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Endogenous opioids: The downside of opposing stress

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ABSTRACT

Our dynamic environment regularly exposes us to potentially life-threatening challenges or stressors. To answer these challenges and maintain homeostasis, the stress response, an innate coordinated engagement of central and peripheral neural systems is initiated. Although essential for survival, the inappropriate initiation of the stress response or its continuation after the stressor is terminated has pathological consequences that have been linked to diverse neuropsychiatric and medical diseases. Substantial individual variability exists in the pathological consequences of stressors. A theme of this Special Issue is that elucidating the basis of individual differences in resilience or its flipside, vulnerability, will greatly advance our ability to prevent and treat stress-related diseases. This can be approached by studying individual differences in "pro-stress" mediators such as corticosteroids or the hypothalamic orchestrator of the stress response, corticotropin-releasing factor. More recently, the recognition of endogenous neuromodulators with "anti-stress" activity that have opposing actions or that restrain stress-response systems suggests additional bases for individual differences in stress pathology. These "anti-stress" neuromodulators offer alternative strategies for manipulating the stress response and its pathological consequences. This review uses the major brain norepinephrine system as a model stress-response system to demonstrate how co-regulation by opposing pro-stress (corticotropin-releasing factor) and anti-stress (enkephalin) neuromodulators must be fine-tuned to produce an adaptive response to stress. The clinical consequences of tipping this fine-tuned balance in the direction of either the pro- or anti-stress systems are emphasized. Finally, that each system provides multiple points at which individual differences could confer stress vulnerability or resilience is discussed.

1. Introduction

The stress response is characterized by a synchronized set of endocrine, immunological, autonomic, behavioral and cognitive responses to perceived threats that is necessary for survival and has been conserved throughout evolution. The prevalence of stressors in the dynamic environment of an animal, make it essential to have mechanisms that limit activity of stress response systems and promote rapid recovery to pre-stress levels. For example, activation of the hypothalamic-pituitary-adrenal (HPA) axis by stress is under tight feedback regulation that serves to restrain and terminate the response (Dallman et al., 1972). Dysfunctions in this feedback as a result of repeated or chronic stress or even a single severe stress are thought to underlie the link between stress and many neuropsychiatric diseases, including depression, post-traumatic stress disorder (PTSD), substance abuse and Alzheimer's disease, as well as medical conditions including obesity, cardiovascular disease, inflammatory disorders and irritable bowel syndrome (Chrousos, 2000a; Chrousos and Gold, 1992; de Kloet et al., 2005; Goeders, 2003; McEwen, 1998; Larauche et al., 2012; Chrousos, 2000b; McEwen and Stellar, 1993). Individual differences in various components of glucocorticoid feedback mechanisms are points of potential vulnerability or resilience to stress. For example, variations in early life maternal care can determine individual sensitivity of this feedback through epigenetic mechanisms that determine glucocorticoid receptor expression (Weaver et al., 2004).

Although feedback inhibition of the HPA axis by glucocorticoids is critical in restraining the endocrine limb of the stress response, neural circuits underlying other limbs of the stress response are not similarly regulated. For example, whereas glucocorticoids inhibit corticotropin-releasing factor (CRF) mRNA expression in neurons of

Abbreviations: CRF, corticotropin-releasing factor; HPA, Hypothalamic-pituitary-adrenal; MOR, μ-opioid receptor; PTSD, post-traumatic stress disorder.

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the paraventricular hypothalamic nucleus that initiate anterior pituitary adrenocorticotropin release, they increase CRF mRNA in neurons of the amygdala and bed nucleus of the stria terminalis that are thought to underlie behavioral aspects of the stress response (Makino et al., 1994a, 1994b). Given the complexity of stress circuitry, there are likely to be multiple mechanisms for counter-regulation of different components of the stress response. Identifying these mechanisms can guide strategies to prevent or treat stress-related neuropsychiatric diseases. Mechanisms for counteracting stress are also potential points at which individual differences can be expressed and thus can be determinants of stress vulnerability and/or resilience.

One mechanism for counteracting stress responses is through stress-elicited engagement of neuromodulators that act in opposition to "pro-stress" systems or neuromediators. Some neuromediators that have been characterized as opposing stress include neuropeptide Y, endocannabinoids, urocortins and endogenous opioids (Bowers et al., 2012; Crowe et al., 2014; Gunduz-Cinar et al., 2013; Heilig and Thorsell, 2002; Hillard, 2014; Kozicz, 2007; Reul and Holsboer, 2002).

This review presents the locus coeruleus (LC)-norepinephrine (NE) system as a model stress-response system that is co-regulated by the opposing influences of the pro-stress mediator, CRF and the opioid neuropeptide, enkephalin during acute stress. We begin with a brief description of the anatomical and physiological characteristics of the LC-NE system with respect to its role in behavioral and cognitive aspects of the stress response (additional detail on anatomical and physiological characteristics of the LC-NE system are reviewed in (Aston-Jones et al., 1995)). This is followed by a discussion of CRF as the orchestrator of the stress response and a neurotransmitter that activates the LC-NE system in response to stress. Endogenous opioids are introduced as "anti-stress" mediators that co-regulate the LC in a manner that opposes CRF. The adaptive nature of maintaining a balance between CRF and endogenous opioid influences in the LC is emphasized. Individual factors that can tip this balance to result in pathology or determine vulnerability are discussed. An underlying theme is that systems that oppose the stress response, while protective, can also be the basis for alternate pathologies.

2. The locus coeruleus and stress

The following section reviews anatomical and physiological characteristics of the LC-NE system that have implicated the system in stress. More detailed information about this system and its other putative functions that are outside the scope of this review can be found in (Aston-Jones et al., 1995; Foote et al., 1983; Berridge and Waterhouse, 2003). The LC is a compact cluster of NE neurons in the pons that serves as the primary source of brain NE (Grzanna and Molliver, 1980). A distinguishing anatomical feature of the LC is its widespread, highly collateralized projection system that innervates the entire neuraxis (Aston-Jones et al., 1995; Swanson and Hartman, 1976). Through this axonal system the nucleus LC can broadly influence neuronal activity throughout the brain. Notably, the LC serves as the primary source of NE in forebrain regions such as the hippocampus and cortex that govern cognition, memory and complex behaviors.

The physiological characteristics of LC neurons have been studied in vivo in rodents and non-human primates and in vitro in slice preparations and have implicated this system in arousal, attention and behavioral flexibility (Aston-Jones and Bloom, 1981a, 1981b; Foote et al., 1980; Williams and Marshall, 1987; Aston-Jones and Cohen, 2005). LC neurons discharge spontaneously and their tonic rate is positively correlated to arousal state (Aston-Jones and Bloom, 1981b; Foote et al., 1980). However, the relationship between neuronal activity and arousal is more than just correlation because selective activation or inhibition of LC neurons results in cortical and hippocampal electroencephalographic (EEG) activation or inhibition, respectively, indicating causality between LC discharge rate and arousal (Berridge and Foote, 1991; Berridge et al., 1993). As described below, LC activation is necessary for cortical EEG activation by stress (Page et al., 1993).

In addition to spontaneous firing, LC neurons are phasically activated by salient, multimodal stimuli that elicit a burst of discharge followed by a period of inhibition (e.g., Fig. 1) (Aston-Jones and Bloom, 1981a)' (Aston-Jones and Bloom, 1981a; Foote et al., 1980). The phasic response precedes orientation to the eliciting stimuli, suggesting that the LC-NE system redirects attention towards salient sensory stimuli. LC neurons are thought to discharge synchronously during phasic activation as a result of electrotonic coupling through gap junctions between dendrites outside of the nucleus, in the peri-coerulear (peri-LC) region (Ishimatsu and Williams, 1996). In contrast, during spontaneous or tonic LC discharge, the neurons are thought to be uncoupled (Usher et al., 1999). When LC neurons are discharging at a relatively high spontaneous rate (high tonic mode), phasic LC activation by stimuli is greatly attenuated so that high tonic discharge precludes phasic activity (Valentino and Aulisi, 1987).

LC neurons switch between phasic and high tonic discharge modes to bias behavior differently and these shifts facilitate adaptation in a dynamic environment (Fig. 1) (see for reviews (Aston-Jones and Cohen, 2005; Bouret and Sara, 2005)). LC neuronal recordings in monkeys performing operant tasks suggest that phasic LC discharge is associated with focused attention and staying on-task whereas high tonic discharge is associated with labile attention and going off-task (Usher et al., 1999; Rajkowski et al., 1994). A shift from phasic to high tonic LC discharge has been suggested to promote behavioral flexibility, disengaging animals from attention to specific stimuli and ongoing behaviors and favoring scanning the environment for stimuli that promote alternate, more rewarding behaviors (Aston-Jones and Cohen, 2005). The ability to shift between phasic and tonic firing modes would promote rapid adjustments in response to a stressor or after stressor termination (Fig. 1).

Convergent lines of evidence suggest that stressors that initiate the HPA response to stress also activate the LC-NE system and the parallel engagement of these two systems serves to coordinate endocrine and cognitive limbs of the stress response (Valentino and

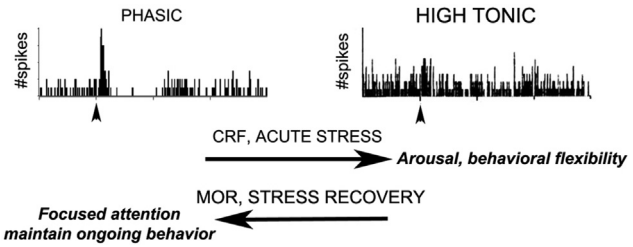

Fig. 1. Schematic depicting the relationship between phasic and high tonic LC activity. Shown are representative peri-stimulus time histograms (PSTHs) of LC neuronal activity during a trial of repeated auditory stimulation occurring at the arrowhead. In the phasic mode LC neurons are more responsive to sensory stimuli and fire with a burst of spikes followed by a period of inhibition before activity returns to pre-stimulus frequency. In the high tonic mode, LC neurons fire faster throughout the trial of sensory stimulation and show little response to the sensory stimuli. These histograms were generated before (PHASIC) and after (HIGH TONIC) CRF administration. Exposure of LC neurons to CRF or exposure of animals to acute stress biases LC activity towards the high tonic mode that is associated with increased arousal, scanning attention and behavioral flexibility. Activating MOR in the LC as occurs during stress recovery biases discharge towards lower tonic and increased phasic activity and this is associated with focused attention and maintenance of ongoing behavior.