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Insulin-like growth factor type 1 and its relation with neuropsychiatric disorders

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Abstract

The study of different neurotrophic factors, including insulin-like growth factor-1 (IGF-1), has become relevant in recent years because of its role in brain activity and its potential therapeutic applications. This article reviews IGF-1 in relation to neuropsychiatric disorders such as autism, anxiety, depression, post-traumatic stress disorder and Alzheimer's disease. An exhaustive search of different original articles, clinical, experimental, and review studies was carried out in MEDLINE/PubMed and ScienceDirect databases, selecting 80 high-impact post-2000 publications. It is concluded that despite the many functions of IGF-1 in the developing nervous system as well as in the adult brain that have been studied, especially with animal models, their role in the human brain with neuropsychiatric disorders is not completely understood, yielding contradictory data in highly prevalent disorders such as mood disorders. However, greater implications are encountered with neurodegenerative disorders. In addition, its high potential as a therapeutic resource in difficult-to-approach neuropsychiatric disorders, such as autism and Alzheimer's disease, is pointed out, but more research is needed at both basic and clinical levels, to fully understand its relevance in these disorders.

Introduction

The development of neuroscience as a multidisciplinary science, is providing the possibility of a deeper study of the human brain, especially the alterations of the central nervous system. Its development is based on experimental studies, genetic analysis, cellular and molecular biology studies, neurocognitive approaches, real-time studies of brain activity (EEG, MEG, iRMF, SPECT, etcetera) among others, which has allowed to unravel the different biological-functional changes of the human brain following neuropsychiatric diseases, especially those with unknown origin that involve a wide neurobiological deregulation [1].

Furthermore, the investigation of metabolic alterations and the relationship of different peptides involved with central nervous system disorders has gained great attention within research in neuroscience [2],[3],[4]. Among them, insulin-like growth factor-1 (IGF-1) has been attracting the attention of researchers in different scientific and medical branches because it is a pleiotropic peptide, involved in various cellular pathways/functional systems [5], and its Influence in the behavior of even other neurotrophic factors and neurotransmitters [2]. The study of IGF-1 cell pathway disruption, its receptors or serum IGF-1 levels, has been linked to various neuropsychiatric diseases and is seen as an important triggering factor. Some of these studies are briefly reviewed in relation to depression, anxiety, post-traumatic stress disorder, neurodegenerative disorders and autism, due to their prevalence, disease burden or high relative disease weight, and the major functional and social impairment they provoke [1].

This article aims to summarize the different studies that indicate the evidence of an alteration or possible relationship between insulin-like growth factor-1 and neuropsychiatric disorders referred, which will allow us to know their possible role in the etiopathogenesis of these disorders.

Methods

An exhaustive search of different original articles, clinical, experimental, and review studies was performed in MEDLINE/PubMed and SCIENCE DIRECT databases, with the search words "IGF-1, autism, autism spectrum disorder, anxiety, depression, major depression disease, post-traumatic stress disorder, Alzheimer's disease, neurotrophic factors". The studies were selected for their relevance and analysis with the IGF-1, to have been published in journals indexed in English and after year 2000. We also analyzed the references of the articles selected to search for additional studies. We found 80 articles that were organized according to the search words.

Within the selection criteria were considered: extensive description of the IGF-1 system and / or neuropsychiatric disorders mentioned; measurements of IGF-1 / IRS1 / IGFBPs, in blood, LCR, tissues, or others; studies carried out in animal models with validated disorder or in diagnosed human patients.

Next, a brief review of IGF-1 is performed, and then its relationship with the neuropsychiatric disorders mentioned is explored.

Insulin-like growth factor type 1

Insulin-like growth factor-1 (IGF-1) shares 48% structural homology with insulin [1],[2]. It is a peptide composed of 70 amino acids and has a weight of 7.5 kDa, mapped on chromosome 12 in humans and chromosome 10 in mice [2],[3]. IGF-1 is produced via a paracrine and endocrine manner by various tissues such as the brain, cartilage, skeletal muscle and pancreas, its main source is liver [4]. Production in the liver accounts for 75% of IGF-1 in the blood and is released by hepatocytes in response to growth hormone stimulation (GH); this production circulating in blood, can also enter the brain to exercise its properties [5].

IGF-1 fulfills important functions of cell growth and development, differentiation, synaptogenesis and mitogenesis [2]. Thanks to transgenic models of knockout mice that had the IGF-1 gene removed (igf1), its effects are known during pre and post natal development [6]. In the adult, in addition to the properties already mentioned, IGF-1 participates in the response to tissue damage. For example, in its synthesis and entry into the brain before trauma [7], or in neurogenesis [8]. In human studies, cognitive approaches have been performed showing better scores on neuropsychological tests that correlate with serum IGF-1 levels [9]. It has also been observed a greater symptomatological presence in neurodegeneration and neuropsychiatric disorders, in relation to changes in the IGF-1 system [10],[11].

As we can see, the IGF-1 system comprises a complex regulatory network that operates throughout the body [12] with multiple neurotrophic, metabolic, cell growth and neuroprotection properties [2],[13].

IGF-1 receptor

IGF-1 exerts its physiological effects, mostly by binding to its receptor (IGF-1R) [14]. The IGF-1R is a tetramer, composed of two extracellular α chains and two intracellular β chains, associated with a tyrosine kinase domain [3],[15]. The binding of IGF-1 to its receptor originates in a cysteine-rich region of the receptor α subunit to generate a conformational change [16]. 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) [15]. The latter would be a crucial element of receptor activation [17], since different intracellular signaling pathways will be activated through it.

IGF-1 also exerts its effects through insulin receptors (IR) in its α and β isoform [18], although with lower affinity [2], because it shares only 50% structural homology with the IGF -1R [19] 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 [20].

IGF-1 signaling mechanisms

The binding of IGF-1 to its receptor initiates intracellular signaling related to cell growth, metabolism and inhibition of apoptosis, among others [2]. The IGF-1R remains in reduced catalytic activity in its non-phosphorylated state [16] until its binding to IGF-1, allowing auto-phosphorylation of the receptor. The latter will serve as a site for coupling to adapter proteins such as the IRS-1/IRS-2, as well as the domain 2 homologue of Src (SH2) that continue with intracellular signaling [16]. When the IRS-1 protein is altered, there is no compensation of the IRS-2 or other related proteins (Shc, p85, and Grb2) [21]. The alteration of IRS-1 in the intracellular action of IGF-1 or insulin would be an indication of resistance to these peptides [22]upon disruption of their signaling pathway.

The phosphorylation of IRS-1 and IRS-2 on multiple tyrosine residues promotes an intracellular signaling cascade in at least two pathways. The first, the phosphatidyl-inositol-3-kinase pathway (PI3-K), implicated in cell growth, metabolic and anti-apoptotic processes. The second, mitogen-activated protein kinase (MAPK) pathway, involved in mitogenesis, cell differentiation, and so on. [2]. Activation of the PI3K pathway leads to activation of Akt (protein kinase B), mTOR (target of rapamycin), and inhibition of GSK3 (glycogen synthase kinase-3) [23].

Resistance to the IGF-1 system

Resistance to IGF-1 and insulin has been especially addressed in neurodegeneration studies [11], indicating alterations of the IGF-1 system, such as a lower affinity of the IGF-1R to its substrate, or an IRS-1 altered signaling [11]. In relation to the latter, higher levels of IRS-

1 phosphorylated serine 616, as well as Akt, in tauopathies, Alzheimer's disease [23] and in other disorders have been observed.

On the other hand, activation of tumor necrosis factor alpha (TNFα) promotes the activation of JNK (N-terminal c-Jun kinase). This stress signaling pathway is involved in neuronal plasticity, regeneration and cell death. Likewise, JNK can directly induce insulin resistance by phosphorylating the IRS-1 by inhibiting its signaling [24], and acting as an antagonist pathway for IGF-1 [25].
IGF-1 entry into the brain

Several of the effects of circulating IGF-1 on its entry into the brain are mediated by the blood-brain-barrier (BBB). The blood-brain barrier is a dynamic and complex interface between the blood and the central nervous system (CNS), which protects the brain from entering foreign molecules, in addition to intervening in its homeostasis [26]. The flow of nutrients and metabolites that pass from the blood to the CNS is largely regulated by the BBB, controlling its availability by different transport systems [26]. The circulating IGF-1 accesses the nervous system by transcytosis, through the choroid plexus [13] and blood vessels [2]. Transcytosis regulates endocytosis and the transport of molecules across the cell, for eventual release [2]. This transport includes the IGF-1R and the low density lipoprotein receptor type-1 (LRP1), to reach the cerebrospinal fluid, the hypothalamus and hippocampus [27].

IGF-1 entry and its effects on the brain are also regulated by IGFBP (insulin-like binding protein) [28]. These proteins modulate the actions of IGF-1 by controlling their availability and their half-life in blood [29]. There are 6 binding proteins that are specifically located in different tissues. The IGFBP-2, IGFBP-4 and IGFBP-5 are highly expressed in the brain [27]. These proteins can be synthesized especially in response to CNS injury [30], and when they bind to IGF-1, they form a complex that allows both their transport and inactivation [31] thus mediating their effects on the brain.

Animal models for the study of IGF-1
Different transgenic animals have been developed to characterize the IGF-1 system [6]. IGF-1 knock out models showed severe alterations in utero. Those animals that survived at birth showed a severe delay in the development of various organs and their growth, reaching only 30% of normal size [6]. The models that overexpress IGF-1 showed an increase in the size of different organs, as well as their growth from 3-4 weeks of age, reaching up to 30% greater size in adulthood. Some of these transgenic lines also showed an increase in brain size between 25-85%, with most animals dying [31].

Other models over-express IGFBP (IGFBP-1 to IGFBP-6). These proteins, by competing with the IGF-1R for binding to their ligand, affect cell growth and other processes mediated by inactivation of IGF-1 [32]. For example, the phenotypic consequences of IGFBP-1 expression are the reduction in brain growth, depending on the level of involvement and the time of development in which it was altered. In contrast, transgenic adult mice overexpressing IGFBP-2 showed only a 10-13% reduction in their body weight [32],[33]. It is thus that each of the transgenic strains exhibit a distinct phenotype, confirming a specific role of IGFBPs in the activity of the IGF-1 system [33].

On the other hand, animals knock out for IGF-1R showed a developmental delay in utero even greater than the knock out for IGF-1 [33]. They also showed abnormalities in muscle development, in the central nervous system and delayed fetal growth, reaching a weight lower up to 45% [6]. In animal knock out for IRS-1, the signaling cascade of IGF-1/PI-3K is shown reduced, and a decrease in growth between 50 and 60% is observed [21].

To better evaluate the endocrine/paracrine production of IGF-1, [34], they developed a conditional knock out model, removing the igf1 gene specifically in the liver. To fulfill their purpose, they used a Cre/loxP system where mice with the flanched igf1 loxP gene were mated to mice expressing the Cre recombinase exclusively in the liver. The complete elimination of the IGF-1 gene allowed mice to be produced with a 75% decrease in circulating IGF-1 [34]. Mice deficient in IGF-1 liver or Liver IGF-1 Deficient (LID) showed normal development, growth and fertility [34]. Subsequent studies have shown that these animals have motor learning, visual discrimination and long term potentiation (LTP) in the neocortex. However, their spatial learning and LTP are altered in granular cells of the hippocampus [35]. These animals also present greater anxious behaviors measured in the forced swimming test and the novelty suppressed feeding test [36].

IGF-1 and neuropsychiatric disorders.

The investigation of metabolic alterations, different peptides involved with perturbations of the nervous system, and the study of the IGF-1 cell pathway, its receptor or serum IGF-1 levels, has been related to various neuropsychiatric diseases and is seen as an important triggering factor [2],[37],[38]. Some of these studies are briefly reviewed below.

Studies on depression and anxiety
Several studies suggest that patients with major depression present alterations in the levels of various neurotrophic factors, such as the brain-derived neurotrophic factor BDNF, fibroblast growth factor FGF, vascular endothelial growth factor VEGF, and insulin-like peptides such as IGF-1 [39],[40]. Although all these neurotrophic factors do not directly control emotion [40], they are linked to the various areas and systems of neurotransmission more related to mood disorders.

On IGF-1, its role in the control and regulation of mood has been suggested because of its implication in processes such as synaptic plasticity, cell differentiation and neurogenesis [20]. Experimental studies show that the decrease in circulating IGF-1 in the hippocampus is related to depressive behaviors [41], and less response to treatment with antidepressants [42]. On the other hand, it

has been observed that the administration of IGF-1 promotes neurogenesis and the reduction of depressive symptoms [43], and that the antidepressant effects of exercise, as well as environmental enrichment, would be mediated by IGF-1 circulating to the brain in animal models [44]. In humans it has been found that low levels of IGF-1 in women, and high in men, predict the incidence of depressive disorders after 5 years [45]. In older adults, a meta-analytic study has found that lower and higher IGF-1 levels would be associated with higher depressive behavior in this population [46].

However, other studies with human populations find disparate results [47],[48], for example Kopczak *et al*., [15] found elevated levels of IGF-1 in depressed patients, as well as an altered response to antidepressant treatment. Likewise, it has been found that elevated plasma IGF-1 levels are higher in subjects with major depression without any treatment [49], or these levels have no direct relationship with the presence of depression [50]. It is possible that these conflicting results are due to several factors not yet explored, such as the implication of various IGFBPs in depression, as well as mechanisms of resistance to IGF-1 involved.

Regarding anxiety, animal studies show that reduced levels of circulating IGF-1 are associated with increased presence of anxious symptoms and less neurogenesis in hippocampus [36],[51]. Research on rats induced by diabetes with streptozotocin revealed higher levels of corticosteroid and anxiety, lower levels of serum IGF-1, prefrontal cortex, and increased apoptosis in the prefrontal cortex [52]. Other studies link the anxiolytic effects of exercise with IGF-1 [8], although it may have gender-specific effects. For example, Munive, Santi, & Torres-Aleman [53] suggest specific brain actions of IGF-1 according to sex, in response to physical exercise, this IGF-1 response is a possible mediator of differences in affective disorders of these populations.

Post-traumatic stress disorder (PTSD)

Traumatic events during development cause hormonal abnormalities in the long term [54],[55], and an increased risk of developing PTSD in humans [56]. Studies with animals at an early age have shown to mimic these characteristics, revealing the importance of hormonal and emotional reactivity in animals [57].

Studies with models of prenatal stress and maternal separation, suggest alterations of different neurotrophic factors [58]. In prenatal stress, IGF-1 levels decrease drastically in the hippocampus and frontal cortex [59],[60], and there is an increase in IGFBP-2, IGFBP-3 and IGFBP-4 levels in these areas [60]. Similarly, maternal clearance in postnatal rats promotes abnormal expression of IGF-1 and IGF-1R in cortex, as well as decreased IGF-1 over time [59]. In the adult animal, it has been observed that decreased levels of circulating IGF-1 are associated with lower hippocampal neurogenesis [8],[35], decreased hippocampal cortex volume and functional alteration [57],[60], although they would not be the only structures affected.

Studies in IRS-1 showed that chronic and acute psychogenic stressors produce a physiological response characteristic of insulin resistance [61],[62], suggesting similar changes in IGF-1. Other possible mechanisms linking IGF-1 and PTSD suggest a decrease in adult hypothalamic neurogenesis, with successive deregulation of the HPA axis by a decrease in neurotrophic agents, especially IGF-1 [63], the hippocampal atrophy by adrenal steroids [64], as well as a possible altered IGF-1 activity in the adenohypophysis [61].

Neurodegenerative disorders

In recent years, several studies are linking the presence of neurodegenerative diseases to the development of diabetes, metabolic disorders and insulin resistance [11],[62]. Studies in animal and human models show that reduced serum IGF-1 levels are associated with cognitive dysfunctions, and it has been shown that these disorders may be reversible through prolonged systemic administration of IGF-1 [27]. In the case of Alzheimer's disease, these patients may present resistance to IGF-1, which promotes the appearance of neurofibrillary tangles and amyloidosis [63].

Decreased circulating levels of IGF-1 in mice, their non-uptake by the brain, or IGF-1R blockade would inhibit the PI3K/Akt pathway, leading to increased amyloidosis and tau phosphorylation, as well as occurrence of cognitive disorders, developing in these animals a phenotype of Alzheimer's disease [64]. Also, other neurotrophic and cell growth factors such as BDNF and the glial cell-derived neurotrophic factor GDNF, have been linked to increased neuronal survival in cellular and animal models of neurodegeneration [65]. Westwood *et al*., [62] found that reduced levels of serum IGF-1 are associated with a higher incidence of Alzheimer's disease in older adults. Regarding healthy subjects, they found that those with higher serum IGF-1 levels showed higher total cortical volume levels, as evidenced by magnetic resonance imaging studies [62].

Insulin resistance, as well as IGF-1 related to Alzheimer's patients, goes beyond those who have comorbidity with type 2 diabetes, for example Talbot *et al.*, [66] studying the hippocampus and cerebellar cortex in cases of EA, found a strong reduction of the IR/IRS1/PI3K signaling pathway, as well as a minor response of the IGF-1/IR/IRS1/PI3K pathway, this resistance to IGF-1 is related to IRS- 1 dysfunction, as well as to larger A-Betha oligomers [66]. Metabolic alterations, as well as IGF-1 and insulin resistance processes are a pathophysiological feature not only of Alzheimer's disease, but also of other neurodegenerative processes [11],[67],[68].

Autism

Due to the importance of the neurotrophic factors in the development of the cerebral system, the approach of its alterations and, especially of the IGF-1, have attracted the attention in the study of the cellular mechanisms of the developmental disorders, especially related to maturation, connectivity and neuronal differentiation [69]. In relation to autistic spectrum disorders (ASD), a disorder characterized by alterations in communication and

language, social interaction, the presence of repetitive and stereotyped behaviors, as well as sensory sensitivity [70], a wide range of genetic variations involved have been reported, many of which are related to synaptic activity and immune function [71],[72]. In one of the first studies that related IGF-1 and autism, the amounts of this peptide in the cerebrospinal fluid of children with autism were studied, finding a significant decrease of this trophic factor in comparison to the controls [73].

Subsequent experimental approaches have analyzed the genetic alterations related to SHANK3, a gene related to the post-synaptic density of the glutamatergic synapses. Treatments of IGF-1 in knock out animals for this gene, showed improvements for the displayed deficits compared to controls that were only injected with saline [74]. A study in subjects with Phelan-McDermid syndrome, the human disorder related to SHANK3 deficiency, and presenting similar alterations to ASD, showed an improvement in social disturbance, as well as a decrease in the repetitive and stereotyped behavior of those children who were treated with IGF-1 for 4 weeks [73]. Despite the different phenotypes related to ASD, these approaches lead to the study of potentially useful treatments in this neurodevelopmental disorder [71],[72].

Discussion

We have reviewed 80 high-impact research articles addressing insulin growth factor type 1, and neuropsychiatric disorders such as autism, anxiety, depression, Alzheimer's disease, and post-traumatic stress disorder.

In conclusion, IGF-1 is an important neurotrophic factor whose regulatory network operates throughout the body, and despite many of its recognized functions in the development of the nervous system, with multiple neurotrophic, metabolic, cell growth properties and neuroprotection [2],[13], their role in neuropsychiatric disorders is not fully understood, yielding conflicting data in highly prevalent disorders such as those affecting mood.

In reference to its relationship with depression, its role in the control and regulation of mood has been suggested because of its implication in processes such as synaptic plasticity, cell differentiation and neurogenesis [20]. In humans it has been found that low levels of IGF-1 in women, and high in men, predict the incidence of depressive disorders after 5 years [45],[46]. It is possible that these conflicting results are due to several factors not yet explored, such as the implication of various IGFBPs in depression, as well as mechanisms of resistance to IGF-1 involved.

Regarding anxiety, animal studies show that reduced levels of circulating IGF-1 are associated with increased presence of anxious symptoms and less neurogenesis in hippocampus [36],[51].

Traumatic events during development cause hormonal abnormalities in the long term and an increased risk of developing PTSD in humans [56]. Several experimental studies show important relationships between altered IGF-1 mechanisms (e.g. IGF-1R, IRS-1, AKT, PI3K, etc.), with PTSD, anxiety and depressive-like symptoms in animals, and structural alterations of the hippocampus, prefrontal cortex, amygdala and hypothalamus. The latter, would be of particular relevance as the starting point of the GH/IGF-1 axis, or the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis mediates the stress response, and at the same time, glucocorticoids appear to be related to the alteration of the intracellular signaling pathway of IGF-1, affecting for example neurogenesis and propitiating atrophy in hippocampus [42],[75],[76].

However, greater implications are encountered with neurodegenerative disorders. In relation to EA, it has been referred to as "type III diabetes" because of its high relation with the mechanisms of type 2 diabetes, the etiological hypothesis of resistance to peptides such as insulin and IGF-1, as well as its experimental treatment with these peptides [77],[78].

The implication of IGF-1 in cerebral maturation, synaptogenesis, cerebral plasticity, neurogenesis, memory and learning, as well as its anti-apoptotic and neuroprotection mechanisms make it a potential therapeutic resource in neuropsychiatric disorders of difficult approach, such as autism and Alzheimer's disease [2],[16],[75],[76]. However, further research is needed both at the basic and clinical level applied to fully understand its relevance in these disorders. Currently, the possible implication in obsessive-compulsive disorder, schizophrenia, Huntington's disease and Parkinson's disease are also being studied, showing their importance in different neuronal mechanisms that affect these disorders [79],[80],[81],[82],[83],[84],[85],[86].

Notes

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The author has completed the ICMJE conflict of interest form translated into Spanish by *Medwave* and declares that he has received funding from the Research Estancia Scholarship of the National University of San Agustín, Arequipa, Peru, to carry out this clinical review; Declares not having financial relations with organizations that could have interests in the published article, in the last three years; And not having other relationships or activities that could influence the published article. The form can be requested by contacting the responsible author or the editorial board of the *Journal*.

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