Insulin in the Brain

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ABSTRACT

Insulin's effects were long thought to be isolated to the periphery; however, we now know that insulin signaling plays an integral role in the brain. In this article, we describe insulin signaling in the brain and explain how insulin resistance could lead to cognitive decline and depressive symptoms, followed by a summary of the animal and clinical data linking insulin resistance to cognitive dysfunction and mood.

Insulin and the Brain: New Findings

Since its discovery over a century ago, insulin is best recognized as a pancreatic β-cell hormone that controls plasma glucose. With the subsequent identification of insulin receptors (IR), this classic role of insulin in lowering glucose levels was firmly established and was long considered to be limited to the peripheral system.[1,2] However, we now know that insulin receptors are also expressed throughout the brain and that insulin signaling plays an integral role in the brain— influencing cerebral bioenergetics, modulating neuronal and glial function, increasing turnover of neurotransmitters, like dopamine, and consequentially impacting mood, behavior, and cognition.[3,4,5]

Alternate splicing of a single gene generates the two isoforms of the insulin receptor (IR), IR-A and IR-B. IR-B is widely expressed in the liver, adipose tissue, and skeletal muscles, while IR-A is predominantly located in the brain. The IRs in the brain are distinct from those in the peripheral tissues with respect to size, shape, mechanism, and glycosylation levels. These receptors are ubiquitously present throughout the brain; incidentally, the regions of the brain that harbor high levels of IR expression (hippocampus, cortex, hypothalamus) are also the same regions known for their roles in cognition.[6] IR-mediated signaling is critical for neurotrophic (neuronal growth, development, and function), neuroprotective (neuronal cell survival), and neuromodulatory (modulating energy expenditure, emotional and behavioral cognition) processes in the brain.[7] These diverse cellular and physiological IR activities are distinct from metabolic IR functions in peripheral tissues, thus highlighting regional specificity of IR properties. Insulin can also cross the blood-brain barrier (BBB) via active transport and is thought to originate from both brain and pancreatic sources.[7]

Insulin Signaling in the Brain

The effects of insulin in the brain are mediated by two main pathways: the phosphoinositide-3-kinase (PI3K)/Akt and the Ras/mitogen-activated kinase (MAPK) signaling cascades. The insulin receptor is a heterotetrameric protein composed of two α-subunits and two β-subunits linked by disulfide bonds.[8,9]

Once insulin is bound to the extracellular α-subunit of IR, it induces the dimerization of the intracellular β-subunit. The α-subunit also promotes autophosphorylation of tyrosine residues on the β-subunit by activation of intrinsic tyrosine kinases. The auto-phosphorylated β-subunit then phosphorylates tyrosine residues on a group of adaptor proteins belonging to IRS (insulin substrate) families 1 through 4 (IRS1-IRS4). In the brain, IRS1 is expressed in the cerebral cortex, and IRs in the hypothalamus. The dephosphorylation of tyrosine residues in IR and IRS1 may also regulate downstream insulin signaling via protein tyrosine phosphatase 1B.[8,9]

The second insulin signaling pathway is insulin-IR-IRS-Raf/Ras/MAPK. This pathway controls various transcription factors and proto-oncogenes; and regulates the transcription, translation, and post-translational modification of various proteins, such as growth factors, receptor genes, and matrix-modifying proteins.[8,9]

The primary difference between peripheral and brain insulin signaling is the regulation of glucose transporters. In peripheral tissues, insulin-mediated Akt activation induces translocation of glucose transporter 4 (GLUT4) from vesicles to the plasma membrane to facilitate uptake from the blood. However, in the brain, the expression of GLUT4 is limited to specific brain regions such as the hippocampus and hypothalamus, resulting in a much smaller impact on glucose uptake. Thus, it is primarily the glucose uptake effects of insulin signaling, rather than the signaling pathways themselves, that differ between the brain and the periphery.[6]

Insulin and Cognition

In addition to regulating neural circuits involved in glucose metabolism, insulin influences cognitive functions through its actions on synaptic plasticity and long-term potentiation in the hippocampus and other brain regions.[10] Spatial memory training in rodent models has been shown to upregulate IR mRNA in certain hippocampal regions, resulting in an increased accumulation of insulin receptors within the hippocampus. In water maze-trained rats, training increases tyrosine phosphorylation of the insulin receptor stimulated by insulin.[11] Thus, learning may influence the concentration of insulin receptors and insulin signaling in various regions of the brain including the hippocampus. Insulin signaling in the CNS also affects emotional regulation. Rats subjected to lentivirus-mediated downregulation of hypothalamic insulin receptors demonstrated depression and anxiety-like behaviors.[12] In another recent study, researchers knocked out the expression of both the insulin and IGF1 receptors in the hippocampus and amygdala, two regions critical for learning, memory, and mood. Disrupting these pathways resulted in impaired learning and memory, increased anxiety-like behaviors, and glucose intolerance.[13]

Consistent with these observations in animal models, impaired insulin signaling is linked to cognitive decline and depressive moods in humans.

Insulin Resistance in the Brain and Impact on Cognition

Impaired insulin signaling or insulin resistance is a characteristic of type 2 diabetes, obesity, and the metabolic syndrome, and affects insulin-sensitive tissues like liver, muscle, and fat. This insulin resistance is also observed in the brain and is termed brain insulin resistance. It is defined as the failure of brain cells to respond to insulin as they normally would, resulting in impairments in synaptic, metabolic, and immune response functions thought to contribute to impaired cognition.[7,14] Brain insulin resistance may likely occur because of reduced expression of insulin receptors, failure of insulin to bind to its receptor, or unsuccessful activation of the insulin signaling pathway. Consequently, deterioration of neuroplasticity, failure of neurotransmitter release, and/or impairment of physiological insulin-related functions can occur.[15]

The role of insulin in cognitive function under conditions of insulin resistance is strongly suggested in several clinical studies. A meta-analysis of 24 studies revealed that the presence of diabetes, obesity, hypertension, and hypercholesterolemia in midlife were associated with the development of dementia in late life.[16] In another similar meta-analysis of 12 studies in 6800 patients, having diabetes for 5 or more years was associated with a 40–60% increased risk for dementia than those recently diagnosed.[17] Conversely, lifestyle changes including exercise and consumption of a healthy diet in midlife were associated with a reduced risk of dementia.[18] Furthermore, metabolic imaging with fluorodeoxyglucose (FDG)-positron emission tomography (PET) scanning in middle-aged and elderly individuals with insulin resistance and type 2 diabetes with normal cognition demonstrated regional cortical hypometabolism in parietal, temporal, and frontal regions—all areas important for cognition and frequently implicated in Alzheimer's disease (AD) and other related dementia.[8] Indeed, brain insulin resistance is a documented feature of AD.[8] Postmortem tissue in patients with AD have been shown to exhibit decreased binding of insulin, reduced levels of activated IR, and increased serine phosphorylation of IRS-1 at sites known to inhibit insulin signaling.[19]

Furthermore, insulin also modulates dopaminergic-mediated pathways critical for motivation and reward. Impairment in insulin signaling reduces dopamine release,[20] potentially explaining mood and anxiety symptoms observed in people with insulin signaling disorders.[3]

Therapeutic Implications of Enhancing Brain Insulin Signaling

These findings thus suggest that a novel approach to therapeutic intervention of cognitive disorders would be to increase the availability of insulin in the CNS or increase sensitivity to insulin. Interestingly, intranasal insulin administration, in which insulin travels via bulk flow to the brain along olfactory nerve channels, bypassing the BBB, has been shown to result in positive effects on memory and learning.[4,18] These improvements in cognition via insulin administration have also been shown to activate IR and its downstream signaling cascade. Two studies in patients with mild cognitive impairment or AD showed that intranasal administration of insulin for 21 days improved episodic memory, an effect that was modulated by the APOE genotype.[21,22] In terms of insulin sensitizers, compounds like metformins and peroxisome proliferator-activated receptor alpha (PPAR-α) agonists have not successfully demonstrated significant clinical evidence of improving brain insulin sensitivity.[4]

Alternatively, treatment with antidiabetic drugs that improve glycemic control would also be expected to improve cognitive function. Promising candidates for these are insulinotropic hormones like GLP-1 that are commonly prescribed to treat type 2 diabetes.[4] Recent data demonstrate that GLP-1 based drugs consistently exhibited beneficial actions in the brain and have the potential to delay cognitive decline in conditions of insulin resistance.[19] An ongoing phase 2, randomized, placebo-controlled clinical trial of daily liraglutide (GLP-1 agonist) treatment in patients with AD is currently in progress. The primary endpoints of this study are to examine treatment effects on FDG-PET, cognitive performance, and other imaging biomarkers (NCT01843075).[23]

Finally, ongoing studies are currently underway to test if the effects of exercise and lifestyle interventions on brain insulin resistance can further modulate risk and increase therapeutic benefit.[4]

Future Prospects

Despite these advances, many outstanding questions still remain. Is diabetes-associated cognitive impairment a consequence of brain insulin resistance or is it due to other factors that occur with systemic insulin resistance? How do antidepressants or cognition-enhancing drugs modify systemic metabolic status?[3] As our knowledge of insulin's action on the brain grows, and its various functional nuances continue to be delineated, our understanding can eventually translate into clinical therapies for treating both metabolic and cognitive disorders. Future strategies to exploit the multiple unique and beneficial actions of insulin in the brain are certainly warranted.

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