The Role of Insulin Receptor Signaling in the Brain
Insulin Receptor
Mechanism of Insulin Action
The Effects of Insulin

- Energy homeostasis
- Learning and memory
- Peripheral glucose metabolism

- Regeneration
- Reinnervation
- Survival

Insulin signaling pathways:
- IRS
- Akt
- p85
- p110

TRENDS in Endocrinology & Metabolism
Expression of the IR in the CNS and source of cerebral insulin

- In 1978, Havrankova et al. localized the IR in the CNS for the first time.
- IR are widely distributed in the brain with a highest concentration in the olfactory bulb, hypothalamus, cerebral cortex, cerebellum and hippocampus.
Expression of the IR in the CNS and source of cerebral insulin

• In order for insulin to initiate signaling in the CNS, insulin has to reach its receptor, which is separated by the Blood brain barrier

• In 1960 Margolis et al. confirmed that insulin crosses the BBB by showing that a peripheral infusion of insulin leads to an increase in insulin levels in cerebrospinal fluid

• Studies were later repeated in mice
Expression of the IR in the CNS and source of cerebral insulin

• Conditions that decrease insulin transport across the blood-brain barrier
  • Fasting
  • Obesity
  • Aging
  • Dexamethasone treatment

• Conditions that increase insulin transport across the blood-brain barrier
  • Some models of Diabetes mellitus
  • Neonatal period
Brain IRs in the control of energy Homeostasis

- Insulin and the adipocyte-derived hormone leptin are adiposity signals that exert modulatory functions at various CNS sites.
- Insulin provides both short-term and long-term homeostatic signals.

Pathway Breakdown

- Insulin binds to insulin receptor leading to autophosphorylation.
- Followed by Tyrosine phosphorylation of IRS which induces downstream pathways (PI3K and MAPK).
- PI3K controls K(atp) via (PIP3 and PIP2).
- Potassium leaves cell which hyperpolarizes cell causing a downregulation of Neuropeptide-Y (orexigenic).
- Release of Corticotropin hormone which is responsible for the increase in anorexigenic behaviour.

- Intracerebroventricular delivery of insulin increases expression of α-melanocyte stimulating hormone.
- Upregulation in α-MSH mediates the anorexigenic effects of insulin because application prevents insulin-induced reduction in food intake due to it being a anorexigenic peptide.
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Central Insulin Action and Peripheral glucose Metabolism

• Hepatic glucose production is not mediated by insulin-induced activation of the melanocortin receptor system, which is activated by MSH

• How do we know?
• When a melanocortin receptor antagonist is administered, we don’t see a weakening of the effects of centrally administered insulin on hepatic glucose production

• Inhibition of PI3K, but not inhibition of MAPK, reverses the reduction

• $K_{ATP}$ blockers suppresses the effect of insulin on hepatic glucose production
Inhibition reverses the reduction

No effect if inhibited

Inhibition suppresses the effect of insulin on hepatic glucose production
CONVERSELY….

- Chronic Antagonism of melanocortin receptor 4 leads to an increase in food uptake and therefore abdominal adiposity.

- There is a reduction in hepatic glucose production

- Reduces the uptake of glucose into the peripheral tissues in response to the excess levels of insulin in the blood (hyperinsulinemia)

- Chronic Intracerebroventricular of the MC4R agonist α-MSH produces opposite effects

- The chronic bidirectional modulation of central melanocortin receptors has a role in regulating body weight, body composition, hepatic and insulin sensitivity.
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Lateral hypothalamus (hunger center)

Ventromedial hypothalamus (satiety center)

Lateral hypothalamic lesions (anorexia)

Normal

Ventromedial hypothalamic lesions (obesity)
Glucose Sensitive

- decreased activity as glucose increased
- Little is known
- Neurons expressing neuropeptide Y and proopiomelanocortin have been suggested to be important because they show expression of glucokinase (an enzyme that phosphorylates glucose)

Glucose Responsive

- increase activity with increased glucose
- Seem to use K-ATP channels
- Indirect evidence suggests that IR is present because insulin has been shown to activate K-ATP channels in this group of neurons

Provides a link between glucose sensing and feeding behavior at a cellular level
Highlights the role of IR in the brain in controlling regulation of energy needs
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a, Ovaries with attached oviducts and fallopian tubes from 8-week-old mice at ×2 magnification. b, Ovaries from 6–8-week-old mice. Sections were stained with haematoxylin and eosin and viewed at ×20 magnification. Representative ovarian sections are from two different animals of each genotype. c, Antral follicles (200–250 μm) and corpora lutea quantified from haematoxylin and eosin stained ovarian sections from 6–8-week-old mice viewed at ×20 magnification. Results are the mean ± s.e.m. of at least eight sets of ovaries from each genotype. d, Quantification of primary germ cells at embryo day 18. Fetal ovaries were collected and fixed in 4% paraformaldehyde. Primary oocytes were quantitated from haematoxylin and eosin stained sections of embryonic ovaries. Results are the mean ± s.e.m. of three females per genotype. e, Immunoblot of ovarian lysates. After in vivo insulin stimulation (5 units human insulin), ovaries were collected and homogenized. Lysates (1 mg total protein) were immunoprecipitated with anti-IRS antibodies as indicated, and immunocomplexes probed with anti-phosphotyrosine antibodies. Results are representative of three independent experiments.
Hypothalamus: Controlling Compensatory Response

- The Hypothalamus is important for controlling compensatory responses to hypoglycemia
- These responses include
  - Glucagon released from the pancreas
  - Sympathoadrenal activation resulting in the secretion of epinephrine
- Evidence strongly suggests that the ventromedial hypothalamus are influenced by glucose abundance
  - Supported by the fact that when VMH is lesioned, compensatory actions are halted
  - Additionally, when the VMH is bilaterally perfused with glucose responses to hypoglycemia is impaired
The role of IR signaling in learning and memory

Systemic infusion of insulin in humans produces significant improvement of verbal memory and selective attention.

-Euglycemic hyperinsulinemic condition
Intranasal administration of insulin induces a rapid increase in the insulin concentration in CSF WITHOUT affecting blood glucose levels.
- This means that insulin can influence brain function directly and independently of glucose levels in the periphery.
- There is an increase in performance in working memory.
Individuals with type 2 diabetes who are 64 or older perform worse in learning tasks as compared to their non-diabetic counterparts.

Alzheimer's patients have lower levels of insulin in their CSF as compared to in their plasma.
- Impairment of insulin metabolism in the brain.
- Administration of insulin shows improvement in memory and performance.

Could insulin spray be administered to those with type 2 diabetes?

What does this mean in terms of insulin resistance? Could there be similar effects as with L-dopa in Parkinson’s patients?
NIRKO mice

- Have insulin receptor knocked out.
- These mice show normal spatial learning when doing the morris water maze task.

  - This implicates the insulin receptor signaling does not play a role in memory formation
  - However, due to the brain’s plasticity, it may be that NIRKO mice compensate using other mechanisms in order to perform these tasks

https://www.homehero.org/blog/health/uci-study-links-sleep-cycle-disturbances-to-alzheimer-s
The role of IR signaling in neurodegenerative diseases

Individuals suffering from Alzheimer’s and Parkinson’s disease have shown reduced expression of IR in the brain. This raised the question of whether reduced expression of IR is a cause or a consequence of neurodegenerative diseases.

What comes first?

The disease or the reduced expression of IR?
Several targets of the insulin signaling machinery with potential influence on the development of neurodegenerative diseases have been identified.

Tau regulation:

- GSK-3 β phosphorylates Tau, hyperphosphorylation reduces affinity of tau for microtubules.
- IR controls the activity of GSK-3 β and thus influences Tau phosphorylation.

Inhibits & therefore reduces hyperphosphorylates = in reduced affinity of tau for microtubules
Furthermore, **NIRKO** mice show a decrease in steady state phosphorylation of both protein kinase B (PKB or AKT) & GSK-3β which leads to hyperphosphorylation of tau.

**IRS-2** deficient mice show tau hyperphosphorylation and develop intracellular accumulation of hyperphosphorylated tau during aging.

Showing that IR & IGF-1 signaling have an essential role in regulating the phosphorylation of tau in **vivo**.
Previous studies have suggested that insulin and IGF-1 support neuronal survival \textit{in vitro} and \textit{in vivo}.

Insulin and IGF-1 → Strongly activates PKB → promotes phosphorylation → Bcl-2 antagonist of cell death & associated proteins → Inhibiting apoptosis → Bcl-2
But, there is a lack of neurodegeneration in both the NIRKO and IRS-2 deficient mice.

This shows that the IR & IRS-2 branch of the signaling pathway is not essential for neuronal survival in vivo, even though alterations here can cause hyperphosphorylation of tau.

So whether these two pathways contribute significantly to neuronal survival under neuropathological conditions remains unclear.
Amyloid-β Levels

IR & IGF1-R mediated signals regulate the secretion of amyloid precursor protein (APP).

Insulin resistance caused by diet-induced obesity = in marked increase in β-amyloid levels & age dependent memory impairment in Tg2576 mice

Tg2576 mice:
- are animal models of Alzheimer’s disease
- express the Swedish double mutation of APP (results in high amyloid-β levels)
- They suffer very little neuronal loss even with accumulation of extracellular amyloid plaques, which is a factor of Alzheimer’s disease
Data suggests that IR and IGFR-1 signaling have a neuroprotective function under conditions of neurodegeneration.
These studies link IR & IGF1R signaling to important features of neurodegeneration.

Findings show that insulin resistance:

- influences tau phosphorylation
- Influences APP metabolism
- Which might contribute to neuronal survival under neurodegenerative conditions
Conclusion

Insulin plays many roles in the brain such as:

- Food intake
- Inhibition of hepatic gluconeogenesis
- Counter-regulation to hypoglycemia
- Reproduction
- Modulation of tau phosphorylation
- Metabolism of APP and beta-amyloid clearance
- Neural survival
- Memory