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Corticotropin releasing hormone and imaging, rethinking the stress axis ☆

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ABSTRACT

The stress system provides integration of both neurochemical and somatic physiologic functions within organisms as an adaptive mechanism to changing environmental conditions throughout evolution. In mammals and primates the complexity and sophistication of these systems have surpassed other species in triaging neurochemical and physiologic signaling to maximize chances of survival. Corticotropin releasing hormone (CRH) and its related peptides and receptors have been identified over the last three decades and are fundamental molecular initiators of the stress response. They are crucial in the top down regulatory cascade over a myriad of neurochemical, neuroendocrine and sympathetic nervous system events. From neuroscience, we've seen that stress activation impacts behavior, endocrine and somatic physiology and influences neurochemical events that one can capture in real time with current imaging technologies. To delineate these effects one can demonstrate how the CRH neuronal networks infiltrate critical cognitive, emotive and autonomic regions of the central nervous system (CNS) with somatic effects. Abundant preclinical and clinical studies show inter-regulatory actions of CRH with multiple neurotransmitters/peptides. Stress, both acute and chronic has epigenetic effects which magnify genetic susceptibilities to alter neurochemistry; stress system activation can add critical variables in design and interpretation of basic and clinical neuroscience and related research. This review will attempt to provide an overview of the spectrum of known functions and speculative actions of CRH and stress responses in light of imaging technology and its interpretation. Metabolic and neuroreceptor positron emission/single photon tomography (PET/SPECT), functional magnetic resonance imaging (fMRI), anatomic MRI, diffusion tensor imaging (DTI), and proton magnetic resonance spectroscopy (pMRS) are technologies that can delineate basic mechanisms of neurophysiology and pharmacology. Stress modulates the myriad of neurochemical and networks within and controlled through the central and peripheral nervous system and the effects of stress activation on imaging will be highlighted.

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1. Introduction

1.1. Relevant biology and physiology

The stress system has ancient molecular roots. A critical stress mediator is corticotropin releasing hormone (CRH) and it is a member of a family of stress-related peptides. It was first isolated and discovered from over 500,000 sheep hypothalami by Vale W et al. in 1981 [1]. Subsequently, a series of CRH-related peptides and receptors were discovered in vertebrates and invertebrates. These peptides include urocortin 1, urocortin 2 or stresscopin-related peptide, sauvagine and urocortin 3 or stresscopin and a series of associated receptors. Vertebrates show wide expression of these molecules in the central and peripheral nervous systems where they activate physiologic responses to changing environmental conditions. CRH and these peptides are integral to reproduction, migratory behavior, timing of metamorphosis and other critical adaptations to environmental changes [2–4]. CRH and receptors are expressed in a variety of other tissues including but not limited to the immune system (cellular elements, lymphatic tissues), integument, the blood brain barrier (BBB), gastrointestinal tract and parasympathetic ganglions. The actions of CRH are principally

Abbreviations: CNS, central nervous system; CRH, corticotropin releasing hormone; CRHR1, corticotropin releasing hormone receptor type 1; irCRH, immune-reactive CRH; PET, positron emission tomography; SPECT, single photon tomography; fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging; pMRS, proton magnetic resonance spectroscopy; PFC, prefrontal cortex; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; aCC, anterior cingulate cortex; EA, extended amygdala; VTA, ventral tegmental area; SNS, sympathetic nervous system; DR, dorsal raphé nuclei; LC, locus coeruleus; BBB, blood brain barrier; HPA, hypothalamic pituitary adrenal axis; AVP, vasopressin; ACTH, adrenocorticotropin; C, cortisol; GCr, glucocorticoid receptors; BNST, bed nucleus of the stria terminals; NAc, nucleus accumbens; MDD, major depressive disorder; GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder; NHP, non-human primate; SS, stress sensitive; SR, stress resistant; DA, dopamine; 5HT, serotonin; ERC, entorhinal cortex; 5HTT, serotonin transporter; GABA, gamma-aminobutyric acid; BOLD, blood oxygenation level dependent; sCC, subgenual cingulate cortex; MD, maternal deprivation; GCr, glucocorticoid receptor; RAC, raclopride; GC, glucocorticoid; GLU, glutamate; mGluR5, metabotropic GLU receptor subtype 5; ETOH, alcohol; DAT, dopamine transporter; NET, norepinephrine transporter; BP, binding potential; SP, substance P; NK-1, neurokinin1; O/H, Orexin/Hypocertin; END, beta-endorphin; CFN, carfentanil; TSST, Tier Social Stress Test; FDG, fluoro-2-deoxy-D-glucose; FA, fractional anisotropy; BMI, body mass index; IR-PCOS, insulin resistant polycystic ovary syndrome; IBS, irritable bowel syndrome; rCMglu, regional cerebral glucose metabolic rate.

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paracrine in loco-regional tissues with indirect effects on the CNS which are beyond the scope of the review.

Increasing complexity of the central and peripheral nervous systems seen in mammals resulted in higher levels of expression of CRH, urocortins and associated receptors, as well as their expression, in immune, reproductive, endocrine and other tissues/organs gaining importance in the central integration of these systems.

An acute stress response involves an abrupt usually self-limited neurohormonal activation as a cascade effect often in response to real or perceived physical or emotional danger i.e. fight, flight or freeze. The inability to mount an adequate stress cascade holds survival disadvantages. A chronic stress state involves prolonged pathologic neurohormonal activity usually over weeks to years. Involvement engages cortisol (C), hypothalamic pituitary adrenal axis (HPA) and SNS (and other) activity that would be out of context for the environmental conditions. Chronic stress causes desensitization of normal feedback systems; this can result in elevation of C, down-regulation of adrenergic receptors (epinephrine, norepinephrine) and loss of normal circadian rhythmicity. Long term effects include immune, metabolic, cardiovascular diseases and increased susceptibility to CNS disorders. The evolutionary benefit from the stress system involves a balance of adequate acute responses that optimize survival advantage while assuring that chronic activation and related adverse consequences are aborted.

Functional imaging technologies involving the central nervous system continue to expand and refine. Imaging is widely used to study disorders associated with or secondary to acute and chronic stress system dysfunction. Metabolic and neuroreceptor positron emission/single photon tomography (PET/SPECT), functional magnetic resonance imaging (fMRI), anatomic MRI, diffusion tensor imaging (DTI), and proton magnetic resonance spectroscopy (pMRS) are all technologies in which stress activation may impact signal sensitivity and specificity and may alter results and study interpretation. Here we hope to demonstrate areas of imaging where stress manifests alterations in neurochemistry, cognition and anatomy and provides new considerations for understanding underlying its variability.

2. Physiology interface with stress activation

In the CNS, CRH and CRHR1 are highly concentrated in the hypothalamus, areas of the neocortex principally the prefrontal cortex (PFC), discrete brain stem nuclei, and the extended amygdala (EA).

2.1. Hypothalamus

The hypothalamus regulates stress hormone release from the pituitary and control of the sympathetic nervous system (SNS) through the brainstem structures, the pontomedullary and raphé nuclei and the locus coeruleus (LC). These areas express very high levels of immunereactive CRH (irCRH) and CRHR1 [5]. Hypothalamic CRH is released from the paraventricular nucleus through the infundibular stalk to the anterior pituitary activating CRHR1 and (with severe stress) arginine vasopressin (AVP) stimulating adrenocorticotrophin (ACTH) release. ACTH is a potent secretagogue releasing C and androgens from the adrenal cortex. There is a potent negative feedback system for the regulation of C at the levels of the pituitary, hypothalamus and the EA. Activation of the HPA with a surge of C secretion will trigger glucocorticoid receptors (GCr) in the pituitary/hypothalamus to deactivate CRH secretion and dampen the neurohormonal stress response (Fig. 1). Negative feedback responsivity will fail during conditions of persistent, frequent stressors exogenous, endogenous or both. GCr are expressed in other brain regions where they have significant effects on neurochemistry, genetic/epigenetic events and neural growth. The hypothalamus activates SNS and adrenal medullary catecholamines, epinephrine and norepinephrine. Direct autonomic innervation and circulating catecholamines stimulate the heart, vascular structures, visceral and lymphoid tissues and increase cardiovascular, metabolic, immune, and other physiologic responses to stressful stimuli [6,7].

2.2. Extended amygdala

CRH and CRHR1 are also expressed in the extended amygdala (EA); it is a complex structure composed of discrete but tightly linked structures. The bed nucleus of the stria terminals (BNST), central, basolateral and medial nuclei of the amygdala, hippocampus, the insulae and medial nucleus accumbens (NAc) form the hub of the EA [7-9]. The EA forms a functional interface between the higher cognitive functions of the prefrontal cortex (PFC) and the cingulate cortex to the endocrine hypothalamus, the reward pathways of the striatum and to autonomic regulation from the brainstem to the peripheral nervous system (PNS). The EA is the seat of memory, emotion and motivational behaviors, fundamental to acute responses to danger and threat, fear, impulsivity, drug abuse and sexual drive. Functional disruption of the CRH in the EA is seen stress related psychiatric and somatic disease; major depressive disorder (MDD), generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), "sickness syndrome," chronic pain, cancer, metabolic syndrome, autoimmune conditions, other chronic medical disorders, substance abuse and addiction [6,7]. Activation of neural circuits to acute stress occurs in micro to milliseconds. The resolution of current technologies to tract rapid neurochemical events at this scale does not yet exist. Refinements in fMRI imaging of neural networks approaching this scale may become feasible at some point in the future. PET/fMRI instruments may enable better correlations of neuroanatomic activation and functional neurochemistry though tracking events at this time scale will likely remain out of reach for several decades.

2.3. Anatomical map of CRH and CRHR1

CRH and CRHR1 show homology in regional expression; they are also found in PFC and frontal cortices, cingulate, insulae, the EA and hippocampus, the BNST and nuclei of the hypothalamus and brainstem. These areas are relevant to the behavioral and somatic adaptive response to stress. Stimulation or inhibition of the CRHR1 by CRH, related peptide analogues, non-peptide agonists or antagonists will precipitate or inhibit behavioral, neuroendocrine and sympathetic stress responses. Rodents show expression in areas primarily responsible for processing environmental stimuli, in sensory organ brain regions as noted above. Primate brains have limited concentrations of CRH and CRHR1 in these structures. There are differences in functional anatomy and circuitry with much lower receptor density and irCRH in sensory structures. Put in context, irCRH/CRHR1 appears to be more "front line" in direct stimulus processing (olfaction, auditory and visual cues) in rodents, whereas in primates neuronal projections from these stimulus processing areas are principally directed to areas with high density of CRH containing neurons that evoke cognitive, executive, emotive processing and social decision making. Limbic system regulation of lower order behaviors is similar between primates and rodents and relative irCRH/CRHR1 density and distribution remain comparable. Together CRH influences higher level integration of behaviors in more socially evolved species, while CRH modulation of autonomic processes remains more analogous to lower species. To date there is no specific radioligand for CRHR1; once developed the anatomic distribution and regional occupancy of CRHR1 would be of great benefit in understanding conditions of chronic and acute stress activation.

3. Acute stress and pathologic changes from chronic activation

Survival is the ultimate goal of all organisms and in humans and non-human primates (NHP); perception of danger both physical and social is critical to that end. Adaptations to these circumstances can be grouped grossly into fight, flight or freeze responses. Central regulation of the stress cascade directly or indirectly integrates multiple