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Review Article

ROLE OF INSULIN-LIKE GROWTH FACTOR IN DEPRESSION: A REVIEW

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ABSTRACT

Depression is a disorder of unknown origin and it involves disturbance of many physiological processes. There are many mechanisms in depression including alterations in neurotrophic factors. It has been suggested in this review that an impairment of synaptic plasticity in specific areas of central nervous system, specifically in hippocampus can be an important factor in the pathophysiology of depression. Further, an abnormal neural plasticity may be related to alterations in the level of neurotrophic factors. In context with this, it can be suggested that there can be a connection between occurrences of depression with the disturbance of neurotrophic factors, raising great attention in the recent years. In the present review, it has been tried to explain the significance of insulin-like growth factor in depression by presenting the several important topics such as neurotrophic factors in depression, insulin like growth factor in central nervous system, insulin like growth factor receptor in depression, neurotrophic role of insulin like growth factor and correlation between insulin like growth factor and brain serotonin levels.

KEYWORDS: Depression, Insulin-like Growth Factors, Neurotrophic Factors

INTRODUCTION

Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest. The common feature of all the depressive disorders is the presence of sad, empty or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function. Depression can be experienced by all individuals at some time in their lives due to many factors that can trigger low mood state and it could be transitory may be described as temporary depression or chronic may be characterized by having the symptoms for long period of time[1]. Depression is complex phenomenon, which has many subtypes and probably more than one aetiology. The pathophysiology of major depressive disorder has not been clearly defined. Current evidence points to a complex interaction between neurotransmitter availability and receptor regulation and sensitivity underlying the affective symptoms. Clinical and preclinical trials suggest a disturbance in central nervous system serotonin activity as an important factor. Other neurotransmitters implicated include nor epinephrine, dopamine or glutamate. Further, role of brain-derived neurotrophic factor and its expression have been well established however the underlying pathophysiology of major depressive disorder has not still been clearly defined.

Various drugs category like selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, serotonin/nor-epinephrine reuptake inhibitors, serotonin-dopamine activity modulators, atypical antidepressants are utilized for the treatment of depression. Apart from drugs, electroconvulsive therapy is also preferred due to its effectiveness in the depression, especially in treatment of choice for patients who do not respond to drug therapy. Some other psychotherapy like cognitive or behavioural therapy or interpersonal therapy alone can relieve depressive symptoms. Combination therapy has also been associated with significantly higher rates of improvement in depressive symptoms; increased quality of life and better treatment compliance. Cognitive behaviour therapy and interpersonal therapy are evidence based psychotherapies that have been found to be effective in the treatment of depression. There is evidence supporting the use of CBT with individuals of all ages. It is also considered to be efficacious for the prevention of relapse. It is particularly valuable for elderly patients, who may be more prone to problems or side effects with medications. Mindfulness based cognitive therapy was designed to reduce relapse among individuals who have been successfully treated for an episode of recurrent major depressive disorder and found effective in reducing risk of relapse in patients with recurrent depression, especially in those with the most severe residual symptoms[2].

Despite availability of various antidepressant treatment and therapies for depression there have been many limitations that are observed which leads to the need for the development of newer antidepressant agents. In light of this, various neurotrophins factors have been taken as research attention. Insulin-like growth factor -1 (IGF-1), also called somatomedin-c, is member of neurotrophic family, may suppose to influence mood regulation, raising its potential utilization in the treatment of depression.

NEUROTROPHIC FACTORS

Neurotrophic factors are defined as endogenous soluble protein regulating survival, growth, morphological plasticity and synthesis of proteins for differentiated functions of neurons. Several neurotrophic factors are 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 -1 (IGF-1) [3].

The Role of Neurotrophic Factors in the Brain

Neurotrophic factors play an important role in both protection and recovery of function following neurodegenerative diseases such as stroke and traumatic brain injury [4]. Regulation of a large spectrum of brain processes and the equilibrium between neuro-regeneration and neuro-degeneration is largely dependent on the availability and activity of specific growth factors. Neurotrophins fulfils modulatory functions on synapse formation and neuronal growth, both during embryogenesis and in adulthood. Neurotrophins such as BDNF and their high affinity receptors are actively produced throughout the brain and are involved in regulating neuronal activity and normal day-to-day function[4]. It has been reported that neurotrophins 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[4].

Neurotrophic Factors and Its Correlation with Depression

It has been reported that NGF levels were altered in the frontal cortex, amygdala or hippocampus in animals which were exposed to the various stressors like forced movement and rough handling followed by a painful injection. Further, it has been demonstrated that an increase in NGF levels in the rat frontal cortex, hippocampus and limbic forebrain after sub-chronic lithium treatment[5]. The influence of duloxetine treatment on NGF levels in different brain areas has been tested and the drug was found to decrease NGF expression. Although the availability of studies investigating the serum levels of NGF in depressed patients is limited, it is generally accepted that the level of NGF is decreased in untreated patients suffering from major depression[6].

Brain derived neurotrophic factors (BDNF), a member of neuroptrophic factor family plays an important role in brain plasticity particularly in the hippocampus, is the most extensively studied member in depression. Many studies have investigated the contribution of BDNF dysfunction in depression- like disorders using animal models of depression. There is some evidence that the expression of not only BDNF but also other neurotrophic factors may be altered in patients suffering from affective disorders[7].

Additionally, the levels and functions of other classical neurotrophic factors such as NT-3 and NT-4/5 are also thought to influence the changes accompanying affective disorders. It is possible that the changes in NT-3 or NT-4/5 levels may be responsible for the behavioural disturbances observed in this animal model of depression. There exist various types of neurotophic factors have role in depression but in this review, more focus has given to IGF-1 enlighten the role of IGF-1 in depression[8].

INSULIN LIKE GROWTH FACTOR (IGF)

Insulin-like growth factor 1 (IGF-1) also called somatomedin C, is a protein that in humans is encoded by the IGF1 gene. IGF-1 is a hormone similar in molecular structure to insulin. It plays an important role in childhood growth and continues to have anabolic effects in adults. IGF-1 has a molecular weight of 7,649 da. Previous studies have indicated the existence of two isoforms of IGF known as IGF-1 and IGF-2. Tissue specific alternative splicing patterns have been shown to exist, but of these IGF-1_{Ea} and IGF-1_{Eb} are the most extensively studied. The first alternate form $IGF1_{Ea}$ is secreted as IGF-1, consisting of 70 amino acids in a single chain with three intra-molecular disulfide bridges and sharing 40% identity with insulin[9]. In the periphery, the liver is the main source of IGF-1 and its expression is regulated by growth hormone. Other organs also synthesize IGF-1 and all cell types respond to IGF-1 signalling. Thus, IGF-1 exerts endocrine as well as paracrine effects. In humans, the IGF-1 gene is located on chromosome 12q22-q23, whereas in the rat, it is on chromosome 7[10].

IGF-1 Receptor as the Target for the Actions of IGF-1 in the Brain

IGF-1 exerts its biological functions mainly through the IGF-1 receptor (IGF-1R), which is a trans-membrane tetramer, composed of two extracellular α chains and two intracellular β chains, associated with a tyrosine kinase domain IGF-1 exerts its physiological effects, mostly by binding to its receptor (IGF-1R) [11] The binding of IGF-1 to its receptor originates in a cysteine-rich region of the receptor α subunit to generate a conformational change. The conformational change allows the activation of its tyrosine kinase domain, phosphorylating the corresponding sites of the β subunit and promoting auto-phosphorylation of the receptor and the substrate of the insulin receptor type 1 (IRS-1). The latter would be a crucial element of receptor activation, since different intracellular signalling pathways will be activated through it[12].

IGF-1 also exerts its effects through insulin receptors (IR) in its α and β isoform although with lower affinity because it shares only 50% structural homology with the IGF -1R[13]. There are also other hybrid receptors formed by the pro-receptors of IR and IGF-1R, however their function has not yet been understood in detail [14].

The binding of IGF-1 to its receptor initiates intracellular signalling related to cell growth, metabolism and inhibition of apoptosis among others. When the IRS-1 protein is altered, there is no compensation of the IRS-2 or other related proteins. The alteration of IRS-1 in the intracellular action of IGF-1 or insulin would be an indication of resistance to these peptides upon disruption of their signalling pathway[13].

Insulin- Like Growth Factor (IGF) and Mood Alterations

Recently, IGF-1 has gained great attention in diseases affecting the CNS due to two reasons. First, IGF-1 is known to increase the synthesis and activity of BDNF which is required to enhance neuronal survival and plasticity in the brain. Second, IGF-1 is a potent regulator of cell growth, survival and differentiation and exhibits neurotrophic, neurogenic and neuro-protective actions[15].

The most important role of IGF-1 in the brain is to control cell growth, differentiation, maturation and metabolic processes at different developmental stages. During early organogenesis, IGF-1 mRNA expression in the CNS is low but significantly increases at later developmental stages. In adults, its expression remains very high, especially in brain areas with large projection neurons such as the cerebellum, olfactory bulb, hypothalamus, hippocampus, cortex and retina. Additionally, various studies indicated that IGF-1 is also expressed in the brain stem and spinal cord[16].

Depression-like mood alterations are frequently observed in growth hormone (GH) - deficient individuals. In mouse models, a reduction of peripheral and central IGF-1 in the hippocampus led to a depression-like behavioural pattern, pointing out once more that both sources of this mediator are eliciting effects in the central nervous[17].

There are several studies reporting a strong association of altered hippocampal neurogenesis with affective disorders such depression. Though evidence in humans is still lacking this might

provide a possible explanation for persistent mood impairments in GH-related diseases. It has been reported that neurogenesis especially in the hippocampus has been assumed to be associated with the therapeutically effectiveness of anti-depressant drugs, since these effects could be blocked by neurogenesis inhibition. However, it remains unclear if increase of neurogenesis per se may have positive effects on depression-like behaviours[18]. These effects could at least partly be recognized to modifications by the GH/IGF-1- system as chronic IGF-1 treatment in mice exerts antidepressant effects and the administration of anti-IGF-1 antibodies resulted in the abolishment of exercise- induced antidepressant effects. In another study, an increase in free serum IGF-1 resulted in antidepressant improvements which consecutively could be reversed by the administration of an IGF-1 receptor antagonist[19]. A study in mice revealed that exogenous administration of the GHRH-antagonist resulted in an in accentuated depressive phenotype[20].

IGF and Brain Serotonin Correlation

Selective serotonin reuptake inhibitors (SSRIs) are the most widely used antidepressants, a significant proportion of depressed patients do not achieve remission with SSRIs[21]. It has been reported that a serotonin type 3 receptor agonist induces antidepressant effects as well as hippocampal neurogenesis independent of Fluoxetine. Furthermore, in vivo micro-dialysis analysis shows that 5HT3R regulates hippocampal extracellular IGF1 levels, and it also reported that $5HT_3$R-dependent hippocampal neurogenesis is mediated by increased IGF1 levels. This may provide a new therapeutic target for depression, especially bringing significant benefits for SSRI-resistant depressed patients[22].

Exogenous administration of IGF-1 in the adult visual cortex restores the susceptibility of cortical neurons to monocular deprivation and promotes the recovery of normal visual functions in adult amblyopic animals[23]. Depletion of serotonin by the tryptophan hydroxylase inhibitor para-chlorophenylalanine blocked the antidepressant-like effects of IGF-I. Administration of IGF-I increased basal serotonin levels in the ventral hippocampus and altered the effects of acute citalopram. Thus, IGF-I administration initiates a long-lasting cascade of neurochemical effects involving increased serotonin levels that results in antidepressant- like behavioural effects[24].

It has been reported that blockade of the IGF-I receptor with the IGF- I antagonist before IGF-I administration prevented the antidepressant-like effects of IGF- I. The pattern of antidepressant-like effects of IGF-I resembled those of selective serotonin reuptake inhibitors. Depletion of serotonin by the tryptophan hydroxylase inhibitor para-chlorophenylalanine, blocked the antidepressant-like effects of IGF-I. Administration of IGF-I increased basal serotonin levels in the ventral hippocampus and altered the effects of acute citalopram. Thus, IGF-I administration initiates a long-lasting cascade of neurochemical effects involving increased serotonin levels that results in antidepressant- like behavioural effects[25].

It has been suggested that lower and higher levels of IGF1 promotes neurogenesis in the hippocampus, effects similar to those produced by chronic antidepressant treatment[26]. It has been reported that that central administration of IGF-I produced antidepressant- like effects in modified rat forced swim test (FST) [27]. It indicated that, drugs that inhibit binding proteins for IGF-1, thereby increasing the effects of free IGF-1, can also produce antidepressant-like effects in mice[28].

THE ROLE OF THE IGF-1 IN DEPRESSION

Because IGF-1 has the ability to influence many processes such as synaptic plasticity, adult neurogenesis and differentiation, it has been suggested that disturbances in the IGF-1 system may be involved in the development of affective disorders. Unlike in the case of BDNF, no genetic polymorphism has been found unambiguously confirming the association between IGF-1 and the occurrence of depression.

The Antidepressant-Like Action of IGF-1

Chronic deficiency of IGF-1 in the periphery and in the hippocampus was observed in mice, showing depressive-like behavioural disturbances[29]. In the light of the discovery of alterations in IGF-1 levels in depression-like states, the question arises whether IGF-1 exerts antidepressant-like activity and whether antidepressants may influence the IGF-1 family of factors. To explore the putative antidepressant activity of IGF-1, several studies included the administration of IGF-1 to animals and then subjected them to behavioural testing like the forced swimming test and/or the tail suspension test. Most data indicated that IGF-1 treatment exerts antidepressant like-activity by normalization of behavioural disturbances in various animal models of depression[30-31].

Furthermore, some studies indicated that IGF-1 treatment is also effective in reducing sickness behaviour caused by intra-cerebroventricular injection of LPS or TNF-alpha[32].Since, it was reported that IGF-1R antagonist abolishes IGF-1 antidepressant activity, this activity is clearly mediated by the IGF-1 receptor. Furthermore, the antidepressant-like effects of IGF-1 were often associated with an increase in cell proliferation in the hippocampus[33].

It was also found that concomitant administration of a nonspecific IGFBP (insulin like growth factor binding protein) inhibitor has antidepressant-like effects[34]. The mechanism of action of IGF in behavioural disturbances has not yet been clearly identified. It was proposed that an anti-depressant-like effect of IGF-1 is mediated by IGF-1 receptor in the brain [35]. However, it was also proposed that IGF-1 influences neuronal plasticity and learning by affecting other neurotrophic factors such as BDNF. This was confirmed by reports of the positive impact of IGF-1 on the synthesis of BDNF and the synergy of these trophic factors in antidepressant action[36]. Most of the data show that the antidepressant effect of IGF-1 is comparable to the effect of antidepressants. The influence of antidepressant drugs on IGF-1 expression has also been examined. It has been reported that acute and chronic administration of fluoxetine affects IGF-1 mRNA expression in different ways, varying between specific brain structures[37]. It has been suggested an additional role of IGF-1R activation in the therapeutic effects of fluoxetine. However, up-regulation of the expression of IGF-1 and its receptor was observed in the frontal cortex after repeated Fluoxetine administration and its downregulation was observed in the hippocampus[38].

Anti-Inflammatory Effect of IGF-1 and Depression

It has been reported that IGF-1 was shown to inhibit inflammatory processes mainly through inhibiting the expression of proinflammatory cytokines like IFN-γ, IL-1β and TNF-α [39]. In contrast, IGF-1 can also enhance the production of anti-inflammatory cytokines, namely, IL-4 and IL-10. In the brain, microglial cells are an important source of IGF-1 during development both during inflammation and after injury. Various reports indicated that chronic neuro-inflammation and up-

regulation of pro-inflammatory cytokines may lead to neurodegeneration by suppressing the production of microglia-derived neuronal growth factors such as IGF-1, which indicates a relationship between IGF-1 and pro-inflammatory cytokines[40].

A well studied inflammatory theory of depression indicated that disturbances in the levels of cytokines are responsible for the development of depressive behaviour. In the LPS - induced depression-like state showed for the first time in vivo that IGF-1 could temper the innate immune response within the brain and reduces the expression of inflammatory markers such as IL-1β, TNF-α and increases the expression of BDNF.

CONCLUSION

It can be concluded from the current review that neurotrophic factors in general and especially IGF-1, may play a crucial role in the regulation of the CNS function. Further, in light of beneficial effects of IGF-1 such as neuroprotective action, anti-depressant action and anti-inflammatory action, it can be suggested that IGF-1 may prove as potential rate limiting target for the treatment of psychiatric disorders especially depression. The current review may motivate the researchers to explore the role of growth factors in CNS function and their potential involvement in development of mental disorders.

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