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ROLE OF ENDOGENOUS OPIOID SYSTEM IN THE REGULATION OF THE STRESS RESPONSE

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Contents

Abstract

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1. Numerous studies and reviews support an important contribution of endogenous opioid peptide systems in the mediation, modulation, and regulation of stress responses including endocrine (hypothalamo-pituitary-adrenal, HPA axis), autonomic nervous system (ANS axis), and behavioral responses. Although several discrepancies exist, the most consistent finding among such studies using different species and stressors is that opioids not only diminish stress-induced neuroendocrine and autonomic responses, but also stimulate these effector systems in the non-stressed state.

2. A distinctive feature of the analgesic action of opioids is the blunting of the distressing, affective component of pain without dulling the sensation itself. Therefore, opioid peptides may diminish the impact of stress by attenuating an array of physiologic responses including emotional and affective states.

3. The widespread distribution of enkephalin (ENK) throughout the limbic system (including the extended amygdala, cingulate cortex, entorhinal cortex, septum, hippocampus, and the hypothalamus) is consistent with a direct role in the modulation the stress responses.

4. The predictability of stressful events reduces the impact of a wide range of stressors and ENK appears to play an important role in this process. Therefore, ENK and its receptors could represent a major modulatory system in the adaptation of an organism to stress, balancing the response that the stressor places on the central stress system with the potentially detrimental effects that a sustained stress may produce. Chronic neurogenic stressors will induce changes in specific components of the stress-induced ENKergic system, including ENK, δ- and μ-opioid receptors.

5. This review presents evidences for adaptive cellular mechanisms underlying the response of the central stress system when assaulted by repeated psychogenic stress, and the involvement of ENK in these processes.

Keywords: adaptation, anxiety, autonomic nervous system, enkephalin, hypothalamo-pituitary-adrenal axis, opiate, paraventricular nucleus of the hypothalamus.

Abbreviations: adrenocorticotropic hormone (ACTH), angiotensin receptors (AT), autonomic nervous system (ANS axis), bed nucleus of the stria terminalis (BST), central nucleus of the amygdala (CeA), corticotropin releasing factor (CRF), enkephalin (ENK), hypothalamo-pituitary-adrenal (HPA axis), locus coeruleus (LC), medial nucleus of the amygdala (MeA), nucleus of solitary tract (NTS), parabrachial complex (PB), paraventricular nucleus of the hypothalamus (PVH), ventrolateral medulla (VLM).

1. Introduction

The maintenance of homeostasis during stressful conditions is mediated through a complex, highly interactive organization of neuroanatomical pathways in the brain. Specific neurotransmitter systems initiate immune, endocrine, metabolic, physiological, and behavioral changes in response to stress. When an organism is subjected to a stressful condition, a host of stress-related neurotransmitters, including endogenous opioids (mainly enkephalin and endorphin), corticotropin releasing factor, and catecholamines are released to act at multiple levels within the brain. There is strong evidence indicating that endogenous opioids act by attenuating or terminating stress responses as a defensive action of the organism. Therefore, endogenous opioids could represent major modulatory systems in the adaptation of an organism to chronic stress, balancing the response demands that the stressor places on the brain with the potentially detrimental effects that a sustained stress response may produce. The dynamic regulation of neurotransmitters and their receptors is an important component of the process of coping and adapting to stress. A more comprehensive analysis of the opioidergic circuitry and of the regulatory mechanisms involved in the stress response is required to achieve a better understanding of the mechanisms responsible for effective short-term coping with intermittent stress exposure as well as long-term adaptation and restoration in the face of chronic or repeated stress. A failure to regulate the endogenous opioid system appropriately during repeated stress may therefore contribute to stress-related pathology. This review will present evidence of involvement of endogenous opioid in the mediation, modulation, and regulation of stress responses.

2. Stress Circuitry and Stress Adaptation

What is stress? A great deal of attention has been given to define stress. The first question is whether to base the definition on the stressful event or on its biological response (Ursin and Olff, 1993). In this review, we have adopted the convention of differentiating the event from the response. We define a *stressor* as any stimulus, internal or external to an individual, that poses a real or perceived threat to the individual's homeostasis. The subsequent interaction between an individual and the stressor results in a pleiade of physiological and behavioral responses to which we refer operationally as the *stress response*. The general concept of "stress" is used somewhat idiomatically to describe situations or contexts that include both an applied stressor and a behavioral or physiological response to that stressor. When considered as such, it is also apparent that an important component of stress is the subsequent impact on the organism of not only the initiating stimulus, but also the possible detrimental effects of the stress response itself.

The earlier concept of stress as a general adaptation to any demand made on an individual is being replaced by a more differentiated model (McEwen and Stellar, 1993). The stress response is a complex orchestrated response, coded at sensory, motor, endocrine, autonomic, and integrative levels. A number of recent studies have attempted to define the organization of neural pathways that convey stress-related information to the effector systems. The literature suggests that the stress-regulatory circuit activated by a particular stressor is crucially dependent on the stimulus attributes. Stressors were commonly subdivided into physical (or systemic) or psychological (or neurogenic) categories. The central components of the stress response system, especially the pathways involved in the HPA regulation, have been recently revisited in the perspective that various categories of stressors are handled, to some extent, in different ways (Herman and Cullinan, 1997; Herman et al., 1996; Sawchenko et al., 1996). In their recent reviews, Herman *et al* proposed the existence of two generalized stress pathways; limbic-sensitive and limbic-insensitive (Cullinan et al., 1995; Cullinan et al., 1993; Herman et al., 1994; Herman et al., 1989). The limbic stress pathway (named also processive) is recruited by stressors requiring higher-order sensory processing. These stressors require assembly and processing of signals from multiple sensory modalities prior to initiation of a stress response. These processive stressors constitute stimuli that become stressful (or unstressful) only by comparison with previous experience. This refers mainly to the psychological and the neurogenic stressors (including restraint, immobilization, foot-shock). In contrast, the limbic-insensitive pathway is recruted by stressors that represent an immediate threat to homeostasis and does not required limbic structures. The components of the limbic-sensitive pathways include prefrontal cortex, septum, extended amygdala, hippocampus, paraventricular nucleus of the hypothalamus (PVH) and hypothalamic nuclei providing GABAergic inputs to the neuroendocrine PVH (Boudaba et al., 1996; Cullinan et al., 1993; Roland and Sawchenko, 1993) including preoptic area and lateral hypothalamus. In contrast, systemic stressors constitute a direct threat to survival. Consequently, there is a need for rapid transmission of an excitatory signal to PVH, bypassing the potential response delay that may be required for cognitive processing. It can be relayed directly to the PVH by visceral efferent pathways through brainstem circuitry (Ericsson et al., 1994; Kovacs and Sawchenko, 1993; Li et al., 1996). The central components of the systemic-stress pathways include brainstem autonomic nuclei, such as the parabrachial nucleus, nucleus of the tractus solitary, and the ventrolateral medulla (Herman and Cullinan, 1997; Herman et al., 1996; Sawchenko et al., 1996). Although these views are very interesting working hypothesis, these two categories

do not account for situation where a stressor can be a mixture of different components (apart from psychological and physical).

We have recently investigated the specificity of stress adaptation to ascertain whether the psychogenic nature of the stressor or the stressor itself is important in the pattern of expression of the stress response. Therefore, we studied the acute and chronic effects of two different painless neurogenic stressors; immobilization and airjet puff. Indeed, our results support the view that the nature of the stressor is a determining factor in the selection of the neural pathways activated during the stress responses. The use of two different psychogenic stressors (immobilization versus airjet stress) did not reveal significant differences between the pattern of expression of angiotensin receptors (AT_1) within the PVH or locus coeruleus (LC) angiotensin AT_2 receptor following stress exposure (Dumont et al., 1999). The same observation was done for other stress responses such as the induction of Fos within the ventrolateral medulla (Mansi et al., 2000) and the PVH (Dumont et al., 2000). Our results showed that exposure to a heterotypic stressor (but still psychogenic) produced responses similar to the homotypic stressor for both Fos and ENK-Fos in each parvicellular subdivisions, suggesting similar processing of responses to psychogenic stressors. The dramatic reduction of the response in some divisions of the PVH following chronic exposure to psychogenic stress confirmed that adaptation can involve modified immediate early gene activation (Chen and Herbert, 1995; Chung et al., 2000; Mansi et al., 2000; Martinez et al., 1998). Indeed, this may suggest that adaptation to psychogenic stressor may be due to modulation of different characteristics (e.g. time course, nucleus division, phenotype specificity) of neural activity patterns that occur during repeated exposure to the same stressor (Dumont et al., 1999; Helmreich et al., 1999; Mansi and Drolet, 1997; Mansi et al., 2000; Watts and Sanchez-Watts, 1995). Taken together, these studies provide strong evidence that heterotypic stressors produce responses similar to homotypic stressors with respect to some stress responses (Fos, angiotensin receptors expression) suggesting similar processing of stress responses to painless psychogenic stressor.

3. Opioid and Stress

Endogenous opioids and their receptors are ubiquitous and located with varying densities throughout the central, peripheral, and autonomic nervous systems as well as in several endocrine tissues and target organs. This widespread distribution is consistent with the involvement of opioids in a broad range of functions and behaviors, including regulation of pain, reinforcement and reward, release of neurotransmitters, autonomic and neuroendocrine modulation (Akil et al., 1984; Holaday, 1983; Olson et al., 1996; Yamada and Nabeshima, 1995). In fact, these anatomical and functional characteristics argue against conceptualization of opioids as a single, functional unit. Three families of endogenous opioid have been identified to date; the enkephalin, dynorphin and endorphin. Each family derived from different multifunctional precursor polypeptides; proenkephalin, prodynorphin and proopiomelanocortin, respectively. The opioids produce their biological effects through three main types of receptors (all being members of the G-protein-coupled receptors family) referred to as mu (μ), delta (δ) and kappa (κ). The different types of opioid receptors have been defined based on pharmacological and radioligand binding experiments, and more recently by cloning (Mansour et al., 1994; Uhl et al., 1994). In vitro studies indicate that enkephalin peptides have a greater affinity for μ- and δ-opioid receptors, although proenkephalin cleavage products also to κ-opioid receptors

(Quirion and Pert, 1981; Wuster et al., 1981). This review will focus on the involvement of ENKergic system in the neurobiology of stress, more specifically on ENK and its endogenous receptors μ- and δ-receptors.

The distribution of ENK-synthesizing neurons in the brain is widespread and complex. Neurons containing ENK-derived peptides can be found virtually at all brain levels, from the telencephalon to the spinal cord, as extensively described in previous studies using immunohistochemistry and in situ hybridization histochemistry (Fallon and Leslie, 1986; Guthrie and Basbaum, 1984; Harlan et al., 1987; Hurd, 1996; Khachaturian et al., 1983; Menetrey and Basbaum, 1987; Petrusz et al., 1985; Watson et al., 1982). However, not all of these ENK neurons are involved in the neurobiology of stress. ENKergic neurons are present in stress-related regions of the telencephalon, including cerebral and piriform cortex, mPFC (cingulate and infralimbic cortex), central (CeA) and medial (MeA) amygdala, lateral septum, bed nucleus of the stria terminalis (BST) and the preoptic area. In the hypothalamus, perikarya were seen in most nuclei, including PVH. At the level of the brainstem, ENK neurons were identified in the parabrachial complex (PB), the nucleus of solitary tract (NTS) and the ventrolateral medulla (VLM). The distribution of ENK fibers and terminals is roughly similar to that of neuronal perikarya. Dense ENK innervation was found in the PB, NTS, and the VLM which are nuclei involved in autonomic regulation. A moderate innervation was also found in PVH, median eminence, CeA, MeA, and LC.

Each opioid receptor type demonstrates a distinct anatomical distribution determined previously by binding studies (Blackburn et al., 1988; Mansour et al., 1987) and, more recently, by in situ hybridization histochemistry (Mansour et al., 1995; Mansour et al., 1994). In relation with the structures that are involved in the neurobiology of stress, cells expressing μ-receptor are distributed in regions such as the septum, BST, hippocampus (dentate gyrus), CeA, MeA, medial preoptic area, LC, PB, NTS, and dorsal motor nucleus of the vagus. Neurons expressing δ-receptors were located in hippocampus, amygdala, and VLM. Therefore, it appears that the majority of stress-related nuclei receive ENKergic innervation, or contain ENK perikarya. Thus, depending on the receptors expressed in these various stress-related nuclei, there may be qualitative, quantitative, and functional difference in the effects and thus, roles for ENK.

Enkephalin and its receptors may exert their action on the HPA axis and the ANS which are the two major effector systems that serve to maintain homeostasis during exposure to stressors (Howlett and Rees, 1986; Katoh et al., 1990; Katoh et al., 1992; Pechnick, 1993; Przewlocki et al., 1991; Szekely, 1990). Particularly, ENK and other opioids are able to modify the synthesis and release of hypothalamic releasing agents, such as corticotropin releasing factor (CRF) (Borsook and Hyman, 1995; Szekely, 1990). Moreover, considerable neuroanatomical and pharmacological data suggest an involvement of ENK peptides in the regulation of sympathetic, cardiovascular, and respiratory neural control systems (Holaday, 1983; McCubbin, 1993). Much interest has been centered on the role of opioids in neuroendocrine regulation, particularly at the level of the PVH. The importance of the PVH in the central regulation and coordination of the stress response is well recognized. Indeed, the PVH is one important coordinating center of the stress system having virtually all the CRFergic neurons that control the release of adrenocorticotropic hormone (ACTH) at the level of the adenohypophysis (Palkovits, 1987; Sawchenko, 1986; Sawchenko et al., 1993; Swanson et al., 1986; Swanson et al., 1987). Furthermore, the PVH is one of the few structures that project

directly onto preganglionic sympathetic neurons (Strack et al., 1989a; Strack et al., 1989b) as well as onto the preganglionic neurons of the parasympathetic system (Lawrence and Pittman, 1985). The PVH also receives afferents from structures that are involved in regulation of the animal's behavior, emotions and cardiovascular system (Beaulieu et al., 1987; Cunningham et al., 1990; Cunningham and Sawchenko, 1988; Palkovits, 1987; Sawchenko, 1986; Sawchenko et al., 1993; Swanson et al., 1986; Swanson et al., 1987). Many studies have examined the expression of ENK mRNA within the PVH in acute stress situations. It was demonstrated that stress caused adaptive increase in ENK gene expression in these neurons. ENK mRNA levels are increased in the PVH after acute stress, such as intraperitoneal injection of hypertonic saline (Harbuz and Lightman, 1989; Lightman and Young, 1987a; Lightman and Young, 1987b; Lightman and Young, 1988; Lightman and Young, 1989; Watts, 1992; Young and Lightman, 1992), ether stress (Ceccatelli and Orazzo, 1993; Watts, 1991), restraint (Ceccatelli and Orazzo, 1993), morphine withdrawal (Harbuz et al., 1991; Lightman and Young, 1987a; Lightman and Young, 1988), or colchicine injection (Ceccatelli and Orazzo, 1993). These findings may all suggest a role for ENK in the PVH with respect to some aspects of adaptation of the organism to stress. However, very few studies examined the expression of ENK mRNA using categories of stress other than osmotic challenges (Watts, 1992: Young and Lightman, 1992) in chronic conditions within the PVH or in other ENKergic regions of the brain. We have recently investigated the effects of acute and chronic exposure to psychogenic stress on ENK-neuron activation (ENK mRNA and Fos immunoreactivity) in the PVH (Dumont et al., 2000) and in the ventrolateral medulla (Mansi et al., 2000) which provides the highest density of ENKergic parvocellular PVH afferents (Beaulieu et al., 1996). Wistar rats were allocated to either an acute or a chronic stress (10 days) paradigm consisting of 90-min immobilization session. Acute immobilization caused a marked increase in both the number of Fos-ir and Fos-ENK double-labeled cells in all the parvocellular subdivisions of the PVH as well as in the caudal and rostral VLM. Chronic immobilization had no effect on basal Fos labeling of both regions but had opposite effects on the basal number of ENK cells (PVH: 43% increase and VLM: 50% decrease). Moreover, chronically stressed rats displayed an attenuated Fos response (PVH: 67% decrease and VLM: 100% decrease) to subsequent immobilization exposure. Conversely, there was no significant attenuation of the activation of PVH-ENK neurons. By contrast, the stress-induced activation of ENK neurons in the VLM was completely abolished following chronic immobilization. These results indicate that chronic psychogenic stress induced a differential adaptation response of the ENK system which seems to be region-specific. The impact of ENK neurons in the PVH appears to be increased following chronic stress as suggested by the increased number of basal ENK neurons and their sustained activation (Dumont et al., 2000). Conversely, the ENKergic influence originating from the VLM is virtually removed following exposure to chronic neurogenic stress (Mansi et al., 2000). These observations therefore imply that during acute stress exposure, activation of ENK neurons from PVH and VLM regulates some aspects of the stress response. During chronic stress conditions, this decrease in ENKergic input may be translated into a decrease inhibition, while the resistance to habituation of the activation of ENK neurons could contribute to buffer the potentially detrimental effects of a physiological response to stress (Fig. 1).

The release of ENK at different levels of the central stress system diminishes the impact of the stress response by attenuating an array of physiologic responses including emotional and affective states. Recent studies published with mice lacking delta opioid receptors (Filliol et al., 2000) or preproenkephalin-derived peptides (Konig et al., 1996) revealed that both knockout mice showed higher anxiety levels. This is

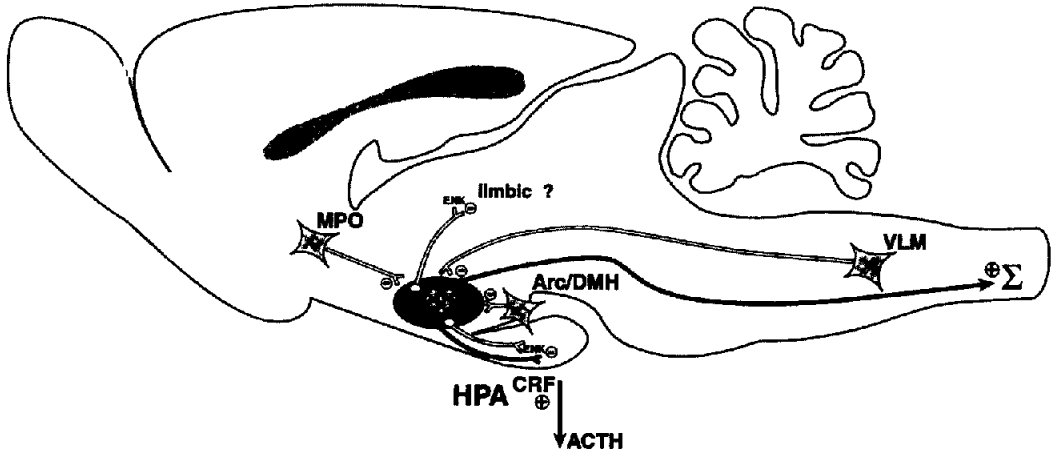

Fig. 1 The release of ENK at different levels of the central stress system could diminish the impact of the stress response by attenuating an array of physiologic responses including emotional and affective states. At the level of the paraventricular nucleus of the hypothalamus (PVH) this could occur through the ENKergic innervation of the PVH that is provided by the medial preoptic region (MPA/MPO), the dorsomedial hypothalamus and arcuate nuclei (Arc/DMH) and the ventral medulla (VLM). The ENK neurons of the PVH could act directly at the level of the sympathetic nervous system (Σ) and the hypothalamo-pituitary adrenal (HPA) axis (CRF and ACTH release). The impact of potential PVH-ENK projections to limbic structures remains to be determined.

concordant with the fact that overexpression of proenkephalin in the amygdala potentiates the anxiolytic effects of benzodiazepines (Kang et al., 2000). Therefore, the ENK system appears to have an important role to play in modulating emotional behaviors particularly at the level of the limbic system which is important in linking aversive stimuli to the normally contingent behavioral neuroendocrine and autonomic responses to psychological stress. There are strong evidences indicating that opioids exert their effects by attenuating or terminating stress responses (defensive action of the organism) (Janssens et al., 1995; McCubbin, 1993). For instance, naloxone (an opioid receptor antagonist) induced a greater increment in the HPA responses in chronically stressed animals as compared to unstressed control suggesting that the impact of opioid systems had increased due to chronic stress (Janssens et al., 1995). Moreover, intra-CeA injections of enkephalin analog attenuate cold restraint-induced gastric mucosal lesions in rats while intra-CeA naloxone potentiated restraint-induced gastric pathology (Ray and Henke, 1990; Ray et al., 1988). Morphine injected within the rostral CeA impaired the acquisition of fear in rats exposed to a hot-plate apparatus suggesting that opioid reduced the expression of fear responses. Indeed, activation of opioid receptors in the CeA during exposure to the hot-plate device may have prevented the formation, storage, or both excitatory connections between representations of the apparatus cues and of the noxious thermal stimulation, thereby reducing the ability of these cues to provoke fear in rats (Good and Westbrook, 1995). An ENKergic pathway from the amygdala had been also involved in the suppression of anxiety-related behaviors (Siegel et al., 1997). This is consistent with the previous study of Gallagher et al (1982) showing that enkephalin analogue injection within CeA attenuated the acquisition of conditioned heart rate responding. Therefore, ENK could represent a major modulatory system in the adaptation of an organism to chronic stress, balancing the response that the stressor places on the brain with the potentially detrimental effects that a sustained stress response may produce.

3. Conclusion

As stated by Hayden-Hixon and Nemeroff in their 1993 review "no review of the role of opioid peptides in stress responding is complete until the words 'complex', 'contradictary' and 'inconsistent' have been introduced". However, it has now become increasingly evident that endogenous opioids play important roles in the regulation of the stress response. The relevance of the role(s) played by ENK in adaptation to stress may be considered critical in the etiology and pathology of certain physiological disorders associated with repeated or prolonged stress, such as affective and behavior disorders as well as cardiovascular and gastric diseases. The role of opioid dysfunction in the etiology of stress-related pathologies is currently unknown as well as the exact contribution of ENK in the process of sensitization or habituation of stress responses (HPA, ANS and central cellular responses). However, there are strong evidences for an opioid role in the attenuation of the stress response reactivity to chronic stressors.

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