REVIEW

Serum insulin-like growth factor I in brain function

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Abstract. Insulin-like growth factor I (IGF-I) is present at high concentrations in the circulation. Tissue-specific genetic ablation has shown that the majority of serum IGF-I is secreted by liver cells, although all major organs synthesize it. IGF-I is an important signal during development, including brain growth. Although the biological role of IGF-I in organs such as muscle or ovary is reasonably well established, its biological significance in the adult brain is far from clear. In this regard, while local IGF-I synthesis decreases during brain development, protein levels remain relatively constant throughout life until old age, where a decline is found, not only in the brain but also in the bloodstream. This mismatch between declining local synthesis early after birth and steady protein levels may be explained by the ability of serum IGF-I to access the brain across the blood-brain-barrier. This peripheral IGF-I input to the brain is a physiologically meaningful process of potential impact in brain diseases. Numerous brain mechanisms are regulated by serum IGF-I. Many of these, such as cell energy modulation or growth and survival are common to other IGF-I target tissues but there are also a number of brain-specific mechanisms regulated by IGF-I which likely underlie the ability of serum IGF-I to modulate the major function of the brain: cognition. We propose that serum IGF-I forms part of the mechanisms involved in the "cognitive reserve" concept of brain responses to homeostasis breakdown. Based on IGF-I pleiotropy not only in brain but elsewhere, we consider that loss of IGF-I function is an important step towards disease. (Keio J Med 55 (2): 59–63, June 2006)

Key words: insulin-like growth factors, brain, blood-brain-barrier, neurodegenerative illness

Introduction

The insulin-like growth factors (IGFs) appeared early in phylogeny (around 600 million years ago[1]) and expanded through gene duplication[1] to include over 30 different molecules in invertebrate species (*C. elegans*) to around 10 in vertebrates (man). In simple organisms IGFs are circumscribed to neural tissues, where they control feeding behavior, energy balance, and cell growth and are also probably involved in longevity determination.[2] In mammals, although a lower number of IGFs have so far been characterized, their biological role has expanded. Firstly, mammals produce IGFs not only in the brain, but in all tissues, and while neural control of energy balance and feeding behavior is still performed through brain insulin pathways,[3] the IGFs participate not only in regulation of body size, but in many other physiological processes, including life-span control,[4] that are slowly been unveiled. Apart from insulin, and due to its importance in endocrine loops, the biological role of IGF-I is probably the best studied.

IGF-I is a multifaceted growth factor acting as a classical hormone in the somatotropic axis under the control of pituitary growth hormone (GH) and as a local humoral factor in all tissues. Genetic manipulation in mice has shown that absence of IGF-I is lethal perinatally, although a reduced number of IGF-I null animals, albeit infertile, survive to adulthood.[5] While the reason for the latter is not clear, the existence of other IGFs in mammals may explain partial rescue. A seminal work from D LeRoith's laboratory[6] showed that circulating IGF-I is mostly produced by the liver, and more importantly, that body growth does not depend on it since serum IGF-I deficient animals (LID mice) show normal body size. However, LID mice show not only specific metabolic defects as expected based on previous observations, but also a wide range of neurological complications,[7] pointing to new aspects of blood-borne

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IGF-I on brain function. This unexpected phenotype of LID mice underscores the biologically relevance of transport of blood-borne IGF-I into the brain through the blood-brain-barrier (BBB).

Although during years several laboratories reported passage of serum hormones across the BBB,[8,9] including IGF-I,[9] these findings were broadly disregarded due to the dominating notion that the BBB establishes a physiological sealing of the brain. Fortunately, this old-fashioned concept is slowly being reverted and the idea of protein traffic at the blood-brain junction is now incorporated into brain physiology networks.[10] In the case of serum IGF-I, we may consider that the brain is just one more target organ. The following sections will illustrate this notion further.

The Choroid Plexus Epithelium: Port of Entry of Blood-Borne IGF-I

The BBB comprises the tight junction-sealed endothelium of brain vessels and the similarly sealed epithelium of choroid plexus, a specialized ventricular organ highly irrigated with normal fenestrated vessels (Fig. 1). Both brain barrier constituents are enriched in IGF-I receptors.[11] Detailed studies have shown that the choroid plexus is a major route of entry of systemic IGF-I into the brain: accumulation of intracarotid injected digoxigenin-labelled IGF-I is readily observed in this epithelium and cerebrospinal fluid (CSF) while brain vessels showed no staining.[12] Furthermore, when the IGF-I receptor in the choroid plexus is inhibited by viral delivery of a dominant negative form of the receptor, blood to CSF translocation of IGF-I is fully blocked[13] and blood-borne IGF-I signaling on brain parenchyma is drastically reduced (Fig. 2). These observations leave open the role of the IGF-I receptor in brain vessels and surrounding glial end-feet.[14] While serum IGF-I is an important growth signal for brain vessels,[15] the presence of IGF-I receptors in glial end-feet located outside the sealed endothelium suggests that blood-borne IGF-I may reach its glial receptors. Alternatively, glial receptors may be activated by IGF-I synthesized by the endothelium, which shows a high IGF-I mRNA content.[16]

Once serum IGF-I translocates into the CSF through the choroid plexus, the mechanism that allows accumulation of IGF-I in target neurons throughout the brain at very specific locations[12] remains undetermined. At any rate, IGF-I present in the CSF accumulates in specific periventricular cell types[17] and intraventricular administration of IGF-I and many other growth factors, has proved neuroprotective,[18] which clearly indicates that CSF-derived growth factors are able to reach target neurons throughout the brain. Both the brain and the CSF have high levels of IGF-binding proteins (IGFBPs), in particular IGFBP-2.[19] These carrier proteins are known to participate in translocation of circulating IGFs to target organs[20] but in the case of CSF-to-brain IGF-I transport, this remains to be shown. At any rate, other serum-derived proteins, including insulin, that lacks a binding protein system,[20] are translocated to the CSF and eventually accumulate in brain parenchyma through poorly described pathways.[21]

Serum-derived IGF-I is present in all brain areas.[12] Since the adult brain synthesizes very low levels of IGF-I and only in very specific locations,[22] most brain IGF-I

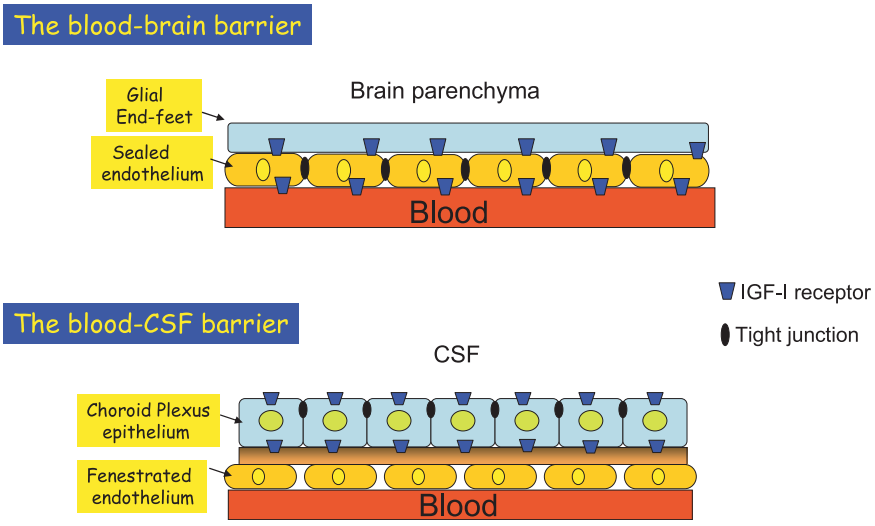

Fig. 1 Schematic representation of blood-brain barriers (BBB) at the brain endothelium (the blood-brain barrier) and at the choroid plexus epithelium (the blood-CSF barrier). In both specialized tight junction-sealed cell linings there is abundant expression of IGF-I receptors, suggesting that the BBB is a target of serum IGF-I.

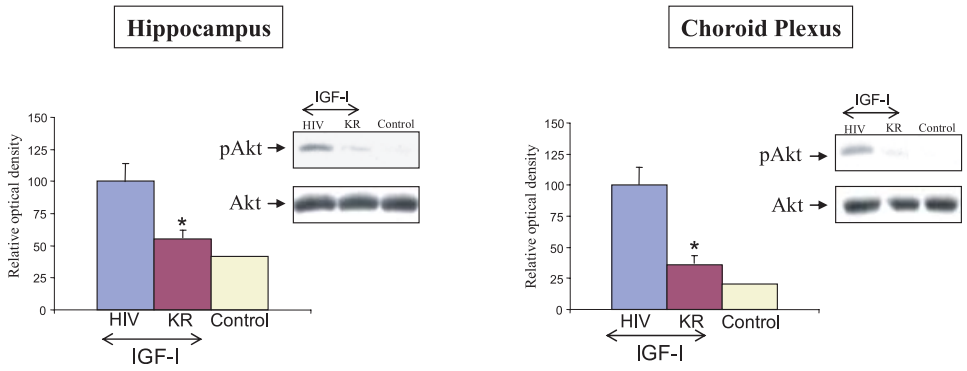

Fig. 2 The choroid plexus is a major site of entrance of serum IGF-I into the brain. Adult rats were infected in the choroid plexus with a dominant-negative IGF-I receptor (KR)-bearing viral vector (a control group received the empty viral vector: HIV group) and after 2 months received a systemic injection (carotid artery) of 10 μg IGF-I. Note that while HIV-infected rats show increased levels of active Akt (phospho-Akt: pAkt, a kinase downstream of the IGF-I receptor) in hippocampus or choroid plexus as compared to saline-injected rats (controls), animals with IGF-I receptor blockade (KR) not only showed impaired responses in choroid plexus, as expected, but also in the hippocampus. Thus, intact IGF-I receptor function at the choroid plexus is needed for systemic IGF-I to modulate Akt function in hippocampus. Representative blots and densitometry histograms are shown. Control rats receiving IGF-I responded identically to HIV rats receiving IGF-I. *$P < 0.05$ by Student's t-test.

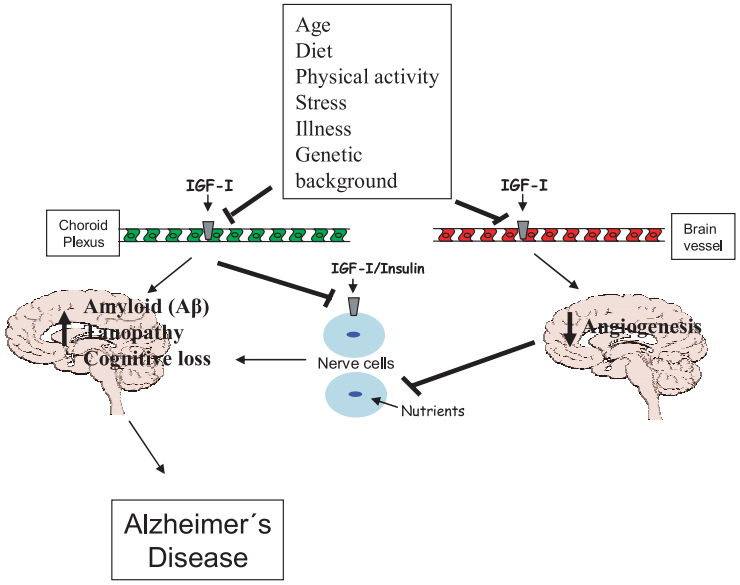

Fig. 3 Impaired IGF-I signaling at the BBB by aging, inappropriate diet, sedentary life, stress, inflammatory mediators associated to illnesses, and inheritance may underlie the influence of all these factors in development of Alzheimer's disease. Diminished serum IGF-I input at the choroid plexus may lead to increased amyloid (Aβ) levels due to impaired clearance,[28] tauopathy and cognitive loss due to reduced levels of brain IGF-I in addition to IGF-I/Insulin resistance in nerve cells (glia and neurons). In brain vessels, reduced IGF-I receptor function will lead to decreased brain angiogenesis[15] and consequently to impaired energy support to brain cells, that in conjunction to altered IGF-I/Insulin signaling will worsen the metabolic balance and in this way further contribute to cell impairment.

in the adult is probably from peripheral origin.[23] Although this suggestion may appear premature at first glance, many observations support it. A biological significance of peripheral IGF-I in brain function is supported by the presence of IGF-I receptors and IGFBPs in all brain areas, including many devoid of detectable IGF-I mRNA.[24] Systemic administration of IGF-I elicits a wide variety of central effects, including increases in neuronal activity,[12,25] hippocampal neurogenesis,[26] expression of growth factors and early genes,[22] resilience to insults[27] or amyloid β clearance,[28] just to name a few (see below). As discussed elsewhere,[29] not only IGF-I, but other neuroactive humoral signals arise also from the periphery even though they may also be synthesized locally by brain cells; i.e., hormonal steroids.

Serum IGF-I Couples Physical Activity and Brain Function

A prominent role of serum IGF-I in the response to physical exercise has long been recognized. Exercise-induced muscle growth is mediated by serum IGF-I,[30,31] and many other aspects of the adaptive response to exercise, including changes in brain function, involve circulating IGF-I.[32] Indeed, and as recently emphasized,[33] brain health relies on physical activity. The mechanisms involved in the beneficial effects of exercise on brain function require serum IGF-I as a critical effector,[32] and form part of the phenotypic expression of the exercise-driven human genome.[34] In other words, physical activity (highly reduced in present-day sedentary societies) is a physiological stimulus needed to provide the brain with peripheral trophic support. Although the mechanism underlying increased transport of serum IGF-I into the brain in response to exercise is not known, exercise-induced increase in brain blood flow is in all probability involved.

A particularly relevant aspect of serum IGF-I in this context is its probable role in building a ''cognitive reserve''; i.e., the activity-dependent processes whereby the brain builds up new functional (cognitive, motor ...) skills allowing to eventually cope better with (cognitive, motor ...) damaging stimuli since more functional resources are available. This concept stems from the observation that increased mental or physical activity reduces the risk of neurodegeneration.[35] Exercise-induced resilience to insult requires serum IGF-I[27] and serum IGF-I is needed not only for exercise-induced adult hippocampal neurogenesis but also for basal neurogenesis[26] and synaptic plasticity: mutant mice with low serum IGF-I levels lack hippocampal long-term potentiation, which is restored upon chronic systemic IGF-I therapy to the mice (unpublished observations). All these observations clearly indicate that serum IGF-I is necessary for building experience-dependent functional plasticity since this process involves synaptic plasticity and, as hypothesized elsewhere[36] probably also newly formed neurons. Although highly speculative at present, declining serum IGF-I associated to aging may underlie cognitive loss commonly found in aged individuals[37] due to diminished functional plasticity as a consequence of lower neurogenetic rate and synaptic plasticity capabilities. Notably, the latter two deficits are common in old age.[38,39]

Conclusion

The IGFs constitute an ancient family of growth factors involved in the control of energy expenditure and in this way affect cell growth, body size and even longevity. This classical role refers to the major actions of these peptides when evaluated at an organism level. However, when analyzed at tissue level, new specific roles are slowly been unveiled. In the case of IGF-I, a prominent role in brain function is gaining increasing acceptance. The fact that not only brain IGF-I, but also blood-borne (mostly liver-derived) IGF-I affects brain physiology and disease may appear at first as a novel way to regulate brain activity through peripheral signals, but feedback mechanisms between the brain and the periphery should be two-sided.

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