Pharmacological Reports
2013, 65, 1622–1631
ISSN 1734-1140

Review

Possible contribution of IGF-1 to depressive disorder

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Abstract:
Depression is an illness of unknown origin and involves the dysregulation of many physiological processes disturbed in this disease. It has been postulated that the pathomechanism of depression is complex, and apart from changes in neurotransmitters, a dysregulation of the immune and endocrine systems also plays an important role in the development of this disorder. Recent studies indicate that an impairment of synaptic plasticity in specific areas of the central nervous system (CNS), particularly the hippocampus, may be an important factor in the pathogenesis of depression. The abnormal neural plasticity may be related to alterations in the levels of neurotrophic factors. On this basis, a theory connecting the occurrence of depression with disturbances in neurotrophic factors has gained great attention.
This review summarizes data suggesting a role for the neurotrophic factors – especially insulin-like-growth factor-1 (IGF-1) – as possible targets for therapy in depression in the context of depressive behavior modulation, anti-inflammatory action and neuroprotection.

Key words:
neurotrophic factors, insulin-like growth factor (IGF) family, depression, antidepressant and anti-inflammatory action, neuroprotection

Abbreviations: BAD – Bcl-2-associated death promoter protein, BDNF – brain-derived neurotrophic factor, CNS – central nervous system, CTNF – ciliary neurotrophic factor, GSK-3β – glycogen synthase kinase-3β, HPA – hypothalamus-pituitary-adrenal, IFN-γ – interferon-γ, IGFBP – insulin-like growth factor binding protein, IGF-1 – insulin-like growth factor-1, IGF-1R – insulin-like growth factor-1 receptor, IGF-2 – insulin-like growth factor-2, IL-1β – interleukin-1β, IL-4 – interleukin-4, IL-10 – interleukin-10, iNOS – inducible NO synthase, IR – insulin receptor, IRS-1 – insulin receptor substrate-1, LIF – leukemia inhibitory factor, LPS – lipopolysaccharide, M6P/IGF-2R – mannose-6 phosphate/insulin-like growth factor-2 receptor, MAPK/ERK – mitogen-activated protein kinases/extracellular signal-regulated kinases, mTOR – mammalian target of rapamycin, NGF – nerve growth factor, NT-3 – neurotrophin-3, NT-4/5 – neurotrophin-4/5, PI3K/AKT – phosphatidylinositide 3-kinase/protein kinase B, PLC – phospholipase C, Src – proto-oncogene tyrosine-protein kinase, TNF-α – tumor necrosis factor-α.

Introduction

Depression is a relatively common and serious mental disorder affecting up to 15% of the population at least once in their lifetime. It is a condition of unknown origin and in severe cases may lead to suicidal attempts and death. Over the years, many different di-

rections have been explored to investigate the mechanisms of the onset of affective disorders such as major depression, bipolar disorder or mania. Currently, it is believed that interactions between genetic and environmental factors are the most important factors in the neurobiological mechanisms of affective illnesses. Antidepressants used in the treatment of depression are effective in only 50% of patients, and clinical data show that patients respond to this medication only after weeks or months of chronic treatment [24]. It has been postulated that the pathophysiology of depression is complex, and apart from changes in the neurotransmitter system, dysregulation of the immune and endocrine systems also plays an important role in the development of this disorder.

Recent studies have indicated that impairment in synaptic plasticity, i.e., axon branching, dendritogenesis and neurogenesis in specific areas of the central nervous system (CNS), particularly in the hippocampus, may be an important factor in the pathogenesis of depression. Abnormal neural plasticity may be related to alterations in the levels of neurotrophic factors. On this basis, a theory connecting the occurrence of depression with disturbances in neurotrophic factors has been the subject of increased attention. In fact, patients suffering from affective disorders exhibit not only morphological changes in the CNS but also functional impairment in some brain areas [27]. Alterations of the hippocampus, prefrontal cortex or amygdala have been linked to changes in the expression or levels of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), nerve growth factor (NGF) and recently insulin-like growth factor (IGF-1) [9].

This paper reviews data suggesting a role for the neurotrophic factors, particularly IGF-1, as possible targets for the therapy of depression, in light of evidence suggesting their involvement in depressive behavior modulation, anti-inflammatory action and downstream signaling activation, all of which lead to neuroprotection.

The role of neurotrophic factors in the brain

Neurotrophic factors are a family of proteins involved in neuronal growth, differentiation, maturation and survival. Therefore, their contribution to proper functioning of both the central and peripheral nervous systems cannot be overestimated. These factors are synthesized and secreted not only by neuronal cells of the brain and spinal cord but also by cells or tissues that depend on peripheral sensory, motor and sympathetic neurons. Neurotrophins fulfill modulatory functions on synapse formation and neuronal growth, both during embryogenesis and in adulthood. In addition to the classical neurotrophins BDNF, NGF, NT-3 and NT-4/5, neuropoietins such as ciliary neurotrophic factor (CTNF), leukemia inhibitory factor (LIF), transforming growth factors and the growth factors IGF-1 and IGF-2 are also considered neurotrophic factors [43].

Neurotrophic factors play an important role in the regulation of a large spectrum of brain processes, and the equilibrium between neuroregeneration and neurodegeneration is largely dependent on the availability and activity of specific growth factors. Apart from exhibiting "classic" neurotrophic actions, these agents may also affect synaptic transmission, modulate the activity of different types of neurons or influence memory formation. However, there are still many undiscovered potential actions of neurotrophins in the brain.

Neurotrophic factors and depression

BDNF, which plays an important role in brain plasticity particularly in the hippocampus, is the most extensively studied member of the neurotrophic factor family in depression. The hippocampus is smaller in depressed patients, but it is unclear whether its diminished size is a consequence of the illness or rather a result of the prior action of factors that lead to the onset of depression. It is known that excessive activation of the hypothalamic-pituitary-adrenal (HPA) axis (often observed in patients suffering from depression) leads to a sustained elevation of corticosteroids and chronic neuroinflammation. The HPA axis is also capable of downregulating hippocampal neurogenesis, and all of these factors may lead to depression. Data from human brain tissue (obtained from subjects with depression) studied *post mortem* showed a downregulation of BDNF mRNA, which is thought to be one of the essential causes of plasticity impairments and changes in the hippocampus that lead to behavioral disturbances.