[Frontiers in Bioscience 13, 85-99, January 1, 2008]

Insulin-like growth factor-1 in plasma and brain: regulation in health and disease

Caroline Sievers[1], Harald Jorn Schneider[1], Gunter Karl Stalla[1]

[1] *Max-Planck-Institute of Psychiatry, Kraepelinstr, 2-10, 80804 Munich*

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1. ABSTRACT

IGF-1 was first described as a growth mediating factor regulated in the context of the somatotrophic axis. During the last decade, it has gained much attention for its role in the regulation of lifespan, brain function, cell growth, and metabolism. Associations of plasma IGF-1 levels in physiological and pathological conditions such as aging, cardiovascular disease, metabolic disorders, dementia, and neurodegenerative disorders, and its potential as a neurotrophic agent, have been intensively studied. Acromegaly due to jGH and IGF-1 excess and growth hormone deficiency with decreased GH and IGF-1 might serve as models to study IGF-1 function, but the effects of GH and IGF-1 in these conditions are often indistinguishable. Due to this overlap, this article will only briefly mention pathophysiological implications in acromegaly and growth hormone deficiency. It will focus on IGF-1 and give an overview of the vast literature on the role and regulation of IGF-1 in plasma and brain, its alteration in health and disease and its possible therapeutical applications.

2. INTRODUCTION

Insulin-like growth factor 1 (IGF-1) is a 70 amino acid, 7649-Da protein that is produced at several sites in the body (1). It shares significant structural homology with insulin and is part of the complex concert regulating growth, metabolism and development in the body, including the central nervous system. IGF-1 was originally detected by Daughaday and colleagues in 1957. The first isolation was performed by Rinderknecht and Humbel in 1978 (2,3). Historically, it was believed that the effects of the growth hormone (GH) were mediated only by IGF-1 (or 'somatomedin') produced in the liver (4) . IGF-1, in its turn, was only regarded as a mediator of GH. This notion was supported by the fact that IGF-1 therapy leads to growth in patients with a growth hormone insensitivity syndrome (5) During the following years, however, further research challenged this simplistic view. It was shown that both GH and IGF-1 have divergent effects independently of each other (6). Moreover, a large body of evidence points to the local mediator effects of IGF-1. Sjogren *et al.* observed that normal postnatal body growth occurred in a

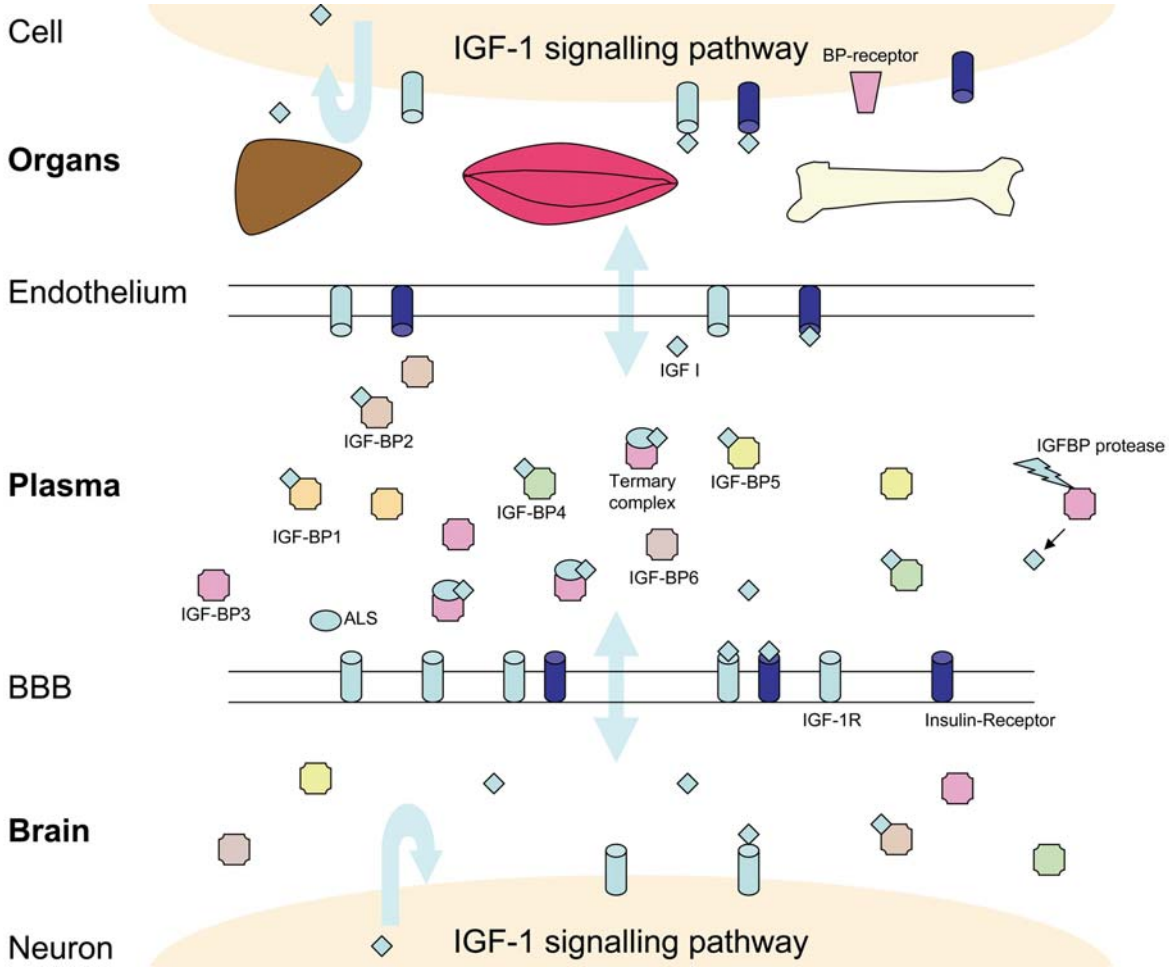

Figure 1. Overview of the IGF-1 system including IGF-1 and 2, IGF-1 binding proteins BP-1-6, IGF- and insulin receptors and IGFBP proteases.

mouse model despite complete absence of IGF-I production by the hepatocytes due to liver-specific knockout of the IGF-1 gene (7-9). D'Ercole *et al.* detected that local production of IGF-1 also occurs in other peripheral tissues and cell types, including muscle and skeleton, which inspired further research to investigate the significance of local versus systemic IGF-1 production (10). Subsequently, due to many preclinical and clinical studies, IGF-1 was identified as a peptide with pleiotropic functions including metabolic, mitogenic, anti-apoptotic, protein synthesis promoting, neuroprotective, neurogenic, gliogenic, synapse formating, neurotransmitter release modulating, and vessel remodelling characteristics (11-14).

Recently, the role of IGF-1 in longevity became a subject of interest. It is now well-established that caloric restriction is associated with an increased lifespan and IGF-1 alterations might be an important mediating system. Studies in animal models like mutant mice, flies and nematodes showed that downregulation of the somatotrophic axis, or reduced action of IGF-1, resulted in a significant extension of lifespan (15-20). However, how this knowledge can be applied to humans is still under debate as low plasma IGF-1 levels, due to growth hormone deficiency or other causes, are associated with higher morbity and mortality in man (21,22).

3. IGF-1 IN PLASMA

The elaborate IGF system encompasses many factors such as the insulin-like growth factors (IGF-1 and IGF-2), the IGF binding proteins, receptors, proteases and signalling molecules (23,24) (Figure 1).

The growth promoting factor GH is the main regulator of IGF-1 production with the liver being the principal source (7). However GH-independent mechanisms, described in more detail below, regulate the peptide and receptor expression in various organs (23-26). Multiple transcripts of the IGF-1 gene that encode different isoforms, generated by differential splicing and post-translational modification with differing roles of the products, underline the complexity of the IGF-1 system (27). The IGF-1 action is mainly mediated through the activation of the IGF receptors, but also through the insulin receptor. The type 1 IGF receptor, a glycoprotein on the

cell surface with 2 α and 2 β subunits with tyrosine kinase activity, binds IGF-1 and IGF-2 (26). The type 2 IGF receptor binds IGF-2 and lysosomal enzymes, but IGF-1 only to a very limited extent (24). The homology of insulin, IGF-1 and IGF-2 enables IGFs also to bind to the insulin receptor, but with a significantly lower affinity than insulin (28). IGF-1 is bound to and transported with IGF binding proteins (IGFBPs), a large family of specific carrier proteins in the plasma (29). The extracellular IGFBPs compete with the IGF-receptors and consequently influence the action of the hormone itself by modulating half-life and clearance(30,31). Six high affinity IGFBPs family members, IGF-BP1-6, have been identified and characterized so far (from 216-289 amino acids, 22.8-31.3 kDA) (29,32). In addition, several IGFBP-related proteins (IGFBP-rP1 to rP9) that bind IGFs with lower affinity have been described (29,31,33). The IGF-BPs are equally produced at different sites of the body with variable functions and regulating factors (34,35). Apart from their role in the pharmacokinetics of IGF-1, recent *in vitro* and *in vivo* findings suggest that IGFBPs function independently of the IGFs as bioactive molecules with a growth modulating action (22,35-38). The major form present in humans is IGFBP-3 that binds most of the IGF-1 and IGF-2 in the plasma. The glycoprotein IGFBP-3 forms a high molecular weight ternary complex (from 150 to 200 kDa) with an IGF molecule (IGF-1 or IGF-2) and an alpha-labile subunit (ALS), all independently regulated by GH (34,39-42). Genetic inactivation of IGFBP-3 or ALS reduced IGF-1 concentrations significantly with only a modest effect on growth in mice (43). In contrast to IGFBP-3, IGFBP-1 for example is regulated by glucose and insulin levels and binds only a very small fraction of IGF-1 (44,45). IGFBP-2, which mainly binds IGF-2, may be of interest with relation to disorders of the central nervous system. It is present, not only in the serum, but also in the cerebrovascular fluid and in microglial cells, and could be involved in the pathogenesis of multiple sclerosis and the repair of neural lesions (29,46,47). Other IGFBPs might also be involved in the proliferation of certain cell types and adaptation processes with their complete functions yet unknown (29). IGFBP 2-6, but not IGF-BP1, are also expressed in the brain (29,48,49). IGFBPs themselves are regulated by binding to the extracellular matrix, phosphorylation and proteolysis with subsequent changes of the IGF affinity (50,51). In the case of IGFBP-3 for example, the proteolytic process is usually low in healthy adults, but can be increased in pregnancy, catabolic states, severe illness or diabetes, with a subsequently altered IGF-1 availability (52-54). Daily secretion and clearance rates of IGF-1 have been estimated in kinetic studies on healthy humans and studies on GHD patients with discontinuation of GH therapy (55-57). The estimated production rate ranges from 3-10mg per day. The half-life for the IGF-1 ternary complex ranges from 7-20h and around 15min for the free IGF-1 form which exists in 0,4-2% (58). IGF-1 clearance occurs via glomerular filtration. Additional mechanisms such as transendothelial transport to the target tissue have been proposed (59).

3.1. Plasma IGF-1 levels in healthy subjects

The measurement of total IGF-1 involves many methodical problems such as interference of the IGF binding proteins, different assays, and missing comparative studies between laboratories and assays (60-62). Normative data for an automated immunoassay (Nichols Advantage, Nichols Institute Diagnostics, USA) have recently been published by Brabant and colleagues in a multi-centre study including 3,961 healthy subjects in six centres (63). Different assays have been compared by other groups. It is assumed that the intra-individual serum IGF-1 variation in healthy subject accounts for around 14% deviation (64-66). Additionally, several studies point out the importance of differentiating between total and free IGF-1 as well as determing ALS and IGFBP during clinical assessment, because some changes in the IGF/IGFBP system might not be seen by only measuring total IGF-1 (31,67-72). Apart from alterations due to methodological constraints, IGF-1 levels change during development and aging, and are altered in various physiological and pathological conditions (22,24,73).The correlation of integrated GH concentrations and IGF-1 is relatively consistent if ultra-sensitive assays are used (22). The age-related decline of IGF-1 levels is a stable and consistent finding in many different studies (60,63,74). IGF-1 levels decrease from birth until six months after birth, and increase slowly in childhood, correlating positively with height velocity before they constantly decline after puberty until senescence (63,75-77). The existence of a temporal pattern of IGF-1 levels is controversially discussed. In conclusion, modest daily and seasonal alterations in the IGF/IGFBP system have been detected in some studies but not in others,probably of minor clinical relevance (22).

Twin studies point to the strong genetic regulation of IGF-1 plasma levels (22,78). Polymorphisms might account for a part of the differences in serum levels and birth weight and might explain variations between ethnical groups, gender and genotypes (79-81). Polymorphisms accounting for different IGF-BP levels have also been described for the binding proteins like for IGFBP-3 (82).

Interestingly, despite the fact that oral estrogens have been shown to reduce IGF-1 levels and that women with growth hormone deficiency need higher GH dosages than men to reach normal values, most of the studies found no impressive effect of gender on IGF-1 plasma levels (23,79). The association of body composition and IGF-1 levels was studied in more than 6000 patients screened in the epidemiological DETECT (Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment) study. Adjusted for age, gender and health conditions, IGF-1 was correlated positively with BMI in subjects with normal weight and negatively in obese subjects (74) (Figure 2).

Positive associations were also found between plasma IGF-1 levels and bone mineral density and muscle strength in most studies. Smoking, alcohol and coffee consumption might influence IGF-1 levels, but epidemiological studies showed equivocal results (22).

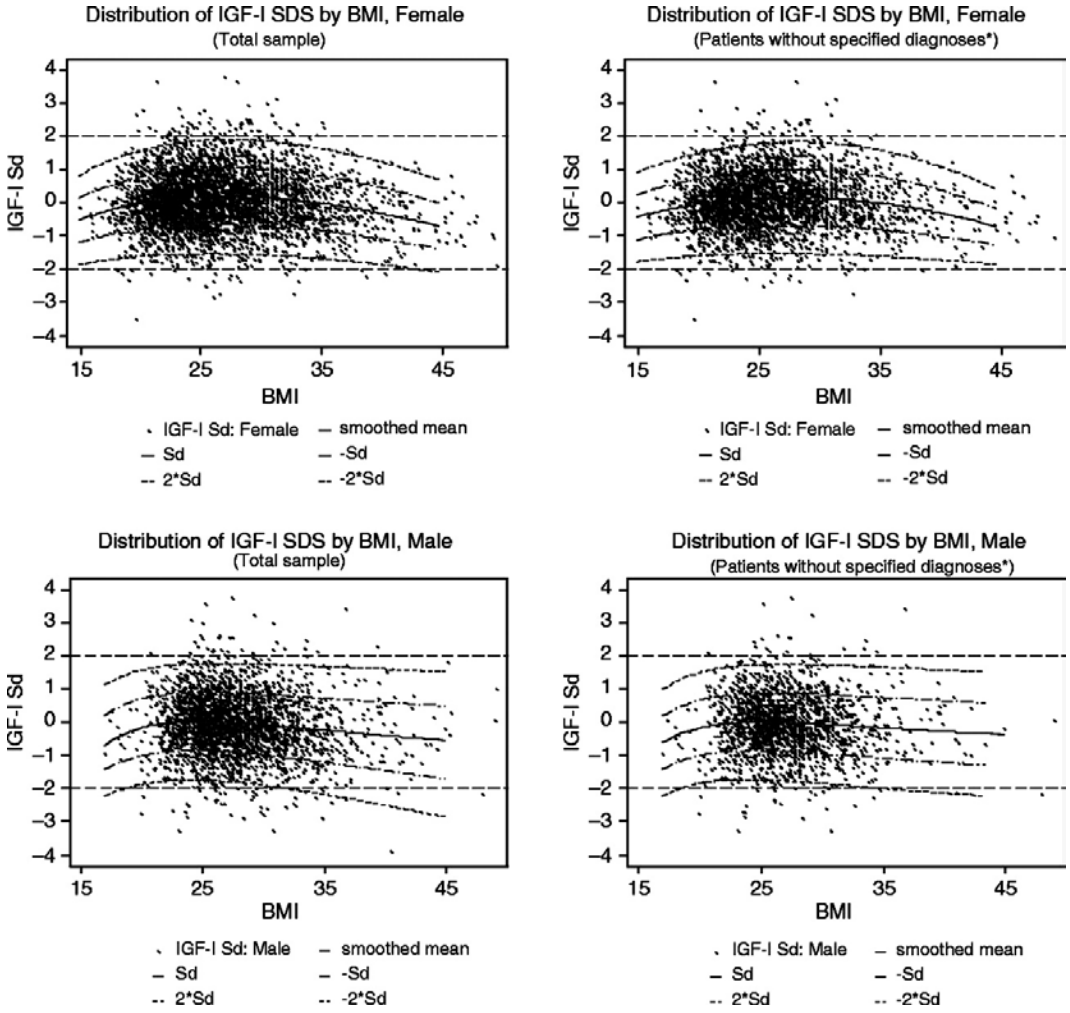

Figure 2. IGF-I SDS blotted over BMI with smoothed lines indicating mean values and 1st and 2nd S.D. (Left panels) Total sample: upper panel, women; lower panel, men. (Right panels) Subjects with diabetes, cancer, kidney or liver diseases, or hormone replacement therapy excluded: upper panel, women; lower panel, men. Reproduced with permission from (74).

Training and physical fitness showed variable effects on IGF-1 levels which was probably due to a complex interplay of glucose, insulin, IGF-1 and body composition (22,83,84).

3.2. Plasma IGF-1 in disease

Being the major mediator of GH, IGF-1 is used to diagnose, screen for and monitor GH related disorders and treatment including growth hormone deficiency (GHD) and GH excess (acromegaly) (65,85-88). In these conditions with both hormones altered, the impact on physiological mechanisms such as metabolism or cardiovascular regulation and brain functions might often be a result of the combined changes of GH and IGF-1 and other endocrine disturbances due to the underlying disease. GHD, characterized by low GH and IGF-1, can be caused by pituitary adenomas, inflammatory disorders, exogenous toxic agents or traumatic brain injury (89,90). This constellation can be associated with premature mortality, cardiovascular diseases, central obesity, insulin resistance, impaired quality of life and altered neuropsychological functions such as changes in memory, processing speed and attention, but also with decreased mortality from malignant diseases (21,91-95). The GH substitution, with a subsequent rise of IGF-1 levels results in improved parameters of the body composition and cardiovascular risk profile (96). It may also have a positive effect on cognition and emotion (97-99). Other regulatory circuits intertwined with the somatotrophic axis, such as sleep, may stay unaltered (100,101).

Acromegaly caused by a pituitary adenoma and in most of the cases with a GH and IGF-1 excess is also accompanied by increased cardiovascular morbidity and mortality, an increased cardiovascular risk profile, insulin resistance, type II diabetes mellitus, reduced quality of life and a higher incidence of malignancies (102-105). Although a fewstudies on acromegalic patients showed some distinctive features or disturbances in psychological characteristics, the role of GH and IGF-1 excess on

neuropsychiatric aspects and brain functions is not completely understood yet (105-108). Treatment that reduces tumor size and normalizes hormonal excess such as surgery, radiotherapy, radiosurgery or medical therapy (somatostatin analogues, dopamin agonists or GH-receptor-antagonist) ameliorates most of the comorbidities (87,109). However it has become evident that the quality of life in treated acromegalic patients may stay reduced despite normal levels of IGF-1 (and/or GH) (105,110,111).

Apart from changes following disturbances of the GH secretion with subsequent IGF-1 level alterations, correlations of IGF-1 levels with diseases or disease risk factors such as cardiovascular disorders, diabetes, cancer, stroke and dementia have been reported by many groups (22,73,112-115). In fact, IGF-1 has now been studied for almost every organ and disease entity. Since this overview can by no means consider all the literature available, it will highlight the relationship between IGF-1 levels and cardiovascular diseases, metabolism, and cancer.

3.2.1. IGF-1 in cardiovascular disease, metabolism, and cancer

The role of plasma IGF-1 in cardiovascular disease and cardiovascular risk factors is a complex issue and studies show conflicting results. GH deficiency with low IGF-1 levels, as well as acromegaly with high IGF-1 levels, are both characterized by cardiovascular morbidity and mortality (102,116). In preclinical studies it has been shown that the cardiovascular system with its various cell types, such as endothelial cells, secretes IGF-I and possesses IGF-1 receptors that promote macrophage chemotaxis, vascular smooth muscle cell growth, release of proinflammatory cytokines, regulation of cholesterol uptake, stimulation and the regulation of extracellular matrix synthesis in atherosclerotic plaques (73,117). In a mouse model of IGF-1 over-expression, myocyte cell death after ischemic myocardial infarction was prevented with a positive effect on cardiac function (118). Additionally, IGF-1 significantly increased the ejection fraction in an ovine model of chronic heart failure when administered intrapericardially (119). On the other hand, high IGF-1 levels might be associated with the progression of coronary lesions, atherosclerosis or restenosis by the increase of artherogenic plaques via mitogen effects and smooth muscle hyperplasia (117,120-122).

In humans, it is consistently reported that low IGF-1 is correlated with cardiovascular risk factors and diseases such as ischemic heart disease, cardiomyopathy, and chronic heart failure (113,114,123-125). In the Rancho Bernardo Study, a prospective association of low IGF-1 and future ischemic heart disease mortality was reported in 1185 elderly men and women (126). Patients with IGF-1 promoter polymorphisms with genetically determined low IGF-1 activity are at greater risk of developing atherosclerosis when hypertensive,type 2 diabetes mellitus, myocardial infarctions and heart failure and of dying from myocardial infarctions as observed in the Rotterdam Study(127-130). In some circumstances though, low IGF-1 levels might be beneficial. The reduction of IGF-1 with bezafibrate in a double-blind, placebo-controlled clinical trial had a positive impact on the progression of coronary artery disease in young male survivors of myocardial infarction (131). Similarly, somatostatin analogues with a consecutive IGF-1 decrease had a favourable effect on restenosis after percutaneous transluminal coronary angioplasty (132). On the other hand, recombinant IGF-1 improved the cardiac performance by afterload reduction and possibly positive ionotropic effects when administered for 4h over 2 days in a cross-over design in a small placebo-controlled study with 8 patients (60 micrograms/kg) (133).

IGF-1 plays an important role in metabolism. As an insulin sensitizing hormone it probably acts through a direct effect on the receptor and cellular level and through GH suppression. Mice with liver-specific IGF-1 gene deletion display hyperinsulinemia and skeletal muscle insulin resistance (8). It is therefore, not surprisinglyinvolved in nutrition, body composition and glucose metabolism in man (134). Caloric restriction, malnourishment or anorexia nervosa are associated with decreased IGF-1 levels (22,135), but also obese subjects and patients with the metabolic syndrome and type 2 diabetes mellitus display low IGF-1 levels (74,136-138). A prospective study by Sandhu *et al.* showed that high IGF-1 in 615 normoglycaemic men and women aged between 45 and 65 years was protective against impaired glucose tolerance (139). And in another clinical study, low IGF-1 levels due to a polymorphism in the IGF-1 promotor region were associated with a greater risk of developing type 2 diabetes mellitus (127). Likewise, the low IGF-1 levels in type 1 diabetes mellitus are associated with aggravated diabetes-specific complications (140,141). Due to these findings, IGF-1 and IGF-1/IGFBP-3 replacement has even been proposed as a possible treatment for type 1 and type 2 diabetes mellitus and associated comorbidities (142-144).

IGF-1 and its binding protein IGFBP-3 mediate cell growth and apoptosis, respectively (145,146). Therefore the relationship of IGF-1 and cancer is of great interest. IGF-1 over-expression in transgenic mice induces spontaneous tumor formation and hyperplasia (147). High concentrations of circulating IGF-I levels in humans are associated with an increased risk of prostate cancer and premenopausal breast cancer according to a meta-regression analysis of case-control studies by Renehan and colleagues (148). Within the brain, IGF-I mRNA and peptide levels are seen to be high in the case of gliomas, meningeomas, medulloblastomas and other tumors suggesting that IGF-I may contribute to the tumorigenicity possibly by acting as an autocrine growth factor (149-151). For this reason the application of an anti-IGF-1 therapy such as a "triple-helix anti-IGF-I" gene therapy or blockade of the IGF-1 signalling cascade might be a future treatment option for malignancies of the brain and other organs (146).

4. IGF-1 in the brain

In mice, IGF-1 over-expression increases brain size by 55% and myelin content by 130% at day 55 (age), and promotes neurogenesis and synaptogenesis in the dentate gyrus during postnatal development (152,153). Conversely, IGF-1 knockout mice develop CNS

hypomyelination, have a reduced number of neurons and oligodendrocytes and a reduction of the total brain size, and GH fails to stimulate postnatal growth in these mice (154). Additionally, it has been shown that IGF-1 and IGF-1R mRNA are abundantly expressed prenatally and postnatally in several brain regions and is differentially regulated during development (155). These experimental findings inspired many researchers to investigate IGF-1 and its role in brain and brain disorders during the last decade. It is now well-established that IGF-1 possesses multiple functions in the neuronal system and plays a key role in the development of the brain including cell differentiation and cell survival, myogenesis, inhibition of apoptosis, mediation of cell cycle progression, and modulation of immune response (14,156-158). IGF-1 seems to exert its proposed neuroprotective and antiapoptotic effects in the brain, via the phosphatidyl-inositol 3-kinase (PI3K)/Akt kinase pathway, a common survival signalling pathway, and its proliferative effect via the MAPK/Erk pathway (47,159).

4.1. Plasma IGF-1 enters the brain

IGF-1 in the brain is derived from different sources. The first source is the endogenous production at specific sites within the brain described below. The second source is the plasma IGF-1 via, or by-passing, the blood-brain barrier (BBB) (47,160,161). Not only the active or passive transport via the BBB is a mechanism for substances to reach the brain from the plasma, but also the circumvention of the BBB by organs such as the median eminence of the hypothalamus, or filtration through the coroid plexus into the cerebrospinal fluid (CSF) with subsequent diffusion.The BBB consists of endothelial cells, a basal membrane and astrocytic feet. IGF-1 receptors are abundantly expresse at the BBB cell linings, d suggesting a specific transport system from the blood to the brain as has been published for other hormones such as insulin, leptin and ghrelin (162). Whereas GH is transported independently by a nonsaturable system, Yu *et al*. recently reported that insulin and IGF-I, with binding capacities to either receptors, cause reciprocal inhibition of each other with partial transportation via the other's transport system (163,164). The saturation rate of the BBB, at least in rats, is already reached at a very low level (IGF-1 around 150 ng/ml), which is below the normal circulating IGF-1 values. It may be increased through exercise and brain injury, probably by opening in the BBB (165-167). In comparison, the transport system of insulin is more potent with the difference that insulin is not locally produced in the brain and therefore has to be transported via the BBB (168). From other hormonal systems it is known that transporter alterations at the BBB level can occur in and be part of disease, but the relevance of this principle for the IGF-1 transporter is not yet clear (169). CSF orginates from the plasma as well and is secreted from the circulation into the brain ventricles by a densely vascularized tissue (choroid plexus). The CSF is in direct contact with neuronal circuits of the central nervous system (CNS) and the likely transport mechanism for IGF-1 from the CSF into the brain has been reported to be diffusion (170).

At the choroid level, the group of Torres-Aleman reported that the choroid plexus endocytic receptor megalin/low-density lipoprotein receptor-related protein-2 (LRP2) is crucial for the transport of IGF-1 from the plasma to the brain. When the choroid plexus megalin levels were blocked through RNA interference, blood borne IGF-1 signalling in the brain was greatly reduced, indicating the significance of this route (171).

4.2. IGF-1 is endogenously produced in the brain

The blood circulation is only one important source of IGF-1 for the CNS. Additionally, IGF-1 is locally and abundantly expressed in both neurons and glial cells in several brain regions where it exerts autocrine and paracrine functions (47,160,161,172-174). In fact, at least in rats, the local production of IGF-1 seems to be the main source for brain cells postnatally (175). The expression is regulated spatially and temporally with IGF-1 m-RNA, mainly detected in the pons and cerebellum in both the fetal and adult brain (176). During embryogenesis, IGF-1 mRNA in rat brain is mainly found in regions rich with neuronal cells such as hippocampus, mid brain and spinal cord, including somatosensory neurons and projecting neurons such as Purkinje cells of the cerebellar cortex (172,173,177-179). After high expression during development, IGF-1 decreases during the first postnatal weeks according to the degree of cell maturation (172,177). In cells of the olfactory bulb with a high turnover, IGF-1 expression stays high during adulthood. In the human fetus, the truncated form of IGF-1 seems to display the potential biological action on brain cells (180,181). After birth, the fetal IGFs switch to adult forms with various transcripts of IGF-1 being found in the brain regulated at the level of transcription, RNA processing, and translation in different tissues and at different stages of development (182-185). Co-expression studies with the GH receptor/BP and IGF-1 revealed that there are tissue specific differences in the expression and although colocalized, distinct at the cellular level (186,187). IGF-BPs, except for IGF-BP1 m-RNA expression, is also detected in the CNS at different sites (48,49,188,189).

4.3. IGF-1 regulation in brain in health and disease

Similar to the plasma IGF-1, disturbances of GH secretion lead to alterations in IGF-1 expression in the brain. In dwarf mice significant increases of IGF-1 mRNA in response to growth hormone administration have been observed(190). In hypophysectomized rats, the expression of IGF-1 is fourfold lower than in normal controls, and is recovered after injection of GH intracerebroventricularly (191). Preclinical and clinical studies revealed that as in the case of plasma levels there are GH-independent factors regulating IGF-1 production and function in the brain (14). For example, fasting for 48h decreases IGF-1 m-RNA levels in the rat brain by approximately 30-40% (192). Glucocorticoids such as dexamethasone and elevated c-AMP levels (in a C6 rat cell line) also reduce IGF-1 m-RNA levels significantly (193,194). An interesting finding was the fact that exercise increased IGF-1 m-RNA levels in the hippocampus of adult rats. This is probably accompanied by an additional effect of enhanced brain

uptake of circulating insulin-like growth factor I with a subsequent increase in the number of new neurons and improved cognitive function (167,195). The effect of IGF-1 on the cellular level in neuronal and non-neuronal cells has been studied by many groups. Apart from its neurogenic, neuroprotective, gliogenic, anti-apoptotic functions, ithas become clear that IGF-1 plays also a pivotal role in brain metabolism (14). In primary ependymal cell cultures, IGF-1 was at least 10 times more potent than insulin in stimulating the rate of ependymal glucose uptake (196) and, in astrocytes, IGF-1 increased intercellular gap junctional communication and connexin43 expression *in vitro* (197). IGF-1 expression, as well as some of its binding proteins such as IGFBP-2 and IGFBP-3, are upregulated in response to brain injury including metabolic, traumatic and hypoglycemic insults, possibly as an endogenous compensatory mechanism (156,198-200). Systemic administration of IGF-1 induced neuronal activity, expression of genes, neuroplasticity, neurogenesis, especially in the proliferative areas of the subgranular zone of the dentate gyrus of the hippocampus and the subventricular zone, and increased vessel density in animal models (47,201-203). It enhanced the biological activity of the brain-derived neurotrophic factor in mouse cerebrocortical neurons, and subcutaneous injections of IGF-1 led to an increase of the proportion of the NR2B subunit mRNA transcript of the NMDA receptor in rat hippocampus, which has been suggested to be crucial for learning and memory (204,205). After a neurotoxic or ischemic insult, IGF-1 administration improves neurological functions in rodents (47,,206,207). IGF-1 even had a long-lasting antidepressant effect in the modified rat forced swimming test when administered intracerebroventricularly in rats (208). Due to these findings in animal models, the role of IGF-1 has been extensively studied in cognitive function and neuronal health and disease in man.

High serum IGF-1 levels are associated with an increase in cerebral blood flow measured by PET in the left premotor cortex and in the dorsolateral prefrontal cortex during a working memory test in humans (209). Additionally, subjects with higher IGF-1 levels performed better in cognitive functions such as speed processing (210-212). In another cross-sectional study in 547 boys and girls between 8 and 9 years, IGF-1 levels were positively correlated with intelligence measured by the Wechsler Intelligence Scale for Children, the Wechsler Objective Reading Dimension test and the Wechsler Objective Language Dimension test (213). Low levels of serum IGF-1 or decreasing IGF-1 are associated with ageing and the age-associated cognitive decline, as well as with neurodegenerative disorders auch as amyotroph lateral sclerosis and Alzheimers disease (22,214). Due to these associations, elevation of IGF-1 has been investigated as a therapeutical option in those diseases with low IGF-1. Beneficial effects have been stated, for example, for Alzheimers disease by influencing the beta-amyloid metabolism and clearance, the cholinergic, catecholaminergic and dopaminergic functions and maybe also by the alteration of the glucose metabolism and anti-inflammatory effects (215-219). In other neurodegenerative diseases such as ataxia-telangiectasia, Charcot-Marie-Tooth 1A disease or multiple sclerosis in which IGF-1 levels are increased or unchanged, IGF-1 is probably not a promising therapeutical tool (220,221).

5. PERSPECTIVE

IGF-1 is a complex and multi-functional peptide. Levels of IGF-1 in plasma and brain are regulated in concert within the growth hormone axis and several other factors. The balance of the different players such as GH, IGF-1, IGFBPs, and IGFBP proteases, regulates the action of IGF-1 on the cellular level. IGF-1 is altered, not only in growth hormone deficiency and acromegaly, but in many other physiological and pathological states of the brain and the whole organism and the detrimental or beneficial effects are under debate in certain circumstances. Apart from the classical IGF-1 treatment indications in IGF deficiency or resistant states, IGF-1 administered intracerebroventricularly, systemically or elevated by exercise, might turn out to be a possible therapeutic strategy for some diseases such as diabetes mellitus or neurodegenerative disorders such as Alzheimers disease or amyotrophic lateral sclerosis (ALS) (222-224). However, the neoplastic potential has to be taken into account when considering IGF-1 treatment for patients.

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Key Words: Endocrinology, Plasma, Brain, GH, IGF-1, IGFBPs, Metabolism, Cardiovascular Disease, Neurodegenerative Disorder, Brain Trauma, Neuroprotection, Review

Send correspondence to: Professor Dr. Gunter Karl Stalla, Max-Planck-Institute of Psychiatry, Kraepelinstr. 2-10, 80804 Munich, Germany, Tel: 49-0-89-30622-270, Fax:49-0-89-30622-7460, E-mail: stalla@mpipsykl.mpg.de

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