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REVIEW

Insulin and insulin-like growth factor receptors in the brain: Physiological and pathological aspects

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Abstract
The involvement of insulin, the insulin-like growth factors (IGF1, IGF2) and their receptors in central nervous system development and function has been the focus of scientific interest for more than 30 years. The insulin-like peptides, both locally-produced proteins as well as those transported from the circulation into the brain *via* the blood-brain barrier, are involved in a myriad of biological activities. These actions include, among others, neuronal survival, neurogenes, angiogenesis, excitatory and inhibitory neurotransmission, regulation of food intake, and cognition. In recent years, a linkage between brain insulin/IGF1 and certain neuropathologies has been identified. Epidemiological studies have demonstrated a correlation between diabetes (mainly type 2) and Alzheimer's disease. In addition, an aberrant decline in IGF1 values was suggested to play a role in the development of Alzheimer's disease. The present review focuses on the expression and function of insulin, IGFs and their receptors in the brain in physiological and pathological conditions.

Contents

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1. Introduction: the insulin-IGF system

The insulin-like growth factor (IGF) system constitutes a hormonal network comprising ligands, receptors and binding proteins. The ligands, insulin, IGF-1 and IGF-2 (herein named IGF-related peptides), have distinct tissues of expression and separate physiological functions. They generally activate different receptors, though both the insulin receptor (IR) and the Type 1 IGF receptor (IGF-1R), despite major differences in expression patterns, are very similar in both structure and activity in regard to signaling pathways. Insulin is primarily a metabolic hormone functioning on muscle, fat and liver *via* activation of its cognate receptor, though it also functions on tissues that are not considered classically metabolic, such as the vasculature and the brain. The IGFs have a more mitogenic role both during fetal development and postnatally. The IGFs are important progression factors during the cell cycle and they affect cell survival in adult tissues. In certain cases, IGF-1 and IGF-2 actually demonstrate specific differentiated functions *via* activation of the IGF-1R, as the IGF-2R does not have signaling capabilities. The IGF-binding proteins (IGFBP1-6) have high affinity for both IGF-1 and IGF-2, protect the IGFs in the circulation and deliver them to the tissues. Hence, IGFBPs' main role is to modulate the bioavailability of the ligands. The IGFBPs exhibit numerous biological functions, both *via* their control of local "free" (unbound) IGFs' interactions with cell-surface receptors and, in some cases, in a ligand-independent manner. As opposed to the IGFs, insulin has no similar binding proteins and circulates freely. In this review we will discuss the expression and function of insulin, IGFs and their receptors in the brain. For clarity we will describe insulin and the IGFs separately.

2. Insulin and the brain

2.1. Insulin receptor expression in the brain

The IR is widely expressed in the brain but demonstrates denser expression in certain regions (Unger et al., 1991). A higher level of expression is found in the olfactory regions, amygdaloid complex, hippocampus, pyriform cortex and thalamus. Importantly, the IR is also highly expressed in the hypothalamus, specifically in the arcuate, supraoptic and dorsomedial nuclei (Havrankova et al., 1978; Unger et al., 1989; Wozniak et al., 1993). The question whether insulin *itself* is expressed in the brain has been the topic of controversial debate for many years. There is significant evidence that insulin mRNA is present in certain regions of the brain during development as well as in adult brain (Devaskar et al., 1993). Peripheral insulin enters the brain *via* a saturable mechanism involving the blood-brain-barrier (BBB), and it seems that the rate of entry varies according to the region. The olfactory bulb, which as mentioned above has the highest level of IR in the brain (Havrankova et al., 1978; Gupta et al., 1992), tends to have the faster rate of transport (Banks et al., 2012). Indeed, this region is being used to transport insulin into the brain for therapeutic purposes. Table 1 summarizes the sites and mechanisms of expression of insulin-like peptides and receptors in brain as well as some of their biological activities.

Table 1 Expression and function of insulin, IGF-1 and receptors in the brain.

Expression of insulin-like peptides in brain
The IR is expressed in specific brain areas (e.g., olfactory regions, amygdaloid complex, hippocampus, pyriform cortex, thalamus, *etc.*).
Insulin mRNA is expressed in certain brain nuclei (mainly during development).
Insulin and IGF-1 enter the brain *via* the BBB.
IGF-1 and IGF1-R are widely expressed in brain.
Bioactivities of insulin-like peptides in brain
Neuronal survival.
Excitatory and inhibitory neurotransmission.
Suppress food intake.
Maintain normal free fatty acid levels.
Improve cognition.
Protection against cellular injury.
Neurogenesis, angiogenesis and amyloid clearance.

2.2. Insulin action on the brain

Classically, IR signaling involves the PI3K kinase/Akt and MAPK kinase pathways, leading to glucose transport in adipocytes by the former pathway and other effects through the MTOR/S6K kinase pathways that affect translation and even gene expression. In addition, there are so-called "non-canonical" IR signaling pathways involving, for example, the protein kinase-C (PKC)/NF-κB pathway. In this context, insulin was shown to regulate p-glycoprotein in rat brain microvessel endothethial cells *via* the PKC/NF-κB cascade and not necessarily through the PI3/Akt pathway (Liu et al., 2009). An important function for insulin in the central nervous system (CNS) appears to be neuronal survival (Mielke et al., 2006). When rat hippocampal cells in culture are stressed by oxygen or glucose deprivation their survival can be rescued by insulin signaling through the IR. Insulin also protects embryonic retinal cells during development from caspase and cathepsin-mediated apoptosis by inhibiting the expression of these pro-apoptotic proteins (Díaz et al., 1999).

There are numerous studies that have demonstrated that IR signaling plays a role in both excitatory and inhibitory neurotransmission, functions that are involved in high neuronal functions. In addition, short- and long-term memory may affect IR expression levels in the rat hippocampus, while the expression levels of other neurotransmitter receptors, such as the NMDA and AMPA receptors, remain unchanged (Plum et al., 2005). Further support for a role of insulin in neuronal modulation was provided by studies showing that intranasal insulin delivery in mice led to an increased expression of the potassium ion channel Kv1.3 in the olfactory bulb (Marks et al., 2009). Mice that received intranasal insulin have improved cognition, as shown by short- and long-term object recognition. These findings suggest that insulin delivered to the CNS increases neuronal activity and improves memory by mechanisms involving changes in Kv1.3 levels.

2.3. Central actions of insulin on peripheral glucose and lipid metabolism and appetite are mediated at the hypothalamic level

Insulin, when applied to the CNS, has been shown to suppress food intake *via* signaling in the hypothalamus (Scherer and Buettner, 2011). Indeed, intranasal administration of insulin in men decreased food intake after short-term treatment while weight reduction was achieved after long-term treatment (Hallschmid et al., 2012). Furthermore, neuroimaging studies have also demonstrated a similar effect in women, although women show a reduced sensitivity to this form of therapy. While most evidence supports the notion that the effect on food intake reduction is the result of direct insulin action on the hypothalamus, other studies suggest effects on extra hypothalamic regions that regulate the reward component of satiety (Hallschmid et al., 2012).

With regard to fat, activation of brain IRs and, to some degree, peripheral IRs, maintain normal circulating free fatty acids levels by suppressing lipolysis and inducing lipogenesis in white adipose tissue (WAT). The central effect of brain insulin on WAT is *via* reduction of sympathetic nervous system outflow to WAT and is apparently separate from its effect on appetite. Infusion of insulin into the brain suppresses hepatic gluconeogenesis without affecting glycogenolysis (Obici et al., 2002; Gutierrez-Juarez et al., 2004). Many of the functions described here are mediated by insulin's interaction with the Agouti-related peptide (AgRP) and pro-opiomelanocortin (POMC) neurons in the hypothalamus, though other CNS IRs might also be involved.

3. Insulin-like growth factors and the brain

IGF-1 and the IGF-1R are expressed in close proximity to each other in the various brain regions, suggesting a paracrine or autocrine functional loop (Bondy et al., 1992). IGF-1 is expressed in the rodent embryo, peaking in the second week post-natally but continues to be expressed in the adult brain (Bondy et al., 1990) and, in particular, in neuronal cells (Shemer et al., 1987). IGF-2, on the other hand, is expressed mostly in mesenchymal tissues, mainly the meninges and choroid plexus (20). The last structure is the main source of cerebrospinal fluid (CSF) IGF-2. Similarly, while the IGF-1R is widely expressed it also demonstrates a degree of regional distribution, with high levels of expression detected in the developing cerebellum, midbrain, olfactory bulb and in the ventral floorplate of the hindbrain (Bondy et al., 1992). The level of IGF-1R expression decreases to adult levels soon after birth but remains relatively high in the choroid plexus, meninges, and vascular sheaths (Russo et al., 2005).

3.1. The two sources of IGF peptides in the brain

The IGF-related peptides may affect brain function by either local tissue expression or by peripheral circulating peptides crossing the BBB. BBB uptake of circulating IGFs involves the IGF-1R and the low-density lipoprotein receptor-related protein 1 (LRP1), thus IGFs can reach the CSF as well as the hypothalamus and hippocampus. Other regions of the brain are then reached *via* specific transport mechanisms. On the other hand, experimental evidence suggests the production of the IGF-related peptides including insulin in certain regions of the brain. Thus, both local production and peptides derived from the peripheral circulation may play a role in regulation of brain function.

3.2. Circulating IGF-1 and central effects

In addition to its neurotrophic effects, circulating IGF-1 also demonstrates effects on cognition. Similar to humans with reduced serum IGF-1 levels and associated cognitive dysfunction (see below), animal models also demonstrate a correlation between endocrine IGF-1 levels and brain-related functions. These cognitive declines were reversible by prolonged systemic administration of IGF-1. These results suggest that the neurotrophic actions of IGF-1 affect glutamatergic synapses within the hippocampal circuitries thereby affecting learning and memory. Other effects of IGF-1 on brain cells include protection against cellular injury, neurogenesis, angiogenesis and even amyloid clearance (Aberg et al., 2000; Carro et al., 2000; Lopez-Lopez et al., 2004; Trejo et al., 2007).

3.3. IGF-2 and the brain

Similar to IGF-1, IGF-2 also plays a role in memory enhancement (Alberini and Chen, 2012). While the IGF-2R demonstrates the highest affinity for IGF-2, it has no intrinsic signaling function and thus IGF-2 effects are mostly mediated *via* the IGF-1R and/or the IR. IGF-2 mRNA and protein expression is increased in hippocampal regions after inhibitory avoidance training in rodents. Furthermore, antisense mediated reductions in IGF-2 in the dorsal hippocampus inhibit the long-term inhibitory avoidance memory consolidation. Similar results were obtained using an IGF-2 inhibitory antibody administered centrally (Chen et al., 2011).

3.4. IGFBPs in the brain

Of the six IGFBPs, IGFBP-2, -4 and -5 are more highly expressed in the brain than the others. As in the peripheral system, IGFBPs play a regulatory role by binding the IGFs. In general, gene-deletion and transgenic overexpression of IGFBPs have affected the brain, mostly commonly *via* affecting IGFs effect on brain development. Thus, an independent effect of IGFBPs has not been demonstrated (D'Ercole et al., 2002).

4. Lessons from animal models

The roles of the insulin and IGF signaling pathways in the brain were revealed by analyses of animal models with specific disruptions of ligand- or receptor-encoding genes and by analyses of transgenic mice overexpressing these genes (Baker et al., 1993). Transgenic animals overexpressing IGF-1 have markedly increased brains and a large number of cellular components, including neurons and oligodendrocytes.

Disruption of the IGF-1R gene by homologous recombination results in animals weighing 45% of normal littermates at the time of birth (Liu et al., 1993). These animals exhibit generalized developmental abnormalities, including abnormal CNS morphology, hypoplasia, impaired skin and bone formation, *etc*. Similar developmental anomalies were seen in animals with a disruption in the IGF-1 gene, though these animals weigh about 60% of normal littermates and the extent of malformations is a bit lower than those seen in IGF-1R KO animals. In the context of the nervous system, abnormalities are linked to a reduced population of neuronal cells, defective myelination, and enhanced apoptosis.

5. IGF-1 and brain pathologies

The linkage between the IGF-1 axis and brain pathologies, particularly Alzheimer's disease (AD), has been the topic of significant interest in recent years. The pathological hallmark of AD, the “neuritic” or amyloid plaque, is a dense conglomerate of amyloid β-peptide (Aβ) fibers and non-fibrillar forms of Aβ. Neuritic plaques are surrounded by a number of cellular components, including activated microglia, reactive astrocytes, *etc*. (Puglielli, 2008). Aβ peptides are generated by proteolysis of a precursor polypeptide, termed amyloid precursor protein (APP). APP homeostasis is tightly regulated by multiple hormonal and cellular pathways, including a series of phosphorylation events (Suzuki and Nakaya, 2008). A large body of evidence has identified IGF-1 as a major regulator of Aβ physiology. Specifically, serum IGF-1 controls Aβ clearance from brain *via* modulation of the levels of carrier proteins transthyretin and apolipoprotein J, among others (Bates et al., 2009). In addition, IGF-1 regulates Aβ degradation through its ability to control insulin degrading enzyme (IDE) availability, an extracellular protease. Finally, IGF-1 affects cellular uptake and lysosomal degradation of Aβ *via* regulation of the lipoprotein receptor protein family of multicargo transporter proteins (Torres-Aleman, 2010). The Torres-Aleman laboratory has also provided evidence that specific blockage of the IGF-1R in the rat choroid plexus leads to brain amyloidosis, cognitive disturbance, and hyperphosphorylated tau deposits similar to those seen in AD (Carro et al., 2006). These findings are consistent with the hypothesis that aberrant decline in circulating IGF-1 values leads to a reduction in IGF-1 uptake in brain, with ensuing development of the Alzheimer's phenotype.

6. Diabetes and brain function

Increasing epidemiological evidence suggests a linkage between diabetes (particularly type 2 diabetes) and AD occurrence. In a recent systematic review of the literature including fourteen studies, a risk ratio greater than one was reported in all of the studies (median, 1.59; range 1.15–2.7). In four of these studies, the added risk of AD was statistically significant (median, 1.73; range 1.59–1.9) (Kopf and Frolich, 2009). Conversely, the incidence of diabetes and impaired fasting glucose levels was much higher among AD patients than in age-matched controls, with 81% of the AD patients exhibiting fasting glucose levels above 110 mg/dL (Janson et al., 2004). In terms of etiology, both diabetes and AD constitute degenerative diseases associated with β-cell destruction and neuronal loss, respectively.

While the biochemical and molecular pathways responsible for the increased risk of developing AD in people with diabetes remain unclear, a number of putative mechanisms were postulated that might underlie this association (Yang and Song, 2013). Some of these pathological processes include: (i) inflammation; (ii) impaired insulin signaling; and (iii) amyloidogenesis.

(i) *Inflammation*: Inflammation has been identified as a major player in the etiology of obesity, insulin resistance and diabetes (Osborn and Olefsky, 2012). Elevated levels of a wide array of cytokines and immune mediators can be measured in the circulation as well as in pancreatic islets of type 2 diabetes patients. A similar pattern of immune activation is seen in AD, with elevated values of pro-inflammatory proteins and chemokines detected in post-mortem brains of AD patients (Akiyama et al., 2000). The role of inflammation as a major driver of AD was suggested by mouse models showing key functions for a number of chemokines in AD etiology (Wyss-Coray, 2006).

(ii) *Impaired insulin signaling*: As described above, insulin, IR and downstream proteins are present in different

areas of the CNS. It has been suggested that cognitive impairment in diabetes and AD could be linked to a defective IR signaling pathway in the brain (Sato et al., 2011). Post-mortem analyses of AD brains have shown reduced levels of insulin, IGFs and receptor mRNAs compared to control brains. Decreases were also seen in downstream mediator transcripts and the extent of these reductions were in correlation with the severity of the disease (Rivera et al., 2005). An enzyme involved in pathophysiological activities in both diabetes and AD is glycogen synthase kinase 3β (GSK3β). GSK3β is a serine/threonine kinase that is usually constitutively active and is regulated by insulin-mediated dephosphorylation (Kaidanovich and Eldar-Finkelman, 2002). Mice overexpressing GSK3β in the brain display elevated concentrations of hyperphosphorylated tau in association with a reduction in cognitive parameters. In contrast, GSK3β abrogation reduced neurodegeneration. Finally, recent studies provided evidence for brain insulin resistance as a potential etiological factor in AD. Using an *ex-vivo* experimental system, Talbot et al. (2012) showed that the hippocampal formation and, to a lesser degree, the cerebral cortex in AD cases without diabetes display diminished response to insulin signaling in the IR→IRS1→PI3K pathway as well as marked reduction in response to IGF-1 in the IGF-1R→IRS2→PI3K cascade. Furthermore, these putative biomarkers of brain insulin resistance increased from normal cases to mild cognitive impairment to AD cases.

(iii) *Amyloidogenesis*: An additional mechanism associated with the etiology of both diabetes and AD is amyloidogenesis. Similarly to the formation of amyloid plaques composed of insoluble aggregates of Aβ fibers in AD, islet amyloid deposits are a characteristic feature in the pancreas of diabetic patients (Yang and Song, 2013). Islet amyloids are composed of aggregates of amylin, also called human islet amyloid polypeptide (hIAPP), a 37-amino acid peptide derived from an 89-amino acid precursor. hIAPP is similar to Aβ fibers on both structural and morphological parameters (Luca et al., 2007). Deposition of amyloid in islets leads to a marked reduction in β-cell mass and function (Clark et al., 1988).

7. Brain IGF-1 receptors and life span

The insulin-IGF-1 signaling pathway plays a key role in the process of aging. Evidence from several animal models ranging from *D. melanogaster* to *C. elegans* and *M. musculus* has clearly established that reduced exposure of tissues to endocrine or autocrine/paracrine IGF-1 is associated with a markedly extended lifespan (Yang et al., 2005). While the mechanisms associated with IGF-1 regulation of lifespan remain unclear, it has been postulated that longevity is dictated by a tightly regulated hypothalamic growth hormone-IGF-1 hormonal axis. The impact of brain IGF-1R on lifespan has been addressed by specific inactivation of the IGF-1R in embryonic mice brain. Partial abrogation of the receptor inhibited the growth hormone and IGF-1 pathways, with ensuing metabolic and developmental anomalies in postnatal life, including a reduction in adult size. However, survival curves indicated that impaired IGF-1R function led to a marked increase in lifespan compared to controls (914±21 compared to 836±28 days) (Kappeler et al., 2008). Of interest, heterozygous brain IGF-1R disruption had no effect on other brain functions. In this context, it is important to emphasize the fact that complete abrogation of brain IGF-1R led to a different phenotype, associated with increased IGF-1 levels. Hence, IGF-1R gene dosage has a key role in establishing the hormonal balance that will shape the final phenotype. Finally, genetic alterations in the human IGF-1R gene were identified in a cohort of Ashkenazi Jewish centenarians. Linkage between over-representation of IGF-1R mutations, short stature and increased serum IGF-1 levels was noticed. These results highlight the central role of the IGF-1R axis in aging and indicate that altered IGF-1 signaling may lead to increased longevity (Suh et al., 2008).

8. Potential clinical applications

Scientific breakthroughs in the area of insulin action in brain may lead to important translational advances. Given the brain insulin resistance in AD patients described above, attenuating this hormonal resistance might constitute a useful pharmacological intervention (Talbot et al., 2012). In this context, the use of antidiabetic agents (e.g. metformin) and GLP-1 mimetic agents (e.g. liraglutide) has been suggested. These drugs cross the BBB, elicit neuroprotective activities and, importantly, are safe and well-tolerated medicines. In a pilot study, increasing doses of insulin were administered intranasally to memory impaired AD patients or patients with mild cognitive disorder. Cognition was tested 15 min after insulin administration. Insulin improved recall on two measures of verbal memory in patients lacking the ApoE-e4 allele whereas it led to a decline in memory tasks in patients expressing the ApoE-e4 allele. The ameliorative effect of insulin displayed a dose-dependent curve, with optimal performance observed at 20 I.U. These results are consistent with the concept that patients with different genetic backgrounds may respond differently to insulin therapy (Reger et al., 2008).

9. Future directions

The large volume of experimental data collected over the past 30 years on the role of insulin, IGFs and their receptors in fundamental biological processes (e.g., development, brain function, metabolism, *etc.*), along with more recent data linking brain insulin/IGF-1 function to the etiology of a number of neurodegenerative diseases will, undoubtedly, translate into more clinically-oriented avenues of research in the near future. As exemplified above, anti-diabetic drugs seem to improve symptoms associated with AD and, probably, other nervous system pathologies (though not in every patient). It is expected that future studies will take advantage of postgenomic technologies in order to generate molecular and/or biochemical signatures aimed at identifying patients who may benefit from these therapies. Finally,

biomarkers identification may help evaluate the risk of diabetes patients to develop AD.

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Prof. Werner and Prof. LeRoith have contributed equally in the writing of the review article. They both have approved the final manuscript.

Conflict of interest

Drs. Werner and LeRoith have no competing interests.

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