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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).

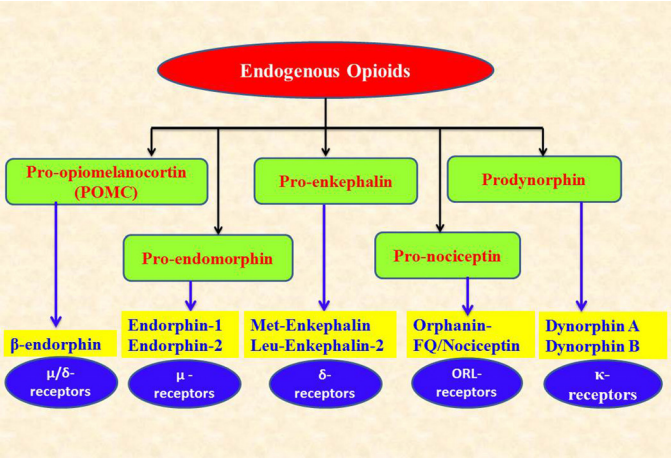

Fig. 1. Endogenous opioids with their precursor molecules and binding receptor sites.

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