The role of insulin receptor signaling in the brain

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<table>
<thead>
<tr>
<th>1978 localized IR in the CNS – widely distributed</th>
<th>Olfactory bulb, hypothalamus, cerebral cortex, cerebellum &amp; hippocampus</th>
<th>Peripheral infusion of insulin leads to an increase in CSF → insulin crosses BBB in a receptor mediated transport mechanism</th>
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<tbody>
<tr>
<td>Factors that affect insulin transport across BBB:</td>
<td>Fasting, obesity, aging, dexamethasone treatment decrease insulin transport into CNS.</td>
<td>Some models of diabetes mellitus &amp; during neonatal period: insulin transport is increased</td>
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Brain IRs in the control of energy homeostasis

**insulin**

Directly administered into the brain leads to anorexigenic behavior (inhibit food intake)

Changes in hypothalamic neuropeptides mediate anorexigenic behavior

Increases α-melanocyte stimulating hormone (α-MSH); mediates anorexigenic effect of insulin.

Reduces expression of NPY in hypothalamic arcuate nucleus (Neuropeptide Y is orexigenic)

Increases corticotropin-releasing hormone

Activates reward pathway – mesolimbic dopamine-mediated pathway

Inhibiting insulin in the brain has an opposite effect: orexigenic effect (increase food intake)

$K_{ATP}$ channels set resting membrane potential of β-cells

- $E_K = -80\text{mV}$
- Mutation in $K_{ATP}$ causes hyperinsulism.
- Without $K_{ATP}$ activity, the resting membrane potential is at a value that enables L-type Ca$^{++}$ channel currents.
- The persistent Ca$^{++}$ influx maintains an increased intracellular Ca$^{++}$ concentration that drives insulin secretion.

“Multiple peripheral factors have been shown to modify food intake and energy expenditure through direct effects on the CNS.”

Leptin is the product of the *ob* gene

Leptin is a circulating hormone produced by white adipose tissue.

Leptin has strong effects on feeding, thermogenesis and neuroendocrine responses.

Ghrelin levels rise before eating and decline after

Ghrelin levels rise after fasting – acutely and chronic

Ghrelin levels rise in response to weight loss

α-MSH melanocyte-stimulating hormone is an appetite suppressant, regulates body weight (hepatic glucose) and peripheral insulin sensitivity.

Neurons in the arcuate n. express the precursor to MSH -> pro-opiomelanocortin (POMC)

Cocaine and Amphetamine Regulated Transcript has an anorexigenic effect.

Dorsomedial hypothalamic nucleus is directly involved in the control of satiety and metabolism.

Lateral hypothalamus causes behaviors that are associated with hunger – the initiation of feeding. LH and VMN can sense ambient glucose levels. Glucose responsive neurons increase firing ($K_{ATP}$ mediated) in the presence of glucose while glucose sensitive decrease firing under the same condition.

Arcuate nucleus is the source of one of the major inputs to the lateral and medial nuclei of the hypothalamus. It functions as a ‘relay’ for the hormonal and afferent inputs from the periphery.

Ventralomedial nucleus of the hypothalamus is associated with the sensation of satiety and compensatory responses to hypoglycemia. VMN contain neurons which are influenced by ambient glucose and affect the activity of the sympathetic nervous system with glucagon, cortisol and NE.
Neuropeptide Y, produced in neurons in the Arcuate nucleus and project to the LH on to neurons expressing NPY-1 receptor increasing feeding behavior.

Agouti-related peptide (AgRP) is an endogenous antagonist of MSH (melanocyte stimulating hormone/melanocortin) receptors. Co-expressed with NPY neurons.

AgRP neurons also project to LH, DM and VM. AgRP (DM/VM) inhibits MSH. NPY and AgRP are released by GHRELIN and inhibited by LEPTIN and are thought to be glucose-responsive; they express glucokinase.

Leptin and insulin activate K_{ATP} channels and hyperpolarize NPY and AgRP neurons.

http://www.cellbiol.net/
neuron-specific insulin receptor knockout (NIRKO)

“These animals exhibit no alteration in neuronal proliferation/survival, memory, or basal brain glucose metabolism.”

- Loss of insulin-mediated activation of phosphatidylinositol 3-kinase
- inhibition of neuronal apoptosis
- Reduced phosphorylation of Akt and GSK3
- Increased phosphorylation of microtubule-associated protein - Tau

Hyperphosphorylated Tau is associated with AD and CTE → Phosphorylation of Tau at Thr-231 – However NIRKO: Tau is phosphorylated at Ser-202

Link between hyperinsulinaemia and AD?

IDE → Insulin degrading enzyme → Degrades both insulin and amylin → T2D → Amyloid-β peptide → AD

Hyperinsulinaemia may elevate amyloid-β through insulin’s competition with amyloid-β for IDE

Genetic studies have shown that IDE variations are associated with clinical symptoms of AD and risk of T2D

Background on: $K_{\text{ATP}}$

Toward Understanding the Assembly and Structure of $K_{\text{ATP}}$ Channels

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Background on NIRKO

Role for neuronal insulin resistance in neurodegenerative diseases

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Insulin, IDE and Amyloid-β peptide and AD?