Insulin and Neurodegenerative Diseases: Shared and Specific Mechanisms

Cog 163
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Overview

A. Insulin and the Brain
B. Alzheimer’s Disease and Insulin
C. Other neurodegenerative disease: vascular dementia, Parkinson’s Disease, Huntington’s Disease
D. Summary
Insulin and the Brain

a. Insulin function dysregulation could have contributing factors (pathophysiology & clinical symptoms) to neurodegenerative diseases via either disease-specific or general mechanisms.

b. There has been recent review and attention to the role insulin plays with the brain in regards to aging alongside the function of insulin dysregulation in regards to neurodegenerative diseases in the later ages of life.
Insulin in the Brain: Insulin Receptors

- IR transports insulin through the blood brain barrier in order to CNS
  - peripheral infusion of insulin leads to an increase in insulin levels in cerebrospinal fluid, suggesting that insulin can indeed cross the blood brain barrier
IRs are most highly concentrated in the

- olfactory bulb
- hypothalamus
- cerebral cortex
- cerebellum
- hippocampus
● Insulin receptors in the hippocampus and medial temporal cortex links to the idea that insulin influences memory
● acute intracerebroventricular insulin enhanced memory on a passive avoidance task
● when administered nasally, insulin showed little effect on blood insulin levels or glucose concentrations—hippocampus & hypothalamus
● learning ←influence→ insulin receptor
Learning and IR Expression: Rats

- trained on spatial memory tasks
  - more IR messenger RNA in the dentate gyrus and hippocampal CA 1
    - dentate gyrus- in hippocampus, thought to contribute to the formation of new episodic memories
    - hippocampal CA1-first region in hippocampus that yields sig output pathway toward entorhinal cortex level V and the subiculum
  - more IR protein in the hippocampal synaptic membrane function

→ learning co-occurs with changes in insulin signalling molecules in hippocampus

- Hyperinsulinemia and insulin resistance exerts a negative influence on memory
  - T2DM → classical conditioning and learning

- overlapping distribution of insulin, IR and insulin sensitive glucose transporters which is consistent with possibility of insulin stimulated glucose uptake in specific brain regions
“Sugar kills rats.”

“But it can’t be that bad for humans.”
SO DOES BRAIN DERIVED INSULIN MAKE SUBSTANTIVE FUNCTIONAL CONTRIBUTION IN ADULT HUMAN BEINGS?
Studies in Humans

- IR in the hippocampus is consistent with idea that insulin influences memory
  - healthy insulin amount = good memory
  - chronic hyperinsulinaemia, insulin resistance, reduced insulin affectiveness = bad memory
- Intravenous insulin enhanced story recall
- Nasal administration of insulin is associated with increased memory performance
- Hyperinsulinemia and insulin resistance has negative influence on memory
  - T2DM → visual & verbal memory decrements
Continued: Studies on Humans

***insulin has regionally specific effects on glucose metabolism***

- insulin effects PET scans show an increase in cerebral glucose metabolism at low insulin concentration that was most apparent in the cortex
  - maybe insulin effects on glucose metabolism is likely to be the distribution of various glucose transporters isoforms
- Insulin may modulate long term potentiation
  - NMDA receptor activation → increasing neuronal CA 2+ influx activated of alpha-calcium-calmodulin-dependent-kinase II and other CA 2+ dependent enzymes → in stronger synaptic associations between neurons
- Insulin also modulates CNS concentrations of neurotransmitters
- insulin also seems to have a role in age-related process
SO DOES BRAIN DERIVED INSULIN MAKE SUBSTANTIVE FUNCTIONAL CONTRIBUTION IN ADULT HUMAN BEINGS?
YES!!!!
Alzheimer’s Disease - US statistics 2014 (Alzheimer’s Association - Indiana)
Alzheimer’s Disease (AD)

- **Simple definition:** A progressive neurodegenerative disease that impairs an individual's memory & other cognitive functions (speech, reasoning, conscious thought, etc.).
- No matter the level of exercise or health in diet, anyone is susceptible to AD
  - Though true that people poor exercise/diet and impaired glucose tolerance carry a high amount of insulin to treat the lacking glucose.
- It’s found that Hyperinsulinemia and/or both insulin resistance can be causing factors for AD patients.
- Hyperinsulinemia: excess levels of insulin relative to glucose- seen often in the beginnings of those with T2D
AD: Peripheral Insulin Abnormalities

Syndromes related to AD

- Hyperinsulinemia, insulin resistance (seen in Type-2 Diabetes)
- Dementia, Diabetes
- Though with these are common patterns, they’re all challenged with unclear epidemiological work done.

Type-2 Diabetes mellitus (T2D)

- Diagnosis of T2D is similar to that of AD,
  - Impaired glucose intolerance- markers of: hyperinsulinemia and insulin resistance
  - Perhaps analogous to dementia- w/ similar syndromes but more causes.
- Study: Japanese-American Men
  - Those diagnosed with T2D were seen to have a high risk of AD.
Further Population Studies

- Association of diabetes & insulin resistance showed an increased risk of AD & vascular dementia.
- Diabetes & APOE∈4 together also increases risk of AD
- Study: Healthy people without either dementia/diabetes but high insulin levels were considered for AD and related to declined memory task scores

Memory

- AD patients lacking the APOE∈4 allele require more insulin to facilitate memory than those w/ AD & APOE∈4 allele.
Insulin, T2D, AD

- Insulin resistance and reduced insulin levels in the brain from T2D = Aβ build up
- Which could be a leading cause for AD
Hoyer

- Low concentrations of insulin in the CNS + reduced receptors in AD = eventual lead to reduced ACH & reduced blood flow
  - this can lead to further brain impairment and brain oxidative metabolism
- Correspondence between low insulin concentration in the brain and low cerebrospinal fluid (CSF) concentrations within AD patients
AD: Insulin, Amyloid Beta (Aβ) & Neuropathology

Aβ

- Peptides of amino acids found in AD. Primary component of amyloid plaques seen in AD patients brains

In Vitro:

- Insulin changes the concentration of Aβ-this change is a neuropathological staple of AD
- Insulin promotes release of intracellular Aβ
- Insulin promotes the release of Aβ, high concentration of insulin in the brain can increase the amount of Aβ.
In vivo in humans:

- In older adults- Insulin infusion = increase in CSF concentration of Aβ.
- Aβ isn’t cleared quickly/just slow for this age group, thus the sustainability of Aβ affects the ability to hold memories.
  - High Aβ concentration = may impair memory
- Potential reasoning to low insulin concentrations in the brain of AD patients, can potentially be seen thru hyperinsulinemia
  - Affecting insulin on Aβ concentrations.
- Hyperinsulinemia could be sparking a signal that stops the synthesis of insulin in the brain. (= hi insulin = potential hi Aβ concentration = harder to clear = may impair memory)
- Inversely: low insulin in brain = reduced Aβ conc. to be cleared.
AD: Insulin & Other neuropathological mechanisms

- Neuropathologies of the CNS (such that of AD) is a result of faulty tau proteins.
- Insulin prevents the phosphorylation of tau making neurofibrillary tangles | a staple seen in AD
AD: Insulin & Other neuropathological mechanisms

Inflammation plays a key factor in AD

- Also commonly seen in peripheral response to insulin
- Insulin can have low dose of anti inflammation
- During chronic hyperinsulinemia/inflammation, insulin can worsen the inflammation and increase oxidative stress.
- Oxidative stress: inability to detoxify or repair any damage done to proteins.
2 main aspects of insulin signalling pathways:

- phosphatidylinositol-3kinase & protein phosphate 1

First association:

- There is a higher risk in women for AD if they do not carry the APOE $\epsilon_4$ allele in association to phosphatidylinositol-3kinase.

Second association:

- Further conclusion is awaited by studies
- Sex nor APOE was not a factor in affecting the phosphate 1 regulatory unit and AD.

Insulin sensitivity & expression of insulin degrading enzyme found in the hippocampus differ depending on the APOE genotype of the person with AD

- polymorphism in the insulin degrading enzyme can be affected by the APOE genotype.
AD: Insulin-related genes [APOE\(\varepsilon_4\)]
AD: Insulin & Other Growth Factors

IGF 1: Insulin like growth factor

Seen in animal studies:

- IGF 1 increased Aβ clearance from brain to periphery
  - upregulating carrier proteins across the BBB, which could be inhibited by TNFα (-inhibiting process)

It’s unknown and inconclusive which receptor insulin or IGF 1 is effective with Aβ clearance
Aβ clearance by IGF. Can be prevented by TNFa
Dementia Risk Factors

- Blood Pressure
- Mood
- Physical Exercise
- Diabetes
- Heart Disease
- Smoking
- Drinking
- Diet
- Cognitive Ability
- Chronic Kidney Disease
Dementia Risk Factors

- Insulin resistance and hyperinsulinemia are risk factors → endothelial dysfunction.
- Essential hypertension coupled with insulin resistance:
  - A cross-sectional study: hyperinsulinaemic-hypertensive group had a much lower cognitive performance.
- Epidemiological studies: higher risk of vascular dementia for T2D mellitus or hypertension patients:
  - Honolulu-Asia Aging Program:
    - Hypertension, hyperglycaemia, and diabetes results in high risk of dementia.
  - 1789 Latin American study:
    - T2D mellitus and stroke increased risk of dementia by a factor of 8.
    - Diabetes was more correlated with vascular dementia than with AD patients.
  - Carantoni and Co-workers:
    - Patients with vascular dementia had high fasting plasma concentrations of insulin & glucose.
    - Note: for AD patients, it was similar to patients that were healthy.
Dementia and AD

- hyperinsulinemia and diabetes are both related independently to AD and vascular dementia
  - actually factors from vascular dementia might contribute to AD
- pattern of vascular injury shared by AD and vascular dementia link to insulin resistance, inflammation & abnormalities of lipid metabolism
  - possibility of shared pathological substrate underlying the overlap between AD and vascular dementia
Parkinson’s Disease

● affects nerve cells in the brain that produce dopamine

● primary neuropathological feature is the loss of dopaminergic neurons in substantia nigra pars compacta → direct and indirect GABA inhibitory pathways to the internal globus pallidus and the substantia nigra reticulata
  
  ● loss of IR immunoreactivity and mRNA and loss of tyrosine hydroxylase (rate of limiting enzyme in DA synthesis) mRNA in the substantia nigra have been also shown in neuropathological studies of patients with PD
  
  ● no abnormal CNS marking in vivo
Parkinson’s and Insulin

- Sandyk
  - high prevalence of insulin resistance in patients with PD, nearly 50-80%

- national survey data from 24,831 (adults filing for Medicare)
  - patients who had PD had much higher rates of diabetes & hypertension

- certain drugs used to treat PD → hyperglycemia and hyperinsulinemia (levodopa) while other drugs increase insulin sensitivity (bromocriptine)
  - this makes it difficult to interpret data in which insulin function is treated in patients with PD
  - STILL the defect in insulin has shown to precede the medication

- Van Woert and Mueller
  - show reduced insulin mediated glucose uptake in newly diagnosed adults with PD

- Boyd and Colleagues
  - inhibition of early insulin secretion and long term hyperinsulinemia and hyperglycaemia after glucose loading in similar sample
Vascular Parkinson’s

- atypical parkinsonism where parkinson symptoms (picture) are produced by small strokes (not loss of nerve cells)
- patients whose parkinsonism is accompanied by subcortical white matter ischaemic lesions commonly in conjunction with basal ganglia or brainstem lacunae
  - histopathological studies in these patients suggest preservation of dopamine producing cells in the substantia nigra
  - in vitro 3-6% of patients with PD have vascular PD
Parkinson’s and Dementia

- Scwabb (examined data from 800 patients with PD)
  - diabetes accelerated progression of both motor and cognitive symptoms
- Andy and Awerbuch
  - 12 patients (5 with diabetes) with PD examined for dementia with bedside mini mental exam
    - ONLY 5 patients that had diabetes had a degree of dementia
    - diabetes and PD may be related to comorbid AD
- case control study: hypertension had an increased risk of PD-related dementia (note link to insulin resistance)
- Levi and Workers
  - self reported diabetes and hypertensions were associated with the development of dementia assessed through the neuropsychological testing in a registry derived group of 180 non dementia patients with PD
  - found no risk factor and development of dementia
- no study has determined whether insulin dysregulation characterises patients with Lewy body dementia
  - LBD affect 1.4 million individuals, refers to both dementia and PD dementia
- theory: all patients with PD eventually become demented but each patient has a different rate
  - association between PD and dementia not examined well and have inconsistent results
  - inc risk of dementia in patients with diabetes and PD
Animals Study: Dopamine and PD

- studies in animals
  - dopaminergic drugs influence insulin production, insulin resistance and glycaemic control
    - hamsters: insulin sensitivity was improved by intracerebroventricular delivery of bromocriptine → dopamine activity in the CNS contributes to peripheral insulin mediated glucose metabolism
  - insulin and dopamine may exert reciprocal regulation
    - intracerebroventricular delivery of insulin increased amounts of dopamine transporter mRNA and activity in the substantia nigra and in D8 cells
    - hypoinsulinaemia by streptozotocin
      - did just the opposite -- decreased dopamine transporter mRNA and tyrosine hydroxylase mRNA in substantia nigra
      - known to decrease basal dopamine and amphetamine induced dopamine overflow in mesolimbic cortex
What does this mean?

a. INCONCLUSIVE RESULTS -- but results from animals and in vitro studies have shown clear role of insulin in the regulations of dopaminergic activity
   i. loss of insulin receptor immunoreactivity and mRNA tyrosine hydroxylase mRNA in the substantia nigra have also been found in neuropathological studies of patients with PD
Huntington’s Disease and Insulin

- affects muscle coordination and leads to mental decline and behavioral symptoms
- HD patients have a higher prevalence of diabetes and insulin abnormalities but few recent well controlled studies have been made
  - Podolsky and Leopold
    - found that 50% of the patients had abnormal glucose tolerance due to hyperglycaemia and hyperinsulinemia
  - Farrer
    - 10.5% had diabetes that exceeded age matched population prevalence
  - Schobotz and colleagues
    - ⅓ of patients had impaired glucose tolerance
Continued: HD and Insulin

- insulin’s role relevant to HD
  - dopamine regulation
  - animal models: impaired glucose metabolism in HD may be caused by impaired insulin gene expression
  - HD mouse model
    - expresses a portion of the human HD gene along with 140 CAG repeats
    - develop impaired glucose tolerance at 8 weeks of age and frank diabetes by 12 weeks
    - progression of glucoregulatory disturbance is similar to the onset of HD symptoms
    - low insulin gene expression in pancreas -- unclear why but may be related to polyglutamine expansion characteristic of HD
    - high numbers of intranuclear inclusions and low concentrations of insulin and coactivators p300 and PDX-1
Disorders related to HD: An Insight

a. polyglutamine expansion disorders are consistent with insulin resistance and poor glucose tolerance -- association?

b. dentatorubral-pallidoluysian atrophy (DRPLA)
   i. caused by CAG expansion in the DRPLA gene, the product of which, atrophin 1, interacts with the insulin receptor tyrosine kinase substrate protein IRSp53
   ii. IRSp53 has been recently identified as a member of the insulin receptor substrate family with a very high selective distribution in brain tissues (@ frontal cortex, caudate nucleus, nucleus accumbens, hippocampus)
   iii. where IRSp53 is located is closely related to where both DRPLA and PD occur and is a hint as to where disrupted signalling could affect a selective neuronal circuit
Conclusions

● does insulin dysregulation jump-starts the general consequences of disrupted energy metabolism, inflammation, oxidative stress, impaired injury response and reduced neurogenesis on a pre-existing disease specific neurobiological template?
● do disease specific defects in insulin metabolism occur that make unique contributions to disorders?
● both of these question’s answers are UNKNOWN
● meaning there’s still room for exploration on both disease specific and mechanisms of insulin dysregulation.
Improvement of insulin sensitivity and reduction of peripheral hyperinsulinemia may have beneficial effects because the body is comprised of a system and dysregulating one area can negatively alter the rest.
Type 2 Diabetes: A Compromised Brain

- Vascular damage
  - Neurovascular dysfunction
  - Microglial activation & reactive gliosis
  - Demyelination & hypermetabolism

- Increased production of Aβ
  - Aβ aggregation
  - Neuronal dysfunction
  - White matter damage and atrophy

- Metabolic disruption
  - Hyperglycemia
  - Insulin resistance
  - Altered insulin signalling
  - AGE production
  - HPA axis dysfunction

- Oxidative stress

- Inflammation

- Tau pathology

- Cognitive impairment, dementia risk including Alzheimer's disease

Adapted from: Meusel et al., J Curr Clin Care 2012; 2(1):6-16.
Be critical of your habits for optimal health!