Insulin and Neurodegenerative disease: shared and specific mechanisms

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Insulin and the Brain

**Insulin:** evidence that perturbation of role of insulin may contribute to symptoms and pathogenesis of various neurodegenerative disorders

- Alzheimer’s
- Vascular Dementia
- Parkinson’s
- Huntington’s
What’s the Brain-Body Connection?

Neurons share similarities with the Insulin producing pancreatic islet cell - possibly an evolutionary tie

Insulin function in the brain not surprising
Insulin Historical Review

Brain previously believed to be “insulin insensitive”

- Evidence now shows insulin transport via Blood-Brain-Barrier by insulin receptor mediated transport in the brain
- Insulin receptors - on synapses of astrocytes and neurons

The Importance?

Ageing of the Brain
Peripheral Insulin Concentration

Insulin in Brain and CSF

Prolonged peripheral hyperinsulinemia

Downregulates BBB Insulin-R

Insulin Transport into Brain

The Gist
Insulin and Memory

Insulin receptors in the Hippocampus (memory) and Medial Temporal cortex in rats- **insulin role in memory**

**Intranasally**: in animals to be transported to hypothalamus and hippocampus without effect on BBB or glucose receptors

**Learning**: learning may also influence insulin-receptor function
**Hippocampus**
- Memory formation

**Prefrontal areas**
- Integration of sensory information
- Inhibitory control of eating

**Fusiform gyrus**
- Object recognition (including food)
- Processing of positive emotions
- Reward

**Hypothalamus**
- Central regulator of whole-body energy homeostasis
- Homeostatic control of food intake
Insulin in Humans/Resistance

Insulin enhanced story recall

Intranasally: enhanced memory performance

Studies suggest that insulin contributes to normal memory function

Insulin not always good for memory

Insulin Resistance - as seen in type 2 diabetes - impairment on memory

animals = on operant and classical conditioning

humans = verbal and visual memory
Insulin Resistance of the Brain

In overweight individuals-

Insulin responses in the human brain reduced or completely disappeared

Brain Insulin Resistance- an association with increased body weight and impaired insulin action

resistance
Insulin and the CNS - A Proposal

Neuronal Insulin Receptor Role in AD

- Low concentration of insulin in the CNS
- Reduced receptor numbers and signalling events

Reduction of Acetylcholine (NT)

Decrease in cerebral blood flow

Chronic/increasing deficits in brain oxidative metabolism

Increase acidosis in intracellular compartments may interfere with processing of proteins favoring generation of Aβ
Insulin and the CNS

- Hypoinsulinemia
- Less insulin in CSF and ISF
  - Changes in CNS metabolism?
  - Chronic Hyperinsulinemia
  - Downregulation of BBB insulin transporters
Insulin and the CNS

Neurodegeneration $\rightarrow$ learning and memory deficits

3 ideas connecting insulin dysregulation and neurodegeneration:

1. Relationship between learning and central insulin.

2. Regionally-specific consequences of insulin concentration on glucose regulation in CNS.

3. (!!) Central Insulin and it’s driving modulatory effect on the LTP cascade.
1. Learning and Central Insulin

Learning selectively modulates insulin receptor (IR) precursors

a. IR mRNA

b. IR protein

Studies:

a. Intravenous insulin enhanced story recall (plasma → ISF) *

b. Rodents trained on spatial memory task → increased IR mRNA in DG and CA1 and crude IR protein **
2. **Insulin and Glucose Regulation**

Insulin appears to have regionally specific effects on glucose metabolism.

**Studies:**

a. Rodents given peripheral insulin → region-specific changes in glucose metabolism *

b. Found insulin-sensitive glucose transporter isoforms (GLUT 4 & 8) in hypothalamus and MTL **


Long-term Potentiation (LTP)

LTP → learning (increase in synaptic efficacy)

Modulated mostly by # of working AMPA-R

AMPA-R = ionotropic glutamate (glu) receptors

1. Glu released

2. Glu → AMPA-R

3. EPSP (strong) + GLu → Mg^{2+} dislodged from NMDA-R
   a. NMDA-R = voltage-dependent calcium channels

4. Ca^{2+} influx → strong depolarization
3. **Insulin and LTP**

A study using *Xenopus* oocytes looked at the effects of central insulin on the LTP cascade.

3. **Insulin and LTP (1)**

**METRIC:**

\[ nA = \text{nanoamps measured using voltage-clamp (Vc set to -60 mV).} \]

\[ nP_0 = \text{channel number (} n \text{) x open probability (} P_0 \text{)} \]

A. In presence of insulin, the voltage-clamped oocyte produced a much stronger change of ion conductance relative to control, implying that there are more channels through which ions are flowing.

B. In presence of nonselective tyrosine kinase inhibitor, the modulating effect of insulin is only slightly negated.

C. In presence of selective IR tyrosine kinase inhibitor, the effect of insulin is eliminated.

D. Taken together, this shows that IRs have a modulatory effect on membrane potential
3. **Insulin and LTP (1)**
Insulin and LTP (2)

Insulin induces an increase in NMDA-elicited whole-cell currents.

Open-channel blocking MK-801

MK-801 = use- and voltage-dependent NMDA-R antagonist that binds to inside of channel.

A. Insulin potentiates current relative to control.  
   ONLY TAKES ACTION ONCE NMDA-R IS ACTIVE

B. In presence of both MK-801 and insulin, oocyte produces a strong rapid depolarization, followed by an exponential return to baseline.

C. Currents from B were normalized to analyze decay tendencies.
Insulin and LTP (3)

Insulin induces an increase in NR1 surface expression.

NR1-1a = 1 of 8 potential NMDA-R subunits

Western Blotting

Method used to identify and quantify types or fragments of proteins using gel electrophoresis and immunoblotting.

B. Greater concentration of NR1 subunits on the surface of the membrane group exposed to insulin. Total cell NR1 is unchanged.

C. No difference in concentration of total NR1 subunits found throughout each oocyte. Exocytosis! [SNAP INFO HERE]

D. Insulin group showed a higher percentage of exocytosed NR1 subunits (~double).
3. **Insulin and LTP (conclusion)**

1. Insulin has a modulating effect on NMDA-elicited changes in whole-cell current.
   a. Changes in insulin concentration preferentially affect tyrosine kinase activity at the insulin receptor, but also seems to more subtly affected by downstream kinase pathways.
   b. These changes are not a consequence of an increase in the number of NMDA-Rs or the likelihood that those receptors will be open.
   c. Instead, these changes seem to occur as a result of an increase in exocytosis propensity.

2. NMDA-R are key players in the induction stage of LTP.

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**INSULIN DEFICIENCY**

**LTP ↓↓↓↓**

**Neurodegenerative Diseases**
Alzheimer’s Disease (AD)

A form of dementia characterized by problems with memory, behavior, and thinking

The most common form of dementia and risk increases with age

*General pathology:* excess beta amyloid (Aβ) and tau proteins leading to plaques and neurofibrillary tangles, respectively
AD and APOE4

AD patients show characteristics of insulin resistance and hyperinsulinemia, which can be an early onset detector.

Common in patients without the APOE4 allele.

APOE4 and AD exact connection is unclear, but can increase the risk for late-onset AD.
APOE4

Gain-of-toxic function

- Aβ aggregation
- Tangle formation
- Neuronal toxicity
- Brain atrophy

Loss-of-physiological function

- Aβ clearance
- Vascular function
- Mitochondrial function
- Neurogenesis
- Glucose metabolism
- Synaptic function

APOE4 and rapid cell aging

APOE4 impacts leukocyte telomere length (TL), which can be an indicator of age-related degenerative diseases and biological aging.

APOE4 carriers undergo premature cell aging relative to non-carriers → age-related dementia and mortality.

Study showed that hormone therapy in postmenopausal women who are APOE4 carriers showed decreased shortening of TL over 2 years (link).

Estrogen upregulates telomerase activity and may reduce oxidative stress (also why men have shorter TL).
Peripheral Insulin abnormalities

Diabetes is associated with an increased risk for dementia, and also for AD

What is the possible connection between Type 2 diabetes and AD?

Damaged blood vessels from strokes and heart disease may contribute to AD because of damage to the brain

Vascular dementia

High blood sugar causes inflammation

Target healthy cells

Changes in insulin concentration in the brain
A

β-amyloid → AD

Neuronal

↓ Brain insulin

Peripheral

Insulin resistance

Relative insulin deficiency → T2D
In vitro insulin effects on Aβ

In vitro, insulin promotes release of intracellular Aβ and modulates its concentration.

Insulin degrading enzyme
- Break down insulin
- Crucial in clearance of Aβ from the brain
- Degradation of intracellular domain of APP

Insulin degradation pathway:
1. Type 2 Diabetes
2. Insulin Resistance in the Brain
3. Hyperinsulinaemia
4. Insulin-Degrading Enzyme
5. Amyloid-Beta
6. Amyloid-beta derived diffusible ligand (ADDL)
7. β-Secretase
8. GSK-3β
In vivo insulin effects on Aβ

Examining difference of CSF concentrations of Aβ42 in humans

- Healthy adults
  - Saline
  - Insulin
  - ↑ CSF concentrations of Aβ42
  - Facilitated declarative memory

- Adults with AD
  - Insulin
  - ↑ CSF Aβ42
  - ↓ insulin-induced memory facilitation

- Older adults
  - Insulin
  - ↑ CSF Aβ42
  - ↓ insulin-induced memory facilitation
How does insulin affect tau?

Hyperphosphorylation of tau forms neurofibrillary tangles - a neuropathological hallmark of Alzheimer’s.

Insulin normally INHIBITS this phosphorylation.
How does insulin affect tau?

In AD brain, the insulin signalling pathway is disrupted so downstream target GSK-3β is no longer inhibiting phosphorylation of tau.
Insulin + other neuropathological mechanisms?

Other processes that may initiate or potentiate amyloid beta and tau abnormalities in Alzheimer’s have been linked to insulin regulation.

Inflammation

Oxidative stress

Hyperinsulinemia/Type 2 Diabetes

Systemic Inflammation

Alzheimer’s disease??

Oxidative stress
**Inflammation**

**Inflammation & Insulin?**

- Insulin plays a part in peripheral response to inflammation.
- Insulin has anti-inflammatory effects at low doses during short term inflammatory provocation.
- However with chronic hyperinsulinemia, insulin may exacerbate the inflammatory response, inducing oxidative stress.

**Diagram:**

- Hyperinsulinemia
- Systemic inflammation
Inflammation: proposed as a critical promoter of Alzheimer’s pathogenesis

Neuroinflammation is a central feature of Alzheimer’s disease (aging cells leads to inflammation and ROS)

Compounds identified in AD brain promoting inflammatory responses: Amyloid beta, C reactive protein, IL-1B, IL-6, TNF-alpha

- Neurons age, less ability to transport/dispose of proteins
- Proteinacious waste builds up in axons
- Neurons release inflammatory cytokines
- Microglia release inflammatory cytokines
- Systemic inflammation
- More AB
- Stresses neurons
- Dec microglia ability to clear waste
- Alzheimer’s
Inflammation + Alzheimer’s

- Hyperinsulinemia
  - Inc oxidative stress
  - Neurodegeneration/cell death
  - Activation of JNK -- disrupted signaling
  - AD pathogenesis
  - Systemic inflammation
    - Upregulation of inflammatory cytokines and AB
Some researchers have found genetic variations in insulin-related genes associated with a higher risk of developing Alzheimer’s!

- p85-alpha regulatory unit isoform of PI3K
- PP1 regulatory unit isoform
- Locus on chromosome 10 in region on IDE gene
- Polymorphisms in IDE gene may be affected by APOE genotype
  - C allele of IDE3 associated with high risk for Alzheimer’s (in people with APOE4)
Insulin and other growth factors

Insulin-like growth factor 1 (IGF 1)

- Hormone that stimulates cell growth and proliferation
- Growth promoting effects on cells throughout the body
- Insulin-like effects
- Helps prevent Alzheimer’s???
Insulin and other growth factors

IGF 1 & Insulin similarities

- Similar in molecular structure
- Belong to same family of tyrosine kinases
- Both receptors composed of 2 extracellular, 2 transmembrane subunits
- Ligand binding initiates similar cellular signalling events
- Bind to each other’s receptors (very low affinity)
- Receptors can heterodimerise
Importance of IGF 1

1. Insulin causes release of AB from cells

2. IGF 1 increases AB clearance from brain to periphery by upregulating entry of carrier proteins across BBB

3. Effect blocked by raising concentrations of TNF-alpha
Importance of IGF 1

With chronic high insulin concentrations (hyperinsulinemia), insulin is more likely to react with IGF 1 system = activates system = prevents Alzheimer’s?

However, chronic peripheral hyperinsulinemia may inhibit synthesis of insulin in the brain, preventing this process.

- Less insulin in brain
- Less AB released from cells into CSF
- IGF 1 cannot transport AB out of brain
- More intraneuronal accumulation of AB
- MORE risk of developing Alzheimer’s
Parkinson’s Disease

Characteristics/Causes

Neuropathological feature of PD is loss of dopaminergic neurons in substantia nigra pars compacta which then affects direct and indirect GABA inhibitory pathways to globus pallidus and substantia nigra reticulata

Genetic Factor

Environmental Factor

Physical Symptoms

Tremor

Slowed movement
Parkinson’s and Insulin

Studies Suggest:

- High prevalence of Insulin resistance in PD patients
- Higher rates of diabetes and hypertension in PD patients compared to controls
- Reduced insulin mediated glucose uptake in PD patients prior to medication for PD

Note- insulin changes not linked to lack of physical activity

Vascular factors as with AD?
Parkinson’s and Dementia

Relation of PD with Dementia- other connections?

Theory suggest all PD eventually get dementia- though rate differs among patients

Studies also found increased risk of dementia in patients with PD and Diabetes

Connection - Dementia in PD may be related to comorbid AD

Case Control Study - found hypertension (linked to insulin resistance) increased risk of PD-related Dementia
Parkinson’s and Insulin Evidence

In PD patients:

Found loss of insulin-receptor immunoreactivity and mRNA and loss of tyrosine hydroxylase mRNA in substantia nigra

Though no difference in insulin concentration in CSF- PD vs. Control—??

In Animals:

Dopaminergic drugs influence insulin production, resistance and glycaemic control

Show in animals dopamine may exert...
Parkinson’s Summary

Clinical studies:

Suggest impaired glucose tolerance and insulin dysregulation in PD

Pattern of insulin dysregulation not fully established

Animal and in vitro studies:

Show role for insulin in regulation of brain dopaminergic activity
Huntington’s Disease

Neurodegenerative movement disorder (like Parkinson’s)

Genetic disorder, runs in families

All people have 2 copies of Huntingtin gene which contains sequence of 3 DNA bases (CAG) repeated multiple times.

CAG is genetic code for amino acid glutamine → series of them results in chain of glutamine.

Number of repeating glutamines determines if you will have disease

<table>
<thead>
<tr>
<th>Repeat count</th>
<th>Classification</th>
<th>Disease status</th>
<th>Risk to offspring</th>
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<tbody>
<tr>
<td>&lt;25</td>
<td>Normal</td>
<td>Will not be affected</td>
<td>None</td>
</tr>
<tr>
<td>27–35</td>
<td>Intermediate</td>
<td>Will not be affected</td>
<td>Elevated but &lt;=50%</td>
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<tr>
<td>36–39</td>
<td>Reduced Penetration</td>
<td>May or may not be affected</td>
<td>50%</td>
</tr>
<tr>
<td>40+</td>
<td>Full Penetration</td>
<td>Will be affected</td>
<td>50%</td>
</tr>
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</table>
Huntington’s Disease

Characteristics of disease

Affects basal ganglia, particularly striatum and substantia nigra, as well as hippocampus, cerebellum, thalamus, hypothalamus

Affects muscle coordination, mental decline and behavior

Unlike Parkinson’s, earlier onset (can be any age, but typically 35-44 years)

Life expectancy ~20 years after symptoms begin
Huntington’s disease + Insulin

People with Huntington’s have higher prevalence of diabetes and insulin abnormalities

In study w/ 14 HD patients, 50% had abnormal glucose tolerance - hyperglycemia and hyperinsulinemia

In study w/ 25 HD patients, 1/3 had glucose intolerance compared to 3% control group

Why??
Huntington’s disease + insulin

Connection between dopamine and insulin

Dopaminergic neurons & insulin receptors densely represented in Substantia Nigra

Clear role for insulin in the regulation of dopaminergic activity

Insulin and DA may exert reciprocal regulation

Insulin dysregulation could lead to loss of dopaminergic neurons in Basal Ganglia

Similar to Parkinson’s
Huntington’s & impaired insulin gene expression?

Transgenic HD mouse model: express portion of human Huntingtin gene with 140 CAG repeats (40+ repeats will develop HD)

Impaired glucose tolerance @ 8 weeks, diabetes @ 12 weeks

Onset of glucoregulatory disturbances similar to onset of HD symptoms

Low insulin gene expression in pancreas

May be partly related to polyglutamine expansion characteristic of HD (CAG repeating) because similar diseases show this as well
Other polyglutamine expansion disorders

Freidrich’s ataxia & myotonic dystrophy

Also associated with insulin resistance and poor glucose tolerance

DRPLA (dentatorubral-pallidoluysian atrophy)

Closely related to HD: CAG expansion in polyglutamine region of *atrophin-1* gene

The product of this gene interacts with the insulin-receptor tyrosine-kinase substrate protein (IRSp53).

Disrupted insulin signaling

Huntington's disease

Receptors in brain affected by DRPLA and HD
Huntington’s and insulin: Summary

- CAG expansion
- Reduced insulin gene expression
- Modulation of IRSp53 protein activity
- Disrupted insulin signaling/insulin resistance
- Huntington’s disease??
Vascular Dementia

A general term describing a deficit in cognitive function caused by a restriction of blood oxygen flow to the brain.

Hypertension and Hypercholesterolemia have long been known as critical risk factors.

What about insulin? LEARN MORE HERE.
Vascular Dementia

Hyperinsulinemia is a predictor of impaired cognition

A study of 4 groups (each without diabetes):

- Normotensive with hyperinsulinemia
- Normotensive
- Hypertensive with hyperinsulinemia
- Hypertensive

Found that only the hyperinsulinaemic-hypertensive group showed significant cognitive deficit.

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Table 3. Neuropsychological Test Scores in Normotensive, All Hypertensive, Normoinsulinemic Hypertensive, and Hyperinsulinemic Hypertensive Subjects

<table>
<thead>
<tr>
<th>Cognitive Subsection</th>
<th>Normotensives (n=366)</th>
<th>Hypertensives (n=378)</th>
<th>Hypertensives, Hyperinsulinemia</th>
<th>ANCOVA P Value*</th>
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<tbody>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Orientation</td>
<td>9.8±0.0</td>
<td>9.8±0.0</td>
<td>9.8±0.0</td>
<td>9.9±0.1</td>
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<tr>
<td>Registration</td>
<td>3.0±0.0</td>
<td>3.0±0.0</td>
<td>3.0±0.0</td>
<td>3.0±0.0</td>
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<tr>
<td>Attention and calculation</td>
<td>3.9±0.1</td>
<td>3.6±0.11</td>
<td>3.7±0.11</td>
<td>3.4±0.21</td>
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<tr>
<td>Recall</td>
<td>1.7±0.1</td>
<td>1.6±0.1</td>
<td>1.7±0.1</td>
<td>1.5±0.1</td>
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<tr>
<td>Copying</td>
<td>0.87±0.02</td>
<td>0.90±0.02</td>
<td>0.92±0.02</td>
<td>0.79±0.05</td>
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<td>Language</td>
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<td>7.3±0.0</td>
<td>7.4±0.1</td>
<td>7.1±0.1</td>
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<tr>
<td>Total</td>
<td>26.6±0.1</td>
<td>26.3±0.1</td>
<td>26.4±0.1</td>
<td>25.5±0.4†</td>
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<tr>
<td>Visual memory and construction</td>
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<tr>
<td>HVR, copying</td>
<td>15.5±0.1</td>
<td>15.4±0.1</td>
<td>15.4±0.1</td>
<td>15.0±0.4</td>
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<tr>
<td>HVR, immediate</td>
<td>9.1±0.2</td>
<td>6.6±0.2</td>
<td>8.6±0.2</td>
<td>8.3±0.5</td>
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<tr>
<td>HVR, delayed</td>
<td>6.1±0.2</td>
<td>5.6±0.2</td>
<td>5.8±0.2</td>
<td>5.5±0.6</td>
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<tr>
<td>Episodic verbal memory</td>
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<tr>
<td>BSR, short-term</td>
<td>8.4±0.3</td>
<td>9.8±0.9</td>
<td>9.8±1.0</td>
<td>9.8±0.7</td>
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<tr>
<td>BSR, long-term</td>
<td>24.2±0.6</td>
<td>22.8±0.9</td>
<td>23.5±1.1</td>
<td>18.9±1.7†</td>
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<tr>
<td>Semantic memory</td>
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<tr>
<td>VFT, number of P words</td>
<td>11.5±0.3</td>
<td>10.6±0.3†</td>
<td>10.8±0.3</td>
<td>9.2±0.6†</td>
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<tr>
<td>S words</td>
<td>11.4±0.3</td>
<td>11.0±0.3</td>
<td>11.2±0.3</td>
<td>9.6±0.7†</td>
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<td>A words</td>
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<td>VFT, animal category</td>
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<td>Problem solving and abstraction</td>
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<td>TMT, seconds</td>
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<tr>
<td>Part A</td>
<td>69.7±1.7</td>
<td>74.4±1.6†</td>
<td>72.3±1.7</td>
<td>65.4±4.6†</td>
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<tr>
<td>Part B</td>
<td>187.5±5.1</td>
<td>201.5±5.3</td>
<td>197.8±5.6</td>
<td>228.1±14.7†</td>
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<tr>
<td>Part C</td>
<td>169.0±4.2</td>
<td>187.5±4.4†</td>
<td>184.0±4.6†</td>
<td>208.7±11.2†</td>
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</tbody>
</table>

ANOVA indicates analysis of covariance; MMSE, Mini-Mental State Examination; HVR, Russell’s Adaptation of the Visual Reproduction Test; BSR, Buschke Selective Reminding Test; VFT, Verbal Fluency Test; and TMT, Trail Making Test. Values are mean±SEM.

*Analysis of covariance was performed over the normotensive, normoinsulinemic hypertensive, and hyperinsulinemic hypertensive groups (covariates: age, sex, education, and fasting blood glucose).

†P<.001, ‡P<.01, §P<.05, compared with normotensive group, Student’s t test.
Vascular Dementia

Honolulu-Asia Aging Program

Reported a high risk of vascular dementia in participants with diabetes, hyperglycemia, or hypertension.

Adjusted for covariates including:

- BMI
- Lipid concentrations
- Education
Shared/Specific Mechanisms

- Decreased cerebral glucose metabolism
- Increased inflammation
- Increased oxidative stress
- Increased advanced glycation end products
- Increased vascular dysfunction
- Decreased neurogenesis

Panel 2. Insulin-related mechanisms specific to individual neurodegenerative disorders

**AD**
Insulin promotes intraneuronal Aβ release and increases carrier protein entry into brain for Aβ transport.

**High peripheral insulin concentrations:**
inhibit peripheral Aβ degradation; decrease number of insulin receptors in the BBB; decrease concentrations of insulin in the brain; decrease transport of carrier proteins.

**Low brain insulin concentrations:**
decrease release of intraneuronal Aβ; decrease amounts of IDE; increase tau hyperphosphorylation.

**Possible genetic polymorphisms include:**
IDE haplotype variants; variants in the PI3K and PP1 regulatory subunits.

**Vascular dementia**
No specific mechanisms proposed.

**PD**
Insulin increases dopamine transporter mRNA in substantia nigra and regulates brain dopamine concentrations.

**HD**
Possible insulin-related abnormalities include a characteristic polyglutamine expansion, which may be associated with reduced insulin gene expression and modulation of IRSp53 protein activity.

BBB = blood-brain barrier; IDE = insulin degrading enzyme; IRS = insulin receptor substrate; PI3K = phosphatidylinositol 3 kinase; PP1 = protein phosphatase 1