THE ROLE OF INSULIN RECEPTOR SIGNALING IN THE BRAIN

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INTRODUCTION

- Insulin is a hormone produced in the pancreas by the islets of Langerhans that regulates the amount of glucose in the blood.

- Insulin regulates food intake, sympathetic activity and peripheral insulin action.

- It regulates ATP-dependent potassium channels and inhibits neuronal apoptosis.

- Also regulates phosphorylation of tau, metabolism of APP

- Insulin has profound effects in the CNS, where it regulates processes such as energy homeostasis, reproductive endocrinology and neuronal survival.
EXPRESSION OF THE IR IN THE CNS AND SOURCE OF CEREBRAL INSULIN

- The insulin receptor is located in the central nervous system.
- These receptors are widely distributed in the brain with highest concentration in the olfactory bulb, hypothalamus, cerebral cortex, cerebellum, and hippocampus.
- To initiate signaling in the CNS, insulin must reach its receptor through the blood-brain barrier.
BRAIN IR IN THE CONTROL OF ENERGY HOMEOSTASIS

• Insulin has an impact on the direct control of food intake and energy expenditure.
• Administration of insulin directly to the brain yields an anorexigenic effect while inhibition of insulin signaling in the brain has an orexigenic effect.
• PI3K is an important factor in mediating the intracellular effects of insulin and leptin.
Insulin receptor signal transduction with respect to neuronal function:

Insulin binds to and activates the insulin receptor (IR). The receptor undergoes a conformational change resulting in the phosphorylation of intracellular insulin receptor substrate (IRS) proteins on tyrosine residues.
Mechanism of insulin action in the hypothalamus: Insulin binds to its receptor. PI3K activates and phosphorylates PIP2 to PIP3, which opens K^+ channels. This produces an outward flow of K^+ ions leading to hyperpolarization and reduced activity of the neuron. Signals in the IR and ObRb have been shown to regulate the expression of neuropeptides in the ARC such as the down regulation of NPY (orexigenic). This results in increased expression of CRH (anorexigenic) in the PVN.
CENTRAL INSULIN ACTION AND PERIPHERAL GLUCOSE METABOLISM

• Insulin also modifies peripheral glucose metabolism through IRs localized in the hypothalamus.

• Introcerebroventricular administration of Katp blockers suppresses the effect of insulin on hepatic glucose production.

• Two different types of glucose-sensing neurons (glucose-responsive & glucose-sensitive) have been identified.

• When interstitial glucose levels rise, the firing rate of glucose-responsive neurons increases and glucose-sensitive neurons decreases.
VENTROMEDIAL HYPOTHALAMUS

- In this portion of the hypothalamus, neurons are influenced by glucose availability and affect the activity of the sympathetic nervous system.
- This area is responsible for the hormonal response to systemic hypoglycemia and activating counter-regulatory mechanisms such as glucagon, cortisol and norepinephrine.

Source: http://knowingneurons.com/2013/03/06/the-hunger-games-of-the-second-brain/
Clinical observations assessing the association of obesity with infertile conditions have identified a potential link between reproductive and metabolic disorders.

- Mice show reduced fertility and mild obesity after hypothalamic dysregulation of luteinizing hormone (reproductive hormone).
- Mice Lacking Insulin Receptor Substrate 2 (IRS-2) in all tissues and brain are obese and have smaller ovaries.

Therefore it can be inferred that the Insulin Receptor has an important role in the CNS for both the regulation of “energy homeostasis” and reproductive health.
THE ROLE OF IR SIGNALING IN LEARNING AND MEMORY

The function of Insulin in regards to learning and memory are controversial due to difficulties in assessing the role of insulin in the CNS due to hypoglycemia when insulin is administered peripherally.

Despite this, injection of insulin into the body either nasally or intravenously is correlated with increased efficacy or working memory and improvement in verbal memory and selective attention respectively.

Alzheimer’s patients have lower concentrations of insulin in their cerebrospinal fluid. Administrations of insulin have been shown to improve memory and performance.
MEMORY RETENTION IN ALZHEIMER’S PATIENTS DIFFERENTIALLY TREATED WITH INSULIN

Higher Memory Recall with insulin administration
Study Conclusion: Hyperinsulinemia without hyperglycemia Enhances memory in adults with AD
Methods: Subjects heard a story that had 44 informational bits. They were tested on how much they recalled

THE ROLE OF IR SIGNALING IN NEURODEGENERATIVE DISEASES

Individuals suffering from Parkinson and Alzheimer’s disease show reduced expression of the IR in the brain.

Insulin and associated growth factors have been shown to regulate neuronal survival.

Insulin resistance influences tau phosphorylation and neuronal survival under degenerative conditions.

(Definition: Tau protein is responsible for the stabilization of microtubules in the CNS. Phosphorylation of Tau results in disruptions in microtubule formation and contributes to neural degradation)
Neuron Survival vs Insulin Concentrations

Figure describing neuron survival with respect to increasing insulin concentration. In two of three cases higher insulin concentrations demonstrated increased neuron survival.

Methods: MTT Assay and Fluorescent apoptotic markers

CONCLUSIONS

The CNS used to be considered an insulin independent tissue, however the CNS is apart of the insulin signaling pathway and insulin has been shown to cross the blood-brain barrier.

Insulin has been show to act as a mediator of energy homeostasis, reproduction and neuronal survival.
FUTURE DIRECTIONS

New novel techniques will need to be used to elucidate the molecular mechanism by which insulin acts on the CNS.

What is almost certain though is that the metabolic processes of the body and its neurological function are inexorably linked and insulin may be a key player in this relationship.
