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Review article

The neural diathesis-stress model of schizophrenia revisited: An update on recent findings considering illness stage and neurobiological and methodological complexities

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ABSTRACT

Over the past decade, our understanding of the role of stress in serious mental illness has become more sophisticated. In this paper, we revisit the *neural diathesis-stress model* of schizophrenia that was initially proposed in 1997 and updated in 2008. In light of cumulative research findings, we must now encompass evidence on the premorbid periods of psychosis, and our more nuanced understanding of hypothalamic-pituitary-adrenal (HPA) axis function and its association with neurodevelopmental, epigenetic, neurotransmitter, and inflammatory processes, as well as brain structure and function. Giving consideration to the methodological complexities that have become more apparent as research in this area has burgeoned, the various indices of HPA axis function, and the different stages of illness, we review relevant research published since the 2008 update of the model. We conclude by proposing an extended neural diathesis-stress model that addresses the broader neurobiological context of stress psychobiology in psychosis progression. Implications of this model for best practice, with regards to both future research and treatment strategies, are discussed.

Contents

Abbreviations: 2-DG, 2-deoxy-D-glucose; ACTH, adrenocorticotropin releasing hormone; AUC, area under the curve; ALT, autoregressive latent trajectory; BDNF, brain-derived neurotrophic factor; CHR, clinical high-risk; CAARMS, comprehensive assessment of at-risk mental states; CRH, corticotrophin releasing hormone; CAR, cortisol awakening response; DST, dexamethasone suppression test; DA, dopamine; ESM, experience sampling method; FEP, first episode of psychosis; fMRI, functional magnetic resonance imaging; GHR, genetic high risk; GWAS, genome-wide association studies; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; IL, interleukin; MR, mineralocorticoid receptor; MIST, Montreal Imaging Stress Task; PET, positron emission tomography; PTSD, post-traumatic stress disorder; SPD, schizotypal personality disorder; SSRI, selective serotonin re-uptake inhibitor; SIPS, structured interview for prodromal syndromes; SNS, sympathetic nervous system; SAM, sympatho-adrenal medullary system; TSST, Trier Social Stress Test; VBM, voxel-based morphometry.

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1. Introduction

Stress has long been implicated in the etiology of mental illness, yet it is only within the past two decades that the neurobiological processes mediating this effect have been elucidated by basic and clinical research. In the case of psychotic disorders, which are among the most debilitating mental illnesses, theorists postulated a role for stress in the 1960s (Rosenthal, 1966), but it was not until the 1990′s that specific neurobiological mediators were considered. In 1997, the "neural diathesis-stress" model of psychosis was proposed, a model that focused on the role of the hypothalamic-pituitary-adrenal (HPA) axis in triggering and exacerbating psychotic symptoms (Walker and Diforio, 1997). The model was later updated to incorporate subsequent empirical findings that were consistent with its predictions (Walker et al., 2008).

Since the publication of the updated neural diathesis-stress model in 2008, research on stress neurobiology, including the role of stress and the HPA axis in mental disorders, has burgeoned. In the present paper, we review the findings from studies of HPA axis abnormalities in diagnosed patients with established and first episode psychosis (FEP), as well as individuals at genetic high risk (GHR) and clinical high risk (CHR) for psychosis, to which the authors of this review have made significant contributions. We consider results obtained with various research designs and methodological approaches, contemplate caveats and challenges in stress research, and take into account the multiple mechanisms that appear to act in concert with the HPA axis in setting the stage for psychosis. We conclude by offering an updated model that considers the complex interplay of vulnerability factors, neurobiological processes and psychosis progression. Finally, we suggest avenues for future research that might help to overcome and understand inconsistencies in this field, and discuss the implications of these findings for treatment options.

1.1. Stress and the HPA axis

As typically conceptualized by researchers, stress entails a threat to the organism's homeostasis (Frodl and O'Keane, 2013; Hostinar et al., 2014). Broadly defined, the events or 'stressors' that precipitate a sense of threat can be psychological (e.g., social rejection) or biological (e.g., physical injury or illness). With respect to the former, the nature of the events that are construed as stressors by humans varies among individuals as a function of their personal histories, personality traits, and cognitive appraisals. Thus a rela-