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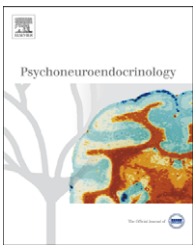

CURT P. RICHTER AWARD PAPER

The link between childhood trauma and depression: Insights from HPA axis studies in humans

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Summary
Childhood trauma is a potent risk factor for developing depression in adulthood, particularly in response to additional stress. We here summarize results from a series of clinical studies suggesting that childhood trauma in humans is associated with sensitization of the neuroendocrine stress response, glucocorticoid resistance, increased central corticotropin-releasing factor (CRF) activity, immune activation, and reduced hippocampal volume, closely paralleling several of the neuroendocrine features of depression. Neuroendocrine changes secondary to early-life stress likely reflect risk to develop depression in response to stress, potentially due to failure of a connected neural circuitry implicated in emotional, neuroendocrine and autonomic control to compensate in response to challenge. However, not all of depression is related to childhood trauma and our results suggest the existence of biologically distinguishable subtypes of depression as a function of childhood trauma that are also responsive to differential treatment. Other risk factors, such as female gender and genetic dispositions, interfere with components of the stress response and further increase vulnerability for depression. Similar associations apply to a spectrum of other psychiatric and medical disorders that frequently coincide with depression and are aggravated by stress. Taken together, this line of evidence demonstrates that psychoneuroendocrine research may ultimately promote optimized clinical care and help prevent the adverse outcomes of childhood trauma.

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1. Introduction

Hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis in major depression is one of the most prominent findings in psychoneuroendocrinology (Arborelius et al., 1999; Nestler et al., 2002). The HPA axis represents the major neuroendocrine stress response system that serves to adapt the organism to change in demand and thereby maintains stability and health (McEwen, 2004). Stress or acute challenge has long been recognized as a potent risk factor for depression, often precipitating the onset of depressive episodes (Hammen et al., 1992; Kendler et al., 1993, 2000). It is conceivable that HPA axis changes in depression may reflect effects of stress and mediate the manifestation of depressive symptoms. However, not every person exposed to stress will develop depression and it is critical to understand sources of individual differences in vulnerability to the pathogenic effects of stress. Thus, preexisting factors known to modulate the organism's ability to compensate in response to emotional challenge might interfere with successful adaptation and convey vulnerability to develop depression.

Epidemiological studies have provided strong evidence that adverse experience during childhood, such as abuse, neglect or loss, is associated with dramatic increases in the risk to develop depression. Edwards et al. (2003) in a CDC study of 8667 adult members of an HMO in the San Diego area reported a strong dose–response relationship between the number of experienced childhood adversities and general mental health problems in adulthood. In the same HMO population, there was a dose–response relationship between the number of experienced childhood adversities and the presence of a depressive episode in the past year or lifetime chronic depression (Chapman et al., 2004). An earlier study in this population found 4-fold increases in the risk of depression in persons with multiple childhood adverse experiences (Felitti et al., 1998). The experience of any childhood adversity increased the risk of attempted suicide in childhood, adolescence or adulthood 2- to 5-fold (Dube et al., 2001). These remarkable studies complemented findings from other landmark studies, including the pioneering studies by Brown and Moran (1994) as well as the seminal McCauley et al. (1997) study demonstrating in a cohort of more than 1900 women from internal medicine practices that childhood, but not adulthood, sexual or physical abuse is associated with increases in depression and anxiety symptoms. Findings of the National Comorbidity Survey (Molnar et al., 2001), the Ontario Health Survey (MacMillan et al., 2001), and a New Zealand community survey (Mullen et al., 1996) have provided concordant findings. A role of childhood trauma in the development of major depression has been confirmed in twin studies (Kendler et al., 1993, 2000; Nelson et al., 2002). In addition to maltreatment, parental loss due to death or separation is also associated with increased risk for depressive disorders (Agid et al., 1999). Of note, individuals with early adverse experience appear to be sensitized to the depressive effects of acute stress in adulthood (Hammen et al., 2000; Dougherty et al., 2004; Kendler et al., 2004). There is also evidence for an interaction between environment and genes, inasmuch as genetic polymorphisms moderate the likelihood of whether or not an individual develops depression in relation to life stress, including early adversity (Caspi et al., 2003; Kaufman et al., 2004, 2006; Kendler et al., 2005; Bradley et al., 2008). It thus appears that interactions between genetic diathesis and environmental influences throughout the lifespan together underlie depression vulnerability in most patients.

The precise mechanism that mediates the effects of early adverse experience on depression risk has been the subject of intense inquiry in translational neuroscience. Studies in rodents and non-human primates have focused on epigenetic modification of phenotypic stress responsiveness as a function of early experience. Results suggest that adverse experience, such as maternal separation or low maternal care, induces persistent structural, functional, and epigenomic changes in neural circuits that are implicated in the integration of cognitive and emotional processing, endocrine–autonomic control, and the regulation of arousal and vigilance. These changes converge in increased endocrine and autonomic reactivity to stress, anxiety-like behavior, anhedonia, cognitive impairment, pain sensitivity, and altered sleep (e.g., reviewed in Ladd et al., 2000; Sánchez et al., 2001; Plotsky et al., 2001; Meaney and Szyf, 2005). In fact, many of the neurobiological and behavioral effects of early-life stress in animal models closely parallel signs and symptoms of major depression. It is therefore conceivable that adverse experience in childhood may indeed be causally associated with developing depression, particularly in response to challenge.

One major question for clinical depression research in the recent years concerned whether childhood adverse experience in humans is associated with neurobiological changes that are similar to those observed animal models and whether these changes are related to depression. To address this question, our group conducted a series of clinical studies. We focused on studying alterations of the HPA axis in subjects with histories of childhood abuse. The central hypothesis underlying these studies was that early adverse experience in humans would lead to sensitization of central stress response systems, particularly corticotropin-releasing factor (CRF) systems, leading to enhanced neuroendocrine, autonomic and behavioral responsiveness to stress as well as altered dynamics of the HPA axis. Such increased stress sensitivity would then lower an individual's threshold to develop depression in relation to further stress.

The current review summarizes results of our studies and presents previously unpublished original data. We further discuss the implications of our results in terms of future research directions and clinical practice. In brief, our results suggest that childhood trauma contributes to the neuroendocrine features of depression, likely reflecting risk to develop depression in response to stress rather than correlates of the illness. Based on an integration of our HPA axis data with results from affective neurosciences, we propose that the primary lesion after childhood trauma is located at the neural systems level and involves failure of a connected neural network to adapt or compensate in response to challenge, leading to exaggerated responses of physiological outflow systems and altered behavior. However, not all forms of depression are associated with childhood adversity and our studies suggest the existence of biologically distinguishable subtypes of depression as a