SYNAPTIC PATHOLOGY IN DEPRESSION

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1. SUMMARY

Depression is an illness in which the reaction to stress and genetic vulnerability come together in such a way that the emotional tone and evaluation of information becomes biased in a negative direction. The pathophysiology lying behind these changes involves monoamine systems as well as the hypothalamus–pituitary–adrenal (HPA) axis and leads to changes in neuronal plasticity, as reflected by decreased levels of neurotrophins, decreased proliferation of neuronal precursors and, most importantly, changes in synaptic structure and function. These concepts are based on indirect evidence from human studies and have been confirmed by animal studies, allowing assessment of behavior as well as detailed functional and structural analyses. Several animal models, namely stress models and genetic models, have demonstrated a good validity for human depression and provided evidence for synaptic pathology in depression.

2. INTRODUCTION

Depression is a serious and widespread disorder which results from an interplay between genetic factors and environmental factors such as stress. Early life exposure to severe stress and acute exposure to stress appear to play a role in the development of the illness. The major theories concerning the etiology of depression involve alteration of the amines such as norepinephrine and serotonin or changes in the HPA axis that mediate stress. These theories reside at the receptor level on the surface of the cell membrane. More recent evidence suggests these are simply parts of a complex network altering second messenger systems and ultimately leading to changes in gene expression which may involve direct structural changes in the brain. These changes have been postulated to involve

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neurogenesis, or alternatively synaptogenesis. This chapter reviews the evidence to date implicating such structural change.

3. DEFINING DEPRESSION

Depression is one of the most common psychiatric disorders, it has a lifetime prevalence of up to 20%. Major depressive disorder (MDD) is associated with considerable suffering and impairment of the patient and consequently there is a high risk for committing suicide during a depressive episode. The WHO recently determined that depression may be the illness which contributes the most to total morbidity, and will clearly attain this position by 2020. Diagnostic criteria for a depressive episode include depressed mood and the loss of interest or pleasure for more than 2 weeks as central features of the disorder. There is a wide variation of associated abnormalities: cognitive symptoms include inappropriate thoughts of guilt or worthlessness occasionally reaching delusional proportions; common are rumination, reduced concentration, and the impaired ability to make decisions. Neurovegetative symptoms include sleep and appetite disturbances, psychomotor changes like agitation or in contrast retardation, and symptoms like decreased energy, fatigue, and tiredness are very common.

Depression is an episodic and recurrent illness. Longitudinal studies suggest that only rarely will a person suffer from only a single episode of depression. The largest data set collected concerning longitudinal course (NIMH collaborative study on depression) showed that nearly 80% of all people suffering an episode of depression will have a reoccurrence within 8 years. Thus, we see that the illness appears to be one with acute changes which are at least partially reversible and each episode somehow increases the risk for subsequent episodes.

The question which received the most research attention over the last three decades is what happens to cause an episode of depression. A host of epidemiological evidence has shown that stressful life events such as family or work-related conflicts, loss of close personal relationships, or major health problems play a role in the initiation of an episode.

Concurrently, there is an overwhelming evidence from epidemiologic studies that – apart from stress – early adverse events and genetic factors also play a role in increasing the risk for depression. With respect to early adverse events Heim and colleagues were able to show long-lasting effects of any kind of abuse in childhood on endocrine responses. These persistent consequences may contribute to the diathesis for adulthood psychopathological conditions such as depression and have implication for therapeutic response and prognosis. In addition, affective disorders share a significant genetic basis: Twin studies provide an estimate that roughly 33% of the risk for depression is genetically determined. Despite this strong genetic influence, it has been difficult to identify the genes conferring the risk for depression with certainty. This is most likely explained by the fact that several genes are involved in mediating the risk and analysis is complicated by the strong genetic–environmental interaction. This means that genes conferring an increased risk for depression are thought to modulate the subject’s ability to cope with environmental demands, and only if a certain environmental challenge – a stressful life event – occurs, the corresponding gene’s property to contribute to the risk of depression can be detected. The polymorphism in the serotonin transporter (5HTT) gene regulatory region can serve as an example of this gene–environment interaction: the short variant of the 5HTT promoter gene results in decreased