The Neurobiology of Depression

Depression is a common illness affecting up to 20% of the population, with up to 5% of cases being severe. It is responsible for considerable morbidity and possibly mortality in terms of suicide risk, and is often associated with other symptoms and syndromes including anxiety states, feelings of worthlessness, hopelessness, guilt, appetite and sleeping disorders and substance abuse.[1]

While specific genes that are proven to confer a risk for depression still remain to be identified, depression appears to be a highly heritable disorder, most likely of polygenic origin, where epidemiologic studies indicate that approximately 50% of the risk for depression is genetic.

Nongenetic factors are also important in the pathogenesis of depression. Stress, emotional trauma, viral infections and events during brain development have been implicated in the aetiology of depression, and many medical conditions, including endocrine abnormalities, collagen vascular disease, Parkinson's disease, traumatic head injury, cancer, asthma, diabetes and stroke may present with depressive syndromes. It is probable that, in most cases, the interaction between a genetic predisposition and environmental factors are the basis for a depressive episode.

The development and study of effective pharmacological treatments for depression has indicated changes in neurochemicals that appear to be important in the pathogenesis and management of the condition. Monoamine oxidase inhibitors and inhibitors of noradrenalin and serotonin reuptake increase the concentrations of these neurotransmitters in the central nervous system. However, not all patients with depression respond to these medications (only approximately 50% will go into remission with treatment) and when a response does occur it does so only after prolonged exposure. The indication is that the mechanisms of mood elevation are more complex than first apparent and that some gradually developing adaptation to increased levels of neurotransmitters, rather than the increased levels themselves, may be responsible for the therapeutic effect.

The parts of the brain that are responsible for mood regulation are poorly understood. Studies suggest that many regions of the brain are involved in the pathogenesis of depression and its different associated symptoms, including regions of the prefrontal and cingulated cortex, hippocampus, striatum, amygdala and thalamus.

One important mechanism by which the brain reacts to stress is activation of the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamus secretes corticotrophin-releasing factor (CRF), which stimulates the synthesis and release of adrenocorticotrophin (ACTH) from the anterior pituitary, which, in turn, stimulates the synthesis and release of cortisol from the adrenal cortex. Under normal conditions, a feedback loop exists, by which an increase in cortisol will inhibit HPA activity via neurons in the hippocampus and paraventricular nucleus. However, under conditions of severe stress, sustained raised levels of glucocorticoids may damage hippocampal neurons, particularly CA3 pyramidal neurons, such that dentritic branching is reduced and dentritic spines where the neurons receive their glutamatergic synaptic inputs are lost. The birth of new granule cell neurons in the adult hippocampal dentate gyrus (an area important in normal memory function) may also be reduced. Damage to hippocampal neurons not only disturbs the normal glucocorticoid feedback loop, thereby exacerbating raised glucocorticoid levels and further hippocampal damage, but may also be responsible for some of the symptoms that are observed in depressed patients. Enhanced CRF transmission in the hypothalamus and other brain regions may also contribute to symptoms of depression.

Neurotrophic factors that regulate neural growth and differentiation during development and regulate plasticity and survival of adult neurons and glia may also play a role in depression, where a deficiency of neurotropic support may contribute to hippocampal pathology.

One of the most prevalent neurotropic factors in the adult brain is brain-derived neurotropic factor (BDNF). In rodents, during acute and chronic stress, BDNF expression in the dentate gyrus and pyramidal cell layer of the hippocampus is reduced. This deficiency is mediated by a number of factors, including glucocorticoids and serotonergic transmission1. Administration of antidepressants upregulates BDNF expression and can prevent stress-induced decreases in BDNF levels. Restoration and elevation of BDNF levels may help to repair stress-induced hippocampal damage and improve hippocampal function. Upregulation of BDNF expression, and the gradual rise in BDNF required for it to have an effect, might also explain the delay in onset of antidepressant efficacy.[1]

Conversely, the atrophy and apoptosis of vulnerable neurons as a consequence of BDNF deficiency may lead to depression, and the consequence of repeated depressive episodes is to potentiate further episodes and a declining response to antidepressant therapy.[2] This may highlight the importance of choosing an effective treatment for depression as early as possible in the course of the disease, because failure to achieve a favourable response has been shown to lead to more frequent relapses and failures of drug therapy.[3]

While these observations are exciting in that they highlight novel targets for antidepressant drug therapy, the mere nature of the multiple brain sites that are most likely involved in the symptom complex of depression, suggests that an understanding of the complete pathogenesis of depression is much more complicated and remains to be elucidated.

References

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