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Review

A critical role for prefrontocortical endocannabinoid signaling in the regulation of stress and emotional behavior

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ABSTRACT

The prefrontal cortex (PFC) provides executive control of the brain in humans and rodents, coordinating cognitive, emotional, and behavioral responses to threatening stimuli and subsequent feedback inhibition of the hypothalamic-pituitary-adrenal (HPA) axis. The endocannabinoid system has emerged as a fundamental regulator of HPA axis feedback inhibition and an important modulator of emotional behavior. However, the precise role of endocannabinoid signaling within the PFC with respect to stress coping and emotionality has only recently been investigated. This review discusses the current state of knowledge regarding the localization and function of the endocannabinoid system in the PFC, its sensitivity to stress and its role in modulating the neuroendocrine and behavioral responses to aversive stimuli. We propose a model whereby steady-state endocannabinoid signaling in the medial PFC indirectly regulates the outflow of pyramidal neurons by fine-tuning GABAergic inhibition. Local activation of this population of CB_1 receptors increases the downstream targets of medial PFC activation, which include inhibitory interneurons in the basolateral amygdala, inhibitory relay neurons in the bed nucleus of the stria terminalis and monoamine cell bodies such as the dorsal raphe nucleus. This ultimately produces beneficial effects on emotionality (active coping responses to stress and reduced anxiety) and assists in constraining activation of the HPA axis. Under conditions of chronic stress, or in individuals suffering from mood disorders, this system may be uniquely recruited to help maintain appropriate function in the face of adversity, while breakdown of the endocannabinoid system in the medial PFC may be, in and of itself, sufficient to produce neuropsychiatric illness. Thus, we suggest that endocannabinoid signaling in the medial PFC may represent an attractive target for the treatment of stress-related disorders.

Contents

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1. The prefrontal cortex: anatomy, homology and role in stress, mood and emotion

The prefrontal cortex (PFC) is the center for executive functioning, responsible for mediating a range of cognitive, behavioral, and neuroendocrine processes that are necessary to plan, control, and direct behavior according to shifting environmental demands. The PFC is a structurally and functionally heterogeneous brain region, and subregions of the PFC have been classically defined based on the presence or absence of a granular zone and their strong reciprocal connections with the dorsomedial nucleus of the thalamus (Rose and Woolsey, 1948; Uylings and van Eden, 1990). Current classifications also account for the functional (*i.e.*, electrophysiological and behavioral) properties of the subregion, the presence and distribution of different neurochemicals and neurotransmitter systems, and its embryological development when comparing homologies between cortical areas in different species (Uylings et al., 2003).

The primate PFC is roughly divided into three anatomically and functionally distinct subregions; a medial region, an orbital region, and a dorsolateral region (Barbas, 1992; Carmichael and Price, 1994). The medial region is the most evolutionarily conserved of the three subdivisions and provides the major cortical output to visceromotor structures in the hypothalamus and brainstem (Ongur and Price, 2000). The orbital subregion has been implicated in social learning and coding of affective stimuli, and receives inputs from several sensory modalities, including olfaction, taste, vision, visceral afferents, and somatic sensation (Ongur and Price, 2000). The dorsolateral PFC by contrast, has evolved into the most highly specialized cortical region in primates, vital for executive functioning tasks such as working memory, behavioral flexibility, attentional control, decision-making, and temporal organization of behavior (Brown and Bowman, 2002).

Similar to the primate PFC, the rodent PFC is also divided into three topographically distinct territories (Brown and Bowman, 2002; Dalley et al., 2004; Heidbreder and Groenewegen, 2003; Kolb, 1984; Uylings et al., 2003). First is the medial PFC, which can be further subdivided into a dorsomedial region that includes precentral, agranular and anterior cingulate cortices, and a ventromedial region that encompasses the prelimbic, infralimbic, and medial orbital cortices (Heidbreder and Groenewegen, 2003). Second is a ventrally located region termed the orbital PFC that encompasses the ventral and ventrolateral orbital cortices. Third is a lateral region of the PFC that includes the dorsal and ventral agranular insular cortices. The medial and orbital regions of the rodent PFC are structurally and functionally quite similar to corresponding regions in the primate PFC, but due to significant cross-species variation in neural connectivity and cytoarchitectonic characteristics, debate has surrounded whether rodents have a region homologous to the evolutionarily advanced primate dorsolateral PFC (Preuss, 1995). For instance, neurons in the medial dorsal nucleus of the thalamus lack projections to dorsolateral regions of the rodent PFC, which is a defining feature of prefrontal classification (Uylings et al., 2003). However, imaging, lesion, and electrophysiology studies have demonstrated that executive functioning and emotional learning tasks similar to those mediated by the primate dorsolateral PFC are carried out by distinct subregions of the medial PFC, and to a lesser extent, the orbital PFC in rodents (Dalley et al., 2004; Seamans et al., 2008; Uylings et al., 2003).

Each division of the medial PFC receives a unique set of afferent projections. There is a dorsoventral shift along the medial PFC, such that connections with the dorsomedial PFC (specifically the agranular and anterior cingulate cortices) are predominantly with sensorimotor areas, while inputs to and from the ventromedial PFC (specifically the prelimbic and infralimbic cortices) are primarily limbic in nature (Hoover and Vertes, 2007). The dorsomedial PFC receives widespread afferent projections from areas of the cortex and associated thalamic nuclei representing all sensory modalities. This information is presumably integrated at, and utilized by, the dorsomedial PFC in goal-directed actions (Hoover and Vertes, 2007). In contrast, the ventromedial PFC shares strong reciprocal connections with subcortical limbic brain structures including the amygdala, ventral hippocampus, lateral hypothalamus, septum, thalamus, striatum, and bed nucleus of the stria terminalis (BNST) (Drevets et al., 2008a; Heidbreder and Groenewegen, 2003; Ishikawa and Nakamura, 2003; Vertes, 2006). The ventromedial PFC also provides forebrain modulation over visceral control centers in the brainstem, including cholinergic neurons originating in the basal forebrain (Gaykema et al., 1991), noradrenergic (NA) neurons from the locus coeruleus (Jodo and Aston-Jones, 1997; Jodo et al., 1998), dopaminergic (DA) neurons emanating from the ventral tegmental area (VTA) and substantia nigra (Carr and Sesack, 2000a,b; Loughlin and Fallon, 1984), and serotonergic (5-hydroxytryptamine; 5-HT) neurons projecting from the dorsal and median raphe nucleus (Hajos et al., 1998). Hence, the ventromedial PFC (encompassing the prelimbic and infralimbic cortices) is ideally situated to modulate the output of limbic and monoaminergic neuronal networks that have long been implicated in the regulation of mood, emotion and stress. Consistent with this anatomical topography, there is substantial evidence that the medial PFC is an important regulator of stress processing and emotional behavior, and that its dysfunction is germane to many mood and anxiety disorders.

The medial PFC is a vital component of a distributed extrahypothalamic network that modulates activation and feedback inhibition of the hypothalamic-pituitary-adrenal (HPA) axis. Convergent evidence from both human and rodent studies demonstrates that subregions of the medial PFC differentially modulate the behavioral and systemic response to psychological stress (Holmes and Wellman, 2009). Acute exposure to stressful stimuli induces robust activation of the immediate early gene c-*fos* (a marker of neuronal activation) and enhanced glucose mobilization in all subdivisions of the medial PFC (Cullinan et al., 1995; Duncan et al., 1993); however, lesion studies have revealed markedly different roles for the dorsomedial and ventromedial subregions in regulating HPA axis activation. For instance, bilateral lesions of the medial PFC centered in the anterior cingulate and prelimbic cortices have been shown to enhance adrenocorticotropic hormone (ACTH) and corticosterone (CORT) secretion as well as c-*fos* activation and corticotropin-releasing hormone (CRH) mRNA expression in the paraventricular nucleus (PVN) of the hypothalamus following exposure to restraint stress (Diorio et al., 1993; Figueiredo et al., 2003; Radley et al., 2006a). In contrast, lesions to the infralimbic region of the medial PFC produce an opposite effect, suppressing the activation of CRH-secreting PVN neurons and improving HPA axis recovery (Radley et al., 2006a). Thus, the prelimbic region of the medial PFC serves to suppress the HPA axis response to acute stress, while the infralimbic cortex serves to activate autonomic PVN outputs and promote stress-induced activation of the HPA axis.

The prelimbic and infralimbic cortex do not innervate the PVN directly, but instead relay through various subcortical intermediaries to modulate HPA axis responsivity. The infralimbic cortex sends direct projections to the lateral septum, anteroventral region of the BNST, the medial, basomedial, and central amygdala, as well as the nucleus of the solitary tract, all regions that have been implicated in activation of the HPA axis (Herman et al., 2003; Hurley et al., 1991; Vertes, 2004). Conversely, the prelimbic cortex projects sparingly to these regions. Instead, this subregion heavily innervates several inhibitory stress-integrative structures, including the GABAergic peri-PVN zone that surrounds the PVN, the paraventricular thalamus, anterior and dorsomedial regions of the BNST, ventral subiculum, and basolateral amygdala (BLA) (Hurley et al., 1991; Jankord and Herman, 2008; Radley et al., 2009; Vertes, 2004).