Insulin Signaling Pathways
The Role of Insulin Receptor Signaling in the Brain

Roann Dela-Vega, Christina Decaro, Annalise Miner,
Claudia Sellers and Robert Walter
Intro to the Insulin Receptor (IR)

- IR is a tyrosine kinase receptor
- Two α chains and two β chains
- Connects to two tyrosine kinases
- Insulin binding changes the shape to activate them, causing autophosphorylation
  - Inactive: mobile loop (turquoise) blocks active site
  - Active: Tyrosines (green) are phosphorylated moving the loop to allow binding of ATP (Magenta)
  - Other signal proteins (light pink) bind and are phosphorylated on their tyrosine amino acids
Intro to the Insulin Receptor (IR)

- Intracellular insulin receptor substrate proteins (IRS) are phosphorolated on tyrosine residues
  - Activates binding sites for p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K), the growth factor binding protein 2 (Brb2) and the protein tyrosine phosphatase (Syp)
    - Activates the Ras-Raf-MAPK cascade allowing for gene expression
    - Activates PIP₃ leading to many other cascades
    - In CNS: inhibition of apoptosis, tau phosphorylation, regulation of gene transcription and more!
    - PIP₃ activates protein kinase B
      - Triggers translocation of glucose transporter (GLUT4)
      - Inhibits glycogen synthase kinase (disinhibition of glycogen synthase)
      - Starts glycogenesis, reducing blood-glucose
IR in the CNS and cerebral insulin sources

- IR localized in CNS in 1978 by Havrankova et al.
- IR’s are widely distributed
  - Highest concentrations in olfactory bulb, hypothalamus, cerebral cortex, cerebellum and hippocampus
- Margolis et al. found that insulin can cross the blood-brian barrier
  - Mechanism unknown
  - Amount that passes varies greatly among species
    - Less than 1% in rodents
- Fasting, obesity, aging and dexamethasone (inflammation steroid) decrease transport
- Diabetes mellitus may increase transport
Central Insulin Action and Peripheral Glucose Metabolism

The Role of Hypothalamic Insulin Receptors
The Hypothalamus

- Brain structure which connects the nervous system to the endocrine system through the pituitary gland (hormone secretion)
- Ventral part of the diencephalon
- Limbic System
- Insulin modifies peripheral glucose metabolism through **insulin receptors** located on the hypothalamus
Ventromedial Hypothalamus (VMH) - The Hypoglycemic Response

- Satiety Center
- Neurons in the VMH influenced by glucose availability and affect the sympathetic nervous system in the body
- Borg et al. (1994)
  - Lesioned VMH in rats → loss of hypoglycemia responses
  - Inhibited glucagon, epinephrine, norepinephrine
  - Mild: 50-60%
  - Severe: 75-80%
- VMH plays a crucial role in triggering the release of glucagon/catecholamines during hypoglycemia → insulin receptors

Borg et al. (1994)
Lateral Hypothalamus - Evidence for Hypothalamic Insulin Receptor Signaling Pathways

- Feeding center
- Specific neurons in the lateral hypothalamus capable of sensing changes in central glucose concentration
  - 1. Glucose-Sensitive (GS)
  - 2. Glucose-Responsive (GR) - IR present
- When brain glucose levels rise, GR neurons increase firing and GS neurons decrease firing (and vice versa)

Levin et al. (1999)
Proposed Function of Glucose-Relative Neurons - *Insulin Release Mechanism in the Brain*

- GR neurons use ATP-sensitive K⁺ channels to regulate firing, GS mechanisms less understood

**ATP-Sensitive K⁺ Channel Function**

- **High Glu Extracellular Glu Levels** → enters cell through GLUT2
- **Increased cellular metabolism, ATP Production**
- **K_{ATP} Channels Close in Response to ATP**
- **Depolarized Membrane opens Ca²⁺ channels**
- **Ca²⁺ Enters Cell and Triggers Insulin Release**

Levin et al. (1999)
To Summarize...

The hypothalamus is important in controlling compensatory responses to hypoglycemia in addition to the regulation of energy metabolism through insulin receptors.

Strong evidence to support the theory that hypothalamic insulin action influences central hypoglycemia response.
Brain IRs in the Control of Energy Homeostasis
What it does. Incredibly Oversimplified.

- Fat cells produce leptin, which lets the hypothalamus know that there is enough fat stored in the body.
- The pancreas produces insulin, which lets the body convert glucose to energy or store it for future use.
- More food = elevated blood = higher glucose levels = more insulin secretion.
Hypothalamic Arcuate Nucleus (ARC)

- Ventral medial part of hypothalamus, near median eminence
- 2 distinct neuronal populations
  - Anorexigenic neurons
    - Proopiomelanocortin (POMC)
  - Orexigenic neurons
    - Neuropeptide Y (NPY)
    - Agouti-related peptide (AgRP)
- Receive input from both peripheral and central nervous system

![Diagram](image)
The Central Melanocortin Pathway (Anorexigenic Pathway)

- POMC neurons release α- melanocortin stimulating hormone (α-MSH)
  - Agonist at the melanocortin 4 receptors (MC4R), also used to decrease appetite
- POMC neurons express serotonin 2C receptors, which, when stimulated, increases the activation of the POMC neurons, in turn releasing more α-MSH
- When IRs in the brain are activated, increase in the production of α-MSH
The Orexigenic Pathway

- Orexigenic: appetite increasing
- Main neurons: neuropeptide Y (NPY) and agouti-related peptide (AgRP)
  - Release neuropeptide NPY (agonist at the Y receptors), AgRP (inverse agonist at the MC4Rs), and the inhibitory neurotransmitter GABA
- Release of GABA mediates the orexigenic effects of NPY/AgRP
  - Ex. deletion of vesicular GABA transporter (vgat) gene in the AgRP results in a more leaner phenotype
- Inhibits the anorexigenic centers of the CNS
- Activation of the IRs in the brain decreases expression of NPY/AgRP
PI3K Pathway

- Phosphoinositide 3-kinase
- Insulin receptors (IRs) and the leptin receptor ObRb activate the PI3K pathway
  - Inhibition prevents anorexic effects of insulin and leptin
  - Connects to the activation of the hypothalamic KATP channels
    - Hyperpolarize and deactivate glucose-responsive neurons
    - Stops insulin secretion
The role of IR signaling in neurodegenerative disease
Alzheimer’s Disease

Characterized by:

Beta amyloid plaques- occur between neurons

Neurofibrillary tangles- within neurons

Associated with buildup of tau protein (which, in normal brain cells, helps to stabilize microtubules)

-neuronal loss
Normal  Mild cognitive impairment  Alzheimer’s disease
Food for thought—literally

-established clinical association between diabetes (type 2) and Alzheimer’s

-both people with Alzheimer’s and Parkinson’s show reduced expression of IR in the brain

-hard to tell if this is a cause or effect of the neurodegeneration; either way, insulin resistance may be considered a risk factor for these diseases
Tau regulated by insulin?

-(Hong et al.) showed enzyme GSK-3 can phosphorylate protein tau

-hyperphosphorylated tau is the main cause of neurofibrillary tangles (hyperphosph. reduces affinity of tau for microtubules)

-insulin reduce phosphorylation of tau by directly inhibiting activity of GSK-3
Plaques regulated by insulin?

- IR mediated signals regulate secretion of amyloid precursor protein (APP)

- Insulin resistance caused by diet-induced obesity results in increase in β-amyloid levels & age-dependent memory impairment (in mice)

  - Insulin also has protective factor on development of amyloidosis

- Insulin involved in clearing β-amyloid & inhibits breakdown of β-amyloid by competitively blocking enzyme
An interesting link...

-in Alzheimer’s patients, ACh neurons are the first to show signs of degeneration

-ACh is also the parasympathetic neurotransmitter which stimulates the pancreatic islets to release insulin into the bloodstream (& therefore lower levels of glucose)
Healthy Food Builds Great Brains!

Alzheimer’s = Type 3 Diabetes?

Does DIABETES Contribute to ALZHEIMER’s?
CNS and Insulin

The Role of IR Signaling in Learning and Memory
The role of insulin in regulating glucose metabolism for learning and memory formation is actually quite controversial. Usually this is because scientists haven’t been able to understand the effects of insulin on the CNS.

However, it has been found only recently that infusing insulin under euglycemic hyperinsulinemic conditions (meaning, healthy humans with normal blood concentrations) causes significant improvement in verbal memory and selective attention.
- It is found that most mRNA of insulin receptors are found in the cerebral cortex, which plays a key role in memory, attention, and thought.
- However, protein levels in the hippocampus are significantly higher than those at the cerebellar level.
  - In the hippocampus, information is consolidated from short-term memory to long-term memory.
Alzheimer’s disease - impairment insulin of metabolism

- Patients with Alzheimer's dementia have abnormal insulin or insulin receptor levels
- Lower cerebrospinal fluid and higher plasma insulin concentrations
In Type 2 diabetes, insulin receptor work normally, yet no signal is sent into the cell.

- Cells do not take up glucose and the resulting high blood glucose levels cause organ damage over time.
Alzheimer disease

Type 2 diabetes

- Brain inflammation
- Activation of cell stress pathways
- Neuronal insulin resistance
- Synapse deterioration
- Memory impairment

- Adipose tissue
- Pancreas
- β-cell failure

- TNFα

- Muscle
- Liver

- Peripheral inflammation
- Activation of cell stress pathways
- Peripheral insulin resistance
- Overall health decline

- Aβ42
- Microglia
- Neuron
- Macrophage
Acknowledgements

- Special thank you to Dr. Boyle, our TAs ....

And you, our wonderful Audience!!!!!

