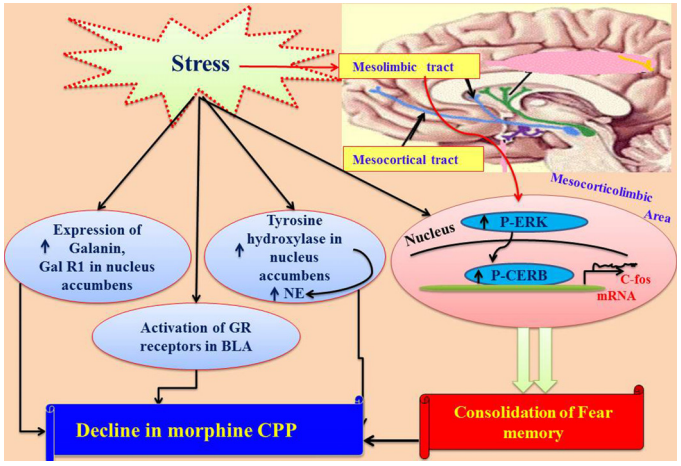

Fig. 6. Stress-induced decline in morphine CPP. Stress increases the mRNA expression of galanin, GalR1, tyrosine hydroxylase and norepinephrine in nucleus accumbens to decrease morphine-CPP. Stress induced activation of glucocorticoid receptors in the basolateral amygdala (BLA) also contribute in decreasing morphine CPP. Stress increases the ratio of phosphorylated extracellular signal-regulated kinase (p-ERK) which triggers the phosphorylation of CREB to increase the c-fos levels in the mesocorticolimbic dopaminergic system. Stress-triggered ERK/CRB signaling contributes in consolidating the fear memory and decline in morphine CPP.

7. Effect of stress on morphine conditioned place preference (CPP)/fear conditioning

7.1. Stress-induced modulation of morphine conditioned place preference (CPP)

CPP is a type of Pavlovian conditioning, which is employed by different scientists to measure the motivational effects of addictive drugs, with reinforcing properties such as morphine. Numerous studies have demonstrated that stress varying in intensity and duration inhibits morphine-induced CPP (Papp et al., 1992; Haghparast et al., 2013). Papp and coworkers demonstrated that chronic exposure to mild unpredictable stress paired with morphine suppresses the acquisition of preferences for morphine without altering picrotoxin or naloxone-induced place aversion. Thus implying that stress specifically impairs the rewarded behavior without causing a general impairment of associative learning (Papp et al., 1992).

Recently, Haghparast and coworkers also demonstrated that the application of sub-chronic forced swim stress (not acute) decreases the conditioning scores in morphine CPP tests (Haghparast et al., 2013). In the same study, the combined application of stress with morphine was shown to increase the p-ERK/ERK ratio, p-CREB/CREB ratio, and c-fos levels in the mesocorticolimbic dopaminergic system. Since both CREB (a transcriptional factor), and c-fos (immediate early gene), are downstream targets of ERK (Qi et al., 2008), an increase in p-CREB/CREB ratio, and c-fos levels during concurrent application of stress and morphine may be secondary to ERK activation (Haghparast et al., 2013). The authors proposed that up-regulation of the ERK/CREB pathway in the mesocorticolimbic region results in memory formation, which in turn may inhibit morphine-induced place preference during concurrent stress exposure (Haghparast et al., 2013) (Fig. 6). Other studies have shown the important role of ERK signaling in memory formation and inhibition of ERK has been shown to prevent the formation of long lasting memories of an event including fear (Imbe et al., 2004; Shiflett and Balleine, 2011). In another recent study, García-Carmona and coworkers demonstrated the activation of brain stress system following a morphine-conditioned place preference test in mice. In this study, an increase in CREB expression in the PVN, central amygdala and BNST regions; increase in the number of CRH neurons in the PVN, and enhanced CRH-immunoreactivity fibers in the nucleus tractus solitarius (NTS) and ventral tegmental area (VTA) regions was demonstrated following morphine-induced CPP paradigm. This suggests that exposure to morphine activates the CREB signaling pathways to increase CRH in the brain stress system and this signaling may be involved in memorizing the events during conditioning paradigm (García-Carmona et al., 2013).

Attarzadeh and coworkers demonstrated that physical stress (forced swim stress) and the administration of corticosterone reduces the acquisition (but not expression of) morphine-induced CPP. Furthermore, the blockade of glucocorticoid receptors in the basolateral amygdala diminishes the inhibitory effects of stress or corticosterone on acquisition of morphine CPP, suggesting the involvement of glucocorticoid receptors of the basolateral amygdala region in modulating morphine CPP during stress exposure (Attarzadeh-Yazdi et al., 2013). In another study, chronic restraint stress was shown to impair the formation and facilitate the extinction of morphine CPP. Furthermore, chronic stress was shown to increase the mRNA expression of galanin, galanin receptor 1 and tyrosine hydroxylase in the nucleus accumbens. Therefore, it was proposed that the activation of the galanin system with corresponding changes in the noradrenergic system may modulate stress-induced changes in morphine CPP (Zhao et al., 2013).

In contrast to earlier reports of reduction in morphine-induced CPP during concurrent stress, Li and coworkers demonstrated that chronic foot-shock exposure (not acute foot shock) or corticosterone treatment (3 and 5 mg/kg, i.p.) potentiates morphine-induced CPP. Furthermore, there was a rise in dopamine levels in the nucleus accumbens region, suggesting that the increase in dopamine levels in this region may be responsible for potentiating morphine CPP (Li et al., 2007). Other studies have shown the differential effect of stress on morphine CPP depending on the controllability of stressors and it has been shown that inescapable stress, but not escapable stress, potentiates morphine CPP (Rozeske et al., 2009). The microinjection of $GABA_A$ agonist, muscimol, in the medial prefrontal cortex led escapable stress to potentiate morphine CPP similar to that of inescapable stress. On the other hand, microinjection of $GABA_A$ antagonist (picrotoxin) blocked the potentiating effects of inescapable stress on morphine CPP. Based on these studies, it may be suggested that during stress exposure, the inhibition of the medial prefrontal cortex through the GABA inhibitory neurotransmitter may potentiate stress-induced morphine CPP and activation of the same brain region through blockade of GABA neurotransmitter may in turn inhibit morphine CPP. Accordingly, it is proposed that the medial prefrontal cortex regulates the differential expression of morphine CPP following controllable/uncontrollable stress and inactivation of the medial prefrontal cortex is an important brain event in stress-induced morphine CPP potentiation (Rozeske et al., 2009). Furthermore, a recent study by the same group described that prior exposure to escapable tail shock prevents inescapable shock-induced potentiation of morphine CPP and anxiety-like behavior in the form of 'behavioral immunization'. However, administration of muscimol in the medial prefrontal cortex was shown to block behavioral immunization, including non-escapable stress-induced potentiation of morphine CPP, suggesting that the prior experience with escapable stress activates the medial prefrontal cortex and produces long-lasting neural alterations to block inescapable-induced potentiation of morphine CPP (Rozeske et al., 2012) (Fig. 7).

There are contradictory reports regarding the effect of neonatal stress on morphine CPP. Exposure of stress in the early life period (by maternal separation) has been shown to increase the time spent in morphine-paired compartment in rat offsprings, indicating that neonatal stress induces the place preference for mu-opioid receptor agonist (Michaels and Holtzman, 2008). On the contrary,

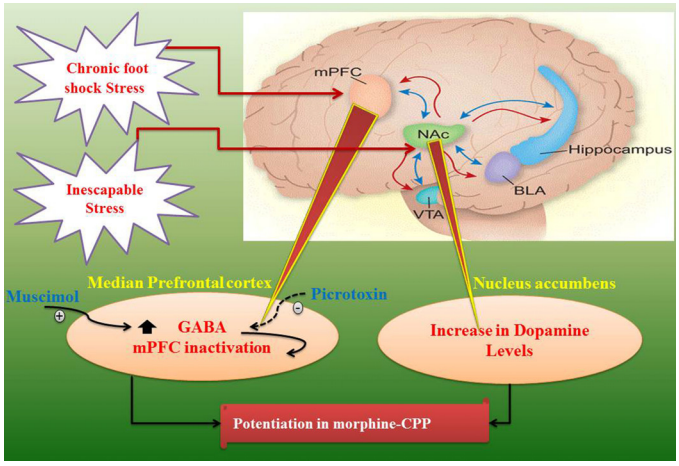

Fig. 7. Inescapable stress and chronic stress-induced potentiation in morphine CPP. Chronic foot shock stress increases the GABAergic transmission and inactivates the median prefrontal cortex (mPFC) to potentiate the morphine induced CPP. Administration of GABA agonist (muscimol) induces mPFC inactivation, whereas GABA antagonist (picrotoxin) inhibits this process. Inescapable stress-induced increase in dopamine levels in nucleus accumbens may also contribute in potentiating morphine CPP.

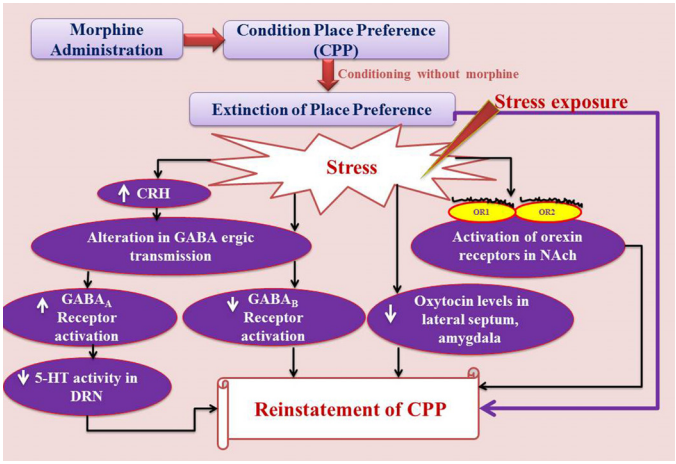

Fig. 8. Stress-induced reinstatement of extinct morphine CPP. Morphine administration induces condition place preference behavior and, conditioning without morphine for prolonged period produces extinction of morphine-CPP. Stress exposure reinstates morphine CPP through various mechanisms including increased release of CRH that alters the GABAergic transmission (increases $GABA_A$ and decreases $GABA_B$ receptor activation); activates orexin receptors 1 and 2 in nucleus accumbens and decreases oxytocin in lateral septum and amygdala.

neonatal exposure to stress/morphine has also been shown to impair morphine-rewarded CPP (Hays et al., 2012; Boasen et al., 2009). The latter group of workers supported the 'stress inoculation hypothesis' whereby stressors experienced in early life prepare animals to tolerate future stress. It was proposed that neonatal stress induces habituation to subsequent handling and thus reduces their arousal and stress responsiveness, including craving for morphine (Hays et al., 2012).

7.2. Effect of stress on morphine CPP reinstatement

Exposure to stress has been shown to reinstate the extinct morphine CPP and it has been related to drug seeking behavior or drug relapse. Scientists have investigated the different mechanisms involved in stress-induced reinstatement of morphine CPP. A recent study investigated the involvement of orexin in the nucleus accumbens shell (NAcSh) in stress-induced drug seeking behavior. The blockade of orexin-1 or orexin-2 receptors in the NAcSh was shown to significantly attenuate stress-induced morphine CPP reinstatement without any effect on morphine priming-induced reinstatement. It suggests that NAcSh is the main brain area in which orexin participates in stress-induced reinstatement to morphine-seeking, with no effect on drug priming-induced relapse of opioid seeking (Qi et al., 2013). During opioid abstinence, the alterations in oxytocinergic system (decreased oxytocin levels and increased oxytocin receptor binding) in the lateral septum and amygdala contribute to the development of anxiety, depression, and social deficits. Administration of oxytocinergic analog carbetocin was shown to attenuate the negative emotional consequences of opioid withdrawal. Furthermore, administration of carbetocin also prevented stress-induced reinstatement to morphine-seeking projecting the oxytocinergic system as a possible target for the treatment of emotional impairment associated with abstinence (Zanos et al., 2013) (Fig. 8). Very recently, Karimi et al. demonstrated that the activation of glucocorticoid receptors in the basolateral amygdala was involved in forced swim stress-induced reinstatement of extinguished morphine CPP (Karimi et al., 2014).

Li and collaborators described that stress inhibits the 5-HT system in the dorsal raphe nucleus via CRH-induced stimulation of GABAergic activity. It was shown that administration of muscimol ($GABA_A$ agonist) in the dorsal raphe nucleus activates the $GABA_A$ receptors to reinstate stress-induced morphine CPP, while bicuculline ($GABA_A$ receptor antagonist) attenuates morphine reinstatement suggesting that $GABA_A$ receptors in the dorsal raphe nucleus predominantly contribute to stress-induced reinstatement of morphine-CPP (Li et al., 2013). Earlier, Staub and collaborators described that exposure to morphine sensitizes the 5-HT system in the dorsal horn neurons to GABAergic inhibitory effects of stress and CRH (Staub et al., 2012). A recent study examined the role of $GABA_B$ receptors in morphine-induced CPP, extinction and stress-induced relapse in chronicstress subjected mice. Administration of baclofen, ($GABA_B$ agonist) blocked chronic stress-induced potentiation of morphine CPP, promoted the extinction, and prevented stress-induced reinstatement of morphine preference. It was proposed that stress may inhibit the functioning of $GABA_B$ receptors to reinstate the extinct morphine preference and accordingly, $GABA_B$ receptor-positive modulators may act as anti-addiction agents in people suffering from chronic stress (Meng et al., 2014).

7.3. Role of dynorphin system in stress modulatory actions on drug craving/conditioned place preference

Studies have shown the role of dynorphin/κ-opioid receptor system in drug craving, therefore, κ-opioid receptor antagonists have been projected as useful therapeutic agents to reduce stress-induced drug craving. Recently, Smith and coworkers reported that repeated forced swim stress activates the dynorphin/κ-opioid receptor system in the amygdala to potentiate the magnitude of drug craving and it is suggested that the activation of dynorphin/κ-opioid receptor system in the amygdala may modulate the rewarding effects of addictive drugs during stressful conditions (Smith et al., 2012). Studies have demonstrated that the activation of dynorphin/κ-opioid receptor (KOR) system by repeated stress exposure/agonist treatment produces place aversion and reinstates extinguished cocaine place preference behaviors. The effects of dynorphin are shown to be mediated through stimulation of p38α MAPK, which subsequently cause the translocation of serotonin transporter to the synaptic terminals of serotonergic neurons (Lemos et al., 2012). Another study by Schindler and coworkers extend the above findings using the serotonin transporter knockout mice and reported that the selective re-expression of serotonin transporter into the dorsal raphe restores the prodepressive effects

of κ-receptor activation. This suggests that stress-induced activation of the dynorphin/κ-receptor system produces a transient increase in serotonin transport that may be responsible for the stress-induced potentiation of cocaine reward (Schindler et al., 2012).

A recent study determined the role of the dynorphin/κ-receptor system in regulating anxiety-related behaviors during an extended period of abstinence from ethanol in animals with a history of ethanol dependence. The exposure of stress to alcohol-dependent rats enhanced the responsiveness to stress to produce anxiety-like behavior. Furthermore, administration of κ-receptor antagonist, nor-binaltorphimine (nor-BNI), was shown to attenuate the increased stress responsiveness suggesting that alcohol withdrawal-associated behavior is regulated (at-least partly) by dynorphin/κ-opioid receptor system (Gillett et al., 2013). Studies have also investigated the role of the dynorphin/κ-opioid receptor system in drug craving during adulthood in neonatal stress-subjected animals. Michaels and Holtzman studied the effects of maternal separation, a model of early postnatal stress, on place conditioning to κ-opioid receptor agonists in rats. Maternally separated animals spent significantly more time in the spiradoline (kappa-opioid agonist)-paired compartment as compared to non-stressed animals, indicating a place preference to kappa-opioid agonist in neonatal stress-subjected animals. It indicates that early postnatal stress induces the significant neuronal changes to affect the reward value of kappa-opioid agonists in the place preference conditioning paradigm (Michaels and Holtzman, 2008). Vien and coworkers reported that neonatal stress increases the activation of kappa opioid receptors, and combined exposure of neonatal stress and morphine further enhances the kappa opioid receptor signaling (Vien et al., 2009). Recently, same group of workers reported that kappa opioid receptor stimulation increases neonatal stress-induced cocaine CPP response in adult mice (Hays et al., 2012).

7.4. Effect of stress on other psychoaddictive drugs-induced CPP and reinstatement

In addition to morphine CPP, there have been studies showing that stress influences other psycho-addictive drugs-induced CPP and reinstatement. Like morphine CPP, acute and chronic stress produces differential effects on psychoaddictive drugs-induced CPP. A study by Garcia-Pardo et al. demonstrated that exposure to acute social defeat stress inhibits 3,4-methylenedioxymethylamphetamine-induced CPP in mice (García-Pardo et al., 2014); while Smith and collaborators described that repeated force swim stress potentiates nicotine-induced CPP (Smith et al., 2012). Furthermore, stress exposure is also suggested to evoke reinstatement of extinct CPP to addictive drugs. Al-Hasani et al. described that acute exposure to a stressor potentiates the reinstatement of cocaine and nicotine-induced CPP (Al-Hasani et al., 2013). Leão et al. demonstrated that exposure of acute restraint stress reinstates nicotine-induced CPP in rats after 15 days of extinction (Leão et al., 2009). Moreover, exposure of acute forced swim stress has also been shown to evoke reinstatement of cocaine CPP. Furthermore, CRH 1 receptor antagonist (antalarmin) prevents stress-induced increase in CRH mRNA in the BNST during reinstatement of CPP, suggesting that the activation of CRH neurons induces the reinstatement of cocaine-induced CPP (McReynolds et al., 2014). A modified force swim test paradigm has also been shown to reinstate nicotine-induced CPP, 3 days after extinction (Jackson et al., 2013). A recent study by Bahi and Dreyer also described that chronic exposure to psychosocial stress exacerbates reinstatement of ethanol induced CPP (Bahi and Dreyer, 2014). Accordingly, the role of stress in modulating morphine CPP may be viewed in a broader context of stress and addiction.

8. Integrative hypothesis

8.1. Effect of different opioids on stress-related behavior

The activation of mu-opioid receptors in the amygdala either by endogenous endorphin or exogenous morphine is generally associated with stress coping behavior (Grisel et al., 2008; Barfield et al., 2010; Rubinstein et al., 1996). Stress-induced release of CRH triggers the release of endorphin that in turn tends to inhibit the over-activation of HPA axis (Nakagawasai et al., 1999). Furthermore, administration of morphine decreases the development of PTSD following a severe traumatic event (Bryant et al., 2009; Stoddard et al., 2009) suggesting the anti-stress and beneficial role of mu-opioid receptors. There are contradictory reports regarding the role of mu-opioid receptors on learning/memory during stressful conditions (Sanders et al., 2005; Westbrook et al., 1997; Bryant et al., 2009). However, careful analysis of these reports suggests that the differential actions of opioids on the memory events during stressful conditions are beneficial for an organism. Results from Sander et al. demonstrating that opioids are essential for fear learning is based upon the acute fear learning paradigm in which a single day stressor of moderate intensity was given to induce learning (Sanders et al., 2005). In contrast, the reports of opioids-induced impairment in memory and memory consolidation are derived from chronic stress or PTSD-based studies (Bryant et al., 2009; Stoddard et al., 2009; Szczytkowski-Thomson et al., 2013). During acute stress, endorphins may serve as a general alert mechanism to avoid confounding effects of stress and hence, endorphins may increase the fear learning to avoid the stress exposure. On the contrary, morphine-induced impairment in memory consolidation and associated fear learning during severe traumatic events or chronic stress may be to avoid post-stress aversive effects. It is a well-known fact that the process of memory consolidation is critical in inducing the post-stress aversive effect following a traumatic event. However, the hypothesis suggesting the differential role of endorphins/opioid receptor agonists on learning/memory depending upon the intensity and duration of stressor needs experimental verification.

An increase in enkephalin and delta opioid receptors in the basolateral amygdala and nucleus accumbens tends to produce anti-stress effects (Chen et al., 2004; Hernández et al., 2009; Kung et al., 2010). Furthermore, in response to acute and chronic stress, the levels of nociceptin are increased in the hippocampus; hypothalamus and medio-dorsal fore brain (Delaney et al., 2012) and the rise in nociceptin tends to produce stress adaptation (Cruz et al., 2012; Reinscheid and Civelli, 2002). Therefore, during stressful conditions, the levels of endorphin, enkephalin and nociceptin are increased that tend to produce stress adaptive and anti-stress effects. In contrast to other endogenous opioids, the activation of dynorphin and kappa opioid receptors in the basolateral amygdala, nucleus accumbens, hippocampus and LC produces depression (Shirayama et al., 2004; Chartoff et al., 2009). However, published data reveals that the dynorphin system is primarily activated during prolonged inescapable stress and accordingly, the activation of these receptors is critical in inducing the state of 'dysphoria' and 'learned helplessness' during prolonged stress-induced depression (Land et al., 2008; Lucas et al., 2011). In consideration of this evidence, it may be hypothesized that endorphin, enkephalin and nociceptin are released during the early stages of stress to cope with a stressor; whereas, during inescapable stress, the levels of dynorphin may increase to induce a state of anxiety and depression.

8.2. Effect of stress on drug craving/reward

CPP is a technique used in animal studies to evaluate the preferences for environmental stimuli including drug of abuse and

morphine CPP is used to evaluate the addiction potential of such drugs. Stressors of different intensities and duration modulate morphine CPP. In general, acute and escapable stressors inhibit morphine CPP (Papp et al., 1992; Haghparast et al., 2013); while chronic and inescapable stressors potentiate morphine CPP (Li et al., 2007; Rozeske et al., 2009). The development of dysphoria during chronic and inescapable stress may be responsible for morphine CPP potentiation, which is supported by reports documenting that the activation of dynorphin system induces drug-craving and enhances rewarding functions of addictive drugs (Smith et al., 2012). The activation of the dynorphin system in the amygdala may potentiate the magnitude of drug craving (Smith et al., 2012) by stimulating p38α MAPK followed by an increased expression of serotonin transporters on the synaptic terminals of dorsal raphe (Lemos et al., 2012; Schindler et al., 2012).

Different scientific groups have explored multiple mechanisms that may be involved in stress-induced inhibition of morphine CPP. An increased expression of galanin system, tyrosine hydroxylase and norepinephrine in nucleus accumbens (Zhao et al., 2013); activation of glucocorticoid receptors in the basolateral amygdala (Attarzadeh-Yazdi et al., 2013); increased ratio of pERK/ERK and pCERB/CERB in the mesocorticolimbic area (Haghparast et al., 2013) and blockade of GABA (inhibitory neurotransmitter) in the median prefrontal cortex (leading to its activation) may be involved in stress-induced inhibition of morphine CPP (Rozeske et al., 2009). On the other hand, chronic stress or inescapable stress-induced increase in GABAergic neurotransmission leading to the inhibition of the median prefrontal cortex along with the rise in dopamine levels in the nucleus accumbens may contribute in potentiating morphine CPP (Li et al., 2007; Rozeske et al., 2012).

Furthermore, stress also reinstates the extinct morphine CPP suggesting that stress induces the craving for drugs of abuse (Qi et al., 2013). Stress exposure may reinstate morphine CPP through various mechanisms, including increased release of CRH that alters the GABAergic transmission (increases $GABA_A$ and decreases $GABA_B$ receptor activation) (Li et al., 2013; Meng et al., 2014); activation of orexin receptors 1 and 2 in nucleus accumbens and decreased oxytocin in lateral septum and amygdala regions (Qi et al., 2013).

9. Conclusion

Research studies have documented that endogenous opioids play an important role in regulating the stress response. β-Endorphins and mu receptor agonists tend to reduce the stress response and produce stress adaptation by preventing the over-activation of the HPA axis. Similarly, brain-derived enkephalin and nociceptin are also shown to attenuate anxiety and produce anti-stress effects. In contrast to these findings, a stress-induced increase in dynorphin levels with subsequent activation of kappa opioid receptors produces learned helplessness, dysphoria and depression. Yet stress also influences the response of opioids, including drug craving, and reinstatement of drug of abuse. Stress triggered ERK/CREB signaling in the mesocorticolimbic dopaminergic system; increase in galanin along with norepinephrine in nucleus accumbens region; and activation of glucocorticoid receptors in the basolateral amygdala contribute to consolidating the fear memory and decreasing morphine CPP. Conversely, inescapable stress-induced increases in dopamine levels in the nucleus accumbens and chronic stress-induced increases in GABAergic transmission and inactivation of the median prefrontal cortex contribute in potentiating morphine-induced CPP. Stress exposure reinstates the extinct morphine CPP by altering the GABAergic transmission, activating orexin receptors in the nucleus accumbens and decreasing oxytocin levels in the lateral septum and amygdala.

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