Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: Relevance to Alzheimer’s disease

Yecenia Arellano
Raymond Liu
1. Insulin and insulin-like growth factor regulate brain development and function

IGF-1 is primarily secreted from the liver

IGF is an anabolic hormone, but not androgenic

Insulin and IGF-1 are neurotropic since they can support neuronal growth, survival and differentiation in the absence of growth factors.

IGF-I regulates oligodendrocyte development, myelination, and survival while insulin regulates food intake, glucose homeostasis, growth and metabolic activity.

Insulin is immunoreactive in the CNS distributed in the hippocampus, thalamus, hypothalamus and amygdala.

Where are their receptors located?
Insulin and IGF-I mediate their effects on cell growth, survival, homeostasis, glucose transport, and energy metabolism by signaling downstream through insulin receptor substrate molecules.

IRS 1-4 have similar structure each with an N-terminus and a C-terminus

N-terminus

Consists of three parts

One pleckstrin homology region

Two regions homologous to a phosphotyrosine binding (PTB) domain

The PTB region interacts with beta subunit of insulin and IGF-1 receptors
3. Insulin and IGF-I signaling mechanisms

Stimulatory effects of insulin and IGF-I are mediated through complex intracellular signaling pathways, from ligand binding through activation of intrinsic tyrosine kinases.

Insulin receptor substrate molecules are activated by tyrosine phosphorylation of C-terminal regions of the peptides.

Tyrosine phosphorylated (TP) IRS proteins transmit intracellular signals by interaction with SH2 domains of downstream molecules (e.g., Grb2, SHPTP-2 protein tyrosine phosphatase, and the p85 sub-unit of PI3 kinase).

TP-IRS binding to Grb2 results in stimulated mitogenesis, neuritic sprouting, and gene expression.
4. Experimental animal models of insulin receptor, IGF-I receptor, and insulin receptor substrate gene over-expression or depletion

-Roles of IGF-I and insulin signaling in CNS were tested using transgenic and knockout mice

-IGF-I and IGF-II both stimulate prenatal brain growth. While only IGF-I stimulates postnatal brain growth.

-IGF-II activates insulin receptor during fetal development. It is a bi-functional ligand meaning it can activate insulin and IGF-I signaling mechanisms (however still not as effective as insulin in growth, energy metabolism, glucose homeostasis, survival, cognition)
Transgenic mice that overexpress IGF-I have larger brains due to increased populations of neurons and oligodendrocytes and increased myelin content.

Genetic depletion of IGF-I, its receptor, or IGF-I binding proteins (inhibit actions of IGF-I) impairs brain growth.

- Reduced populations of neurons, deficiency in myelination, increased neuronal apoptosis

**Homozygous knockout of insulin receptor**

- Lethal: no insulin receptors

  - Severe diabetic ketoacidosis: body cannot use glucose as a fuel source because there is no insulin so fat is used for fuel. When fat is broken down ketone acids build up.

**Hemizygous-partial knockout of insulin receptor**

- Diabetes in 10%

**CNS depletion of gene encoding insulin receptor**

Found in AD and other neurodegenerative diseases
Gene depletion of IRS-1

- Hindered somatic growth due to IGF-1
- Small reduction in brain weight
  - Intact IGF-1 -> means other IRS molecules can transmit IGF-1 signals in CNS

IRS-2 depletion causes diabetes due to reduced beta cell mass

- Impairs neuronal proliferation
- Promotes accumulation of phosphorylated tau in the hippocampus of mice.

Insulin resistance caused by diabetes is linked to AD and other neurodegenerative disease lesions.
Diabetes Mellitus is a metabolic disorder associated with hyperglycemia

Type 1: destruction of pancreatic islet beta cell (autoimmune) and insulin deficiency

Type 2

Caused by insulin resistance in peripheral tissues

Hyperglycemia and hyperinsulinemia

Possibly caused by:

- Down regulation of insulin receptors
- Insulin receptor tyrosine kinase activity
- IRS-1 expression
- PI3K activation in skeletal muscle and adipocytes
6. Possible relationship between diabetes mellitus and clinically detectable AD

Consequences of diabetes mellitus on CNS function and disease have not been determined

Data has been weak

Data does not support diabetes and AD

Data was reinterpreted to say there is increased prevalence of insulin resistance in AD

MRI: possible association of DM /insulin resistance and degree of hippocampal and amygdalar atrophy

Individuals with DM had more hippocampal and amygdalar atrophy

Severity of insulin resistance correlated with amygdalar atrophy
7. Evidence for impaired insulin responsiveness in AD

AD showed high glucose plasma levels

Administered glucose and saw improvement in memory

Early onset AD showed improvement with glucose administration and insulin administration

early stages of AD had 45% lower levels of cerebral glucose utilization
8. Potential mediators of impaired insulin responsiveness in AD

Impaired insulin responsiveness could be attributed to three possible causes:

1. Reduced local CNS levels of insulin
2. Altered receptor binding in Alzheimer’s disease
3. Impaired signaling through insulin stimulated pathways in brains with AD

That AD-type neurodegeneration represents a neuroendocrine disorder with major abnormalities in the hippocampus and hypothalamus was examined in 1986, with a relationship implicated with somatostatin. Studies showed increased IGF-I immunoreactivity in astrocytes along with higher intensities of insulin and c-peptide immunoreactivity in pyramidal neurons of AD brains in comparison to control brains. Normally there are age associated reductions in insulin and c-peptide.

Another study showed that levels of somatostatin and IGF-I in AD and control samples were similar along with similar levels of insulin and c-peptide in AD and normal aged brains.

AD = neuroendocrine disorder also because IGF-I levels reduced in AD associated with amyloid precursor protein mutation.

Insulin or IGF-I responsiveness may be reduced by lowered binding affinity, decreased ligand availability, or impaired signaling through insulin stimulated pathways in brains with AD.
9. Insulin and IGF-I signaling and mal-signaling in the brain: Contributions to AD-pathology

Tau phosphorylation is regulated by insulin and IGF-I

- impaired insulin or IGF-1 signaling results in hyper-phosphorylation of tau
- impaired insulin signaling in CNS results in increased GSK-3β activity, which leads to tau hyper-phosphorylation

GSK-3β is a multifunctional serin/threonine kinase that regulates many intracellular signaling pathways

- Regulates tyrosine kinases, G-protein-coupled receptors and responses to Wnt pathways.

GSK-3β is a negative inhibitor in insulin signaling

- GSK-3β phosphorylates two important targets of insulin signaling, the IRS protein and glycogen synthase, and by this phosphorylation it inhibits the function.

Impaired insulin signaling can disrupt the normal physiological processing of betaAPP

- betaAPP is the main constituent of the amyloid deposits that accumulate in brains with aging or AD
Earlier findings of AD suggested that desensitization of neuronal insulin receptors caused impaired glucose utilization, mitochondrial dysfunction, reduced ATP production, and energy shortage.

Also possibly could be caused by reduced insulin levels and insulin receptor function

Found that by injecting STZ intracerebroventrically it modeled diabetes

reduced glucose and glycogen metabolism by 10–30%

learning, memory, cognitive behavior, cerebral energy balance

Modeled AD closely
11. Potential therapeutic role for insulin sensitizers in the treatment of AD

Thiazolidinediones are PPAR ligands that improve insulin sensitivity.

Modeled in rats with type 2 diabetes they found that it reduced body weight and intracellular lipid content, and increased insulin sensitivity.
12. Hypothesis

Epidemiological and clinicopathological studies designed to demonstrate the role of Type 2 diabetes in AD or vascular dementia have generated data that is largely conflicting and inconclusive.

Still uncertain of the source of insulin

Hypothesis: Taking all information into account, we propose that AD-type neurodegeneration and attendant cognitive impairment are fundamentally mediated by CNS insulin/IGF depletion and secondary loss of cells that are dependant on these growth factors.