Psychiatric Clinics of North America

Volume 21, Issue 2, 1 June 1998, Pages 293-307

PSYCHONEUROENDOCRINOLOGY OF DEPRESSION: Hypothalamic-Pituitary-Adrenal Axis

Paul M. Plotsky PhD [a, b] ... Charles B. Nemeroff MD, PhD [c]

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https://doi.org/10.1016/S0193-953X(05)70006-X

Advances in the technologic armamentarium available to basic and clinical investigators have enabled increasingly sophisticated studies of brain function in health and disease. This information has been complemented by a vast expansion in our basic knowledge of developmental neuroscience. Together these studies have provided a strong foundation supporting the thesis that neurobiologic alterations leading to plasticity and sensitization in the central nervous system underlie the origin and pathogenesis of psychiatric disorders such as major depression. This synthesis permits a neurobiologic reinterpretation37, 89 of Sigmund Freud's psychoanalytic theory[44] which, consonant with current theory,64, 65, 106 focused on conflicts early in life as the cardinal factor in the development of mental disorders. The emergent â€œstress-diathesisâ€ theory of major depression predicts that multiple factors contribute to the onset and course depression as illustrated in Figure 1. These factors include the existence of one or more currently unidentified genetic liabilities11, 13, 41, 43, 99 and epigenetic factors, especially in the form of adverse life events16, 29, 30, 47, 64, 72, 78, 136 with or without the

trigger of additional stressors. While a definitive linkage between stressful life events and major depression has not been unambiguously established, considerable evidence supports such an association. Stressful life events frequently precede the onset of major depression and anxiety disorders.16, 17, 18, 19, 40, 48, 136 The genetic and epigenetic factors are considered complementary, in that alone neither is sufficient to produce depression but, rather they interact throughout a prolonged developmental period extending from the perinatal period through the peripubertal period in a complex manner to either enhance an individual's vulnerability to expression of the disease under further exposure to adverse circumstances.

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Address reprint requests to Paul M. Plotsky, PhD, Department of Psychiatry & Behavioral Science, Emory University School of Medicine, 1639 Pierce Drive, Suite 4000, Atlanta, GA 30322

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