

Stress sensitivity and the development of affective disorders

Tracy L. Bale

Department of Animal Biology, University of Pennsylvania, 3800 Spruce Street, Philadelphia, PA 19104, USA

Received 23 May 2006; accepted 28 June 2006

Available online 8 August 2006

Abstract

Depressive disorders are the most common form of mental illness in America, affecting females twice as often as males. The great variability of symptoms and responses to therapeutic treatment emphasize the complex underlying neurobiology of disease onset and progression. Evidence from human and animal studies reveals a vital link between individual stress sensitivity and the predisposition toward mood disorders. While the stress response is essential for maintenance of homeostasis and survival, chronic stress and maladaptive responses to stress insults can lead to depression or other affective disorders. A key factor in the mediation of stress responsiveness is the neuropeptide corticotropin-releasing factor (CRF). Studies in animal models of heightened stress sensitivity have illustrated the involvement of CRF downstream neurotransmitter targets, including serotonin and norepinephrine, in the profound neurocircuitry failure that may underlie maladaptive coping strategies. Stress sensitivity may also be a risk factor in affective disorder development susceptibility. As females show an increased stress response and recovery time compared to males, they may be at an increased vulnerability for disease. Therefore, examination of sex differences in CRF and downstream targets may aid in the elucidation of the underlying causes of the increased disease presentation in females. While we continue to make progress in our understanding of mood disorder etiology, we still have miles to go before we sleep. As an encouraging number of new animal models of altered stress sensitivity and negative stress coping strategies have been developed, the future looks extremely promising for the possibility of a new generation of drug targets to be developed.

© 2006 Elsevier Inc. All rights reserved.

Keywords: Stress; Affective disorder; CRF; Sex differences; Stress sensitivity

Depressive disorders affect nearly 19 million American adults and are the most common form of mental illness in America, affecting females twice as often as males (Nestler et al., 2002). Evidence from research and clinical investigations demonstrates that the development of depression encompasses a profound neurocircuitry failure comprising distributed sites throughout the brain, including the hypothalamus, hippocampus, amygdala, and striatum (Liotti and Mayberg, 2001; Nestler et al., 2002). These brain regions are important in the coordinated regulation of behaviors and responses that when disrupted are symptomatic of depression such as eating, sleeping, circadian rhythm, stress response, learning and memory, and pleasure seeking. Depressed patients present with a great variability of their symptoms as well as in their response to drug treatment, thus emphasizing the complex nature of this illness. The difficulty in identifying new drug

targets lies in the elaborate neurobiology of this disease and the underlying predisposing factors.

While females are diagnosed with affective disorders far more often than males, the mechanisms underlying possible sex differences remain insufficiently studied and virtually unknown (Frackiewicz et al., 2000; Kendler, 1998; Kornstein, 1997) (see also companion paper by Altemus in this issue). Heightened stress sensitivity may be a risk factor in affective disorder onset and susceptibility. Females show a post-pubertal increase in stress response magnitude and recovery time compared to males. In stress studies in rodents, females typically respond to a stress with a greater release of both adrenal corticotropic hormone (ACTH) and corticosterone compared to males and show a more prolonged pattern of heightened plasma levels of these hormones following the stress, indicating a greater resistance to recovery (McCormick et al., 2002). Evidence supports a possible influence of reproductive hormones on the development of an increased sensitivity to stress. Cyclic changes in estrogen and progesterone enhance the sensitivity

E-mail address: tbale@vet.upenn.edu.

to and ability to respond to stress (Seeman, 1997), and the physiological rise in estrogen is an important inhibitory factor of ACTH release following acute stress (Young et al., 2001). Sex differences in the CRF system have not been well characterized, but may be a fundamental factor influencing female susceptibility to stress and depression (Young, 1998).

Strong evidence links stress, and the sensitivity of the individual to stressful encounters, to the development of depression. The stress response is essential for adaptation, maintenance of homeostasis, and survival. However, chronic stress can accelerate disease processes, cause neural degeneration, and lead to depression or other affective disorders (Nestler et al., 2002). A key factor in the response to stress is the neuropeptide corticotropin-releasing factor (CRF) (Vale et al., 1981). CRF and its receptors (CRFR1 and CRFR2) are important regulators of the hypothalamic–pituitary–adrenal (HPA) axis and central stress responses. During a stress response, CRF is released from the paraventricular nucleus of the hypothalamus (PVN) and activates CRFR1s on anterior pituitary corticotropes to stimulate the release of ACTH. ACTH then enters the blood stream and acts at MC2 receptors in the cortex of the adrenal gland to stimulate the synthesis and releases of glucocorticoids. A prominent negative-feedback system acts to inhibit further CRF production and release from the hypothalamus. Hypothalamic vasopressin (AVP) has been shown to act synergistically with CRF to augment the release of ACTH in rodents and humans, suggesting that AVP may also play a physiologic role in the neuroendocrine stress response (Bilezikjian and Vale, 1987; DeBold et al., 1984; Liu et al., 1983; Rivier et al., 1984). Stress input also stimulates central CRF release, capable of activating the autonomic nervous system producing a classic “fight or flight” response and a stimulated release of norepinephrine and epinephrine into the circulation. Interestingly, this centrally responsive CRF is also influenced by the glucocorticoid feedback of the HPA axis, but in the opposing direction such that limbic CRF, especially within the central nucleus of the amygdala (CeA) is increased with glucocorticoid exposure (Altemus et al., 1994; Schulkin et al., 1998).

Alterations in CRF expression in the CeA have been linked to increased emotionality and stress responsivity, a likely factor contributing to an increased vulnerability for disease onset (Adamec, 2003; Adamec and McKay, 1993). Conceivably, chronic stress or even acute stress in an individual genetically predisposed to stress sensitivity could cause such a dysregulation in homeostatic balance by disrupting normal feedback mechanisms. Studies examining effects of chronic stress or models of elevated glucocorticoid levels have demonstrated a potential mechanism of reduced sensitivity to the negative feedback resulting in an HPA axis that is hyper-responsive to new stimuli (Murakami et al., 1997; Young et al., 1990). This decrease in negative feedback sensitivity may be due to affects on hippocampal tone and its normally inhibitory role on PVN activity (Herman et al., 1989a,b; Young et al., 1990). These studies suggest that CRF pathway dysregulation could impact multiple sites within the brain to influence stress feedback systems, stress responses, and the sensitivity to further stress inputs, allowing for a proposed model of how stress influences

mood disorder development (Herman et al., 1995; Herman et al., 1989a,b).

A growing body of evidence links a dysregulation of CRF pathways with the development of depression (Arborelius et al., 1999; Holsboer, 1999; Nemeroff, 1988; Nemeroff, 1992; Reul and Holsboer, 2002). Clinical studies have found increased CRF levels in the cerebral spinal fluid and decreased central CRF receptors in postmortem examination of suicide victims. Further, excessive activation of the HPA axis has been reported in over half of patients with depression, and these symptoms have been ameliorated following a course of antidepressant treatment (Arato et al., 1989; Banki et al., 1987; De Bellis et al., 1993; Nemeroff et al., 1984). However, it is not yet clear as to whether this increase in HPA axis hormones is a primary contributor of depression or possibly a secondary response to an as yet undetermined cause. It is clear that the delicate balance of CRF pathways is critical for maintenance of mental and physical homeostasis. Dysregulation of this system is likely a foundation of the maladaptive coping strategies, such as behavioral responses on either end of the spectrum including increased learned helplessness and reduced pleasure or hyperarousal and reward seeking and dependence, resulting in an increased incidence of disease presentation (Fig. 1).

Studies in rodents have also found supportive evidence for CRFR1 antagonists to be useful in alleviation of stress-induced maladaptive coping responses in the forced swim and learned helplessness models (Arborelius et al., 2000; Bale and Vale, 2003). Treatment with the small molecule CRFR1 antagonist, antalarmin, in male rats diminished plasma elevations of HPA axis stress hormones in models of acute and chronic stress as well as decreased CRF-induced anxiety-like behaviors and elevated blood pressure, both of which are associative symptoms of major depression in humans (see review in Bale and Vale, 2004). Further, in primates, antalarmin treatment dramatically decreased stress-induced behaviors such as body tremors and grimacing, while increasing exploratory behaviors normally suppressed during stress (Habib et al., 2000). Recent clinical trials in which depressed patients have been treated with

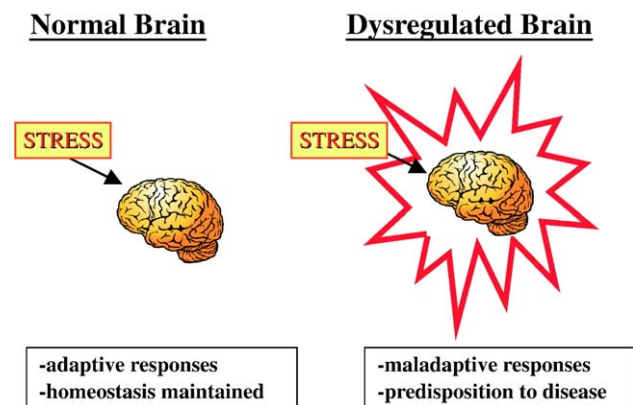


Fig. 1. Schematic representation of the hypothesis that the vulnerability to disease is related to an individual heightened stress sensitivity resulting in the production of maladaptive coping mechanisms and exaggerated stress responses compared to normal adaptive responses necessary for maintenance of homeostasis.

متن کامل مقاله

دریافت فوری ←

ISIArticles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات