ROLE OF INSULIN IN BRAIN: DELVE INTO THE MOLECULAR MECHANISMS

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ABSTRACT

We have learned over the last several decades that the brain is an important target for insulin action. In central nervous system (CNS) it mainly affects feeding behaviour and various aspects of memory and cognition. Insulin signalling in CNS has emerged as a novel field of research since decreases brain insulin levels and signalling were associated to impaired learning, memory and age-related neurodegenerative diseases. Alterations of these functional activities may contribute to the manifestation of several clinical entities, such as central insulin resistance, type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD). A close alliance between T2DM and AD has been reported, to the extent that AD is twice more frequent in diabetic patients. There are links between T2DM and AD through mitochondrial alterations and oxidative stress, altered energy and glucose metabolism, cholesterol modifications, dysfunctional protein O-GlcNAcylation, formation of amyloid plaques, altered A β metabolism and tau hyperphosphorylation. Herewith, we aim to integrate the metabolic, neuromodulatory, and neuroprotective roles of insulin in two age-related pathologies: T2DM and AD, both in terms of intracellular signalling and potential therapeutic approach.

INTRODUCTION

Insulin plays a central role in the regulation of human metabolism. It is a peptide hormone secreted by the β cells of the pancreatic islets of Langerhans and maintains normal blood glucose levels by facilitating cellular glucose uptake, regulating carbohydrate, lipid and protein metabolism and promoting cell division and growth through its mitogenic effects. Glucose production and secretion by the liver is strongly inhibited by high concentrations of insulin in the blood. Circulating insulin also affects the synthesis of proteins in a wide variety of tissues. It is therefore an anabolic hormone, promoting the conversion of small molecules in the blood into large molecules inside the cells. Low insulin levels in the blood have the opposite effect by promoting widespread catabolism, especially of reserve body fat. Although the control of peripheral glucose homeostasis is one of the main functions of insulin, its action on the brain is now also being studied carefully, as it is considered an insulin-sensitive organ because insulin receptors (IR) and their signal transduction pathways have been identified in several regions of the brain that mediate important physiological effects on this organ, such as neuronal development, glucoregulation, feeding behavior, and body weight, as well as cognitive processes, including attention, executive functioning, learning, and memory.

STRUCTURE OF INSULIN

- ✓ Human Insulin composed of two peptide chains as Chain A & Chain B
- ✓ A and B chains are linked together by two disulfide bonds
- ✓ An additional disulfide is formed within the A chain
- ✓ Chain A consists of 21 amino acids and chain B of 30 amino acids
- ✓ Both chains contain alpha helices but no beta strands
- ✓ Insulin can also form dimers in solution due to the hydrogen bonding between the B chains
- ✓ The dimers can further interact to form hexamers due to interaction between hydrophobic surfaces.

MECHANISM OF ACTION OF INSULIN

- ✓ Insulin initiates its action by binding to a glycoprotein receptor on the surface of the cell
- ✓ Receptor consists of α -subunit, which binds the hormone, and β -subunit, which is an insulin-stimulated, tyrosine-specific protein kinase
- ✓ Activation of this kinase generate a signal that eventually results in insulin's action on glucose, lipid, and protein metabolism

EFFECT OF INSULIN ON BRAIN ENDOTHELIAL CELLS AND BLOOD-BRAIN BARRIER CELL FUNCTION

- ✓ BBB formed by a type of brain endothelial cell that is unique
- ✓ Cell membranes are exposed both to the blood stream and to the CNS, whereby these cells receive signals from both the periphery and the CNS
- ✓ BECs have insulin-binding sites that appear to have two distinct functions: as transporters of insulin across the BBB and as classic receptors, both affecting the function of the barrier cell by activating intracellular machinery and mediating the effects of insulin on these cells, such as the increase in the transport of tyrosine and tryptophan, azidothymidine, and leptin from blood to brain

MECHANISMS OF INSULIN SIGNAL TRANSDUCTION IN THE BRAIN

INSULIN ACTIONS IN THE BRAIN

EFFECTS ON ENERGY & GLUCOSE HOMEOSTATISIS

NEUROPROTECTIVE EFFECTS

NEUROMODULATORY EFFECTS

EFFECTS ON COGNITION AND MEMORY

RELATIONSHIP BETWEEN DIABETES AND ALZHEIMER'S DISEASE

CONCLUSION

As reviewed herein, decreased brain insulin function is associated to impaired cognitive performance and late-life neurodegenerative diseases like Alzheimer's disease. Thus, besides its wellknown therapeutic role in diabetes, insulin may constitute a promising therapy against neurodegenerative disorders based on its metabolic, neuroprotective, and neuromodulatory effects. Although restoring central insulin levels and/or its receptor-mediated signaling cascades have been the potential interest of many researches and some clinical trials have been also performed for the treatment of Alzheimer's disease, finding a way to keep the euglycemic condition following insulin administration is still a major concern.

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