Inflammation and Insulin/IGF-1 Resistance

The possible link between obesity and neurodegeneration

By: The Neurodegenerates
1. Why/How does our body become inflamed?
   a. Types of Inflammation
   b. What problems does this cause?
2. Mechanisms of inflammation in adipose tissue
   a. Stress on cytokines & direct link to degeneration
3. Mechanisms of insulin/IGF-1 in obesity
   a. Stress on resistance & direct link to degeneration
4. Epidemiological evidence linking obesity and neurodegenerative diseases
   a. Parkinsons
   b. Alzheimer's
   c. Huntington
5. Pathophysiological pathways of neurodegenerative diseases
   a. Parkinsons
   b. Alzheimer's
   c. Huntington
6. Conclusion
A couple of questions to consider…

Is there a relationship between obesity and neurodegeneration?

Should Alzheimer’s be considered Type 3 Diabetes? And if so, why?

How does this neurodegeneration impact society?
Inflammatory Response

3 main functions:

● Wall off infection
● Call cells of the immune system to the area of injury
● Initiate the immune system response
Peripheral Inflammation

- Harmful stimuli signals vasodilation, which increases blood volume
- Leukocytes go from blood into damaged tissue
- Neutrophils phagocytize pathogens via macrophages, like microglia
- This causes the release of inflammatory mediators:
  - cytokines
  - chemokines
  - TNF-\(\alpha\)
Chronic Inflammation

- Persistence of inflammation after absence of stimuli
- Healthy neighboring cells suffer damage
- Chronic inflammation proliferates diseases
- **Obesity is regarded as a chronic pro-inflammatory disease state**
Neuroinflammation

- Induced by **over-activated glial cells**
  - Astrocytes maintain the blood brain barrier, provide physical support & nourishment to neurons, and modulate synaptic function
  - Microglia are considered **Macrophages**, meaning they are immune cells that phagocytize pathogens
- Microglia produce reactive oxygen & nitrogen which initiate **phagocytosis**
  - **upregulates** ANTI-proliferative & proinflammatory mediators
    - Ultimately results in neuronal death
Glial Cell Activation in Obesity

- Obese pups increased concentration of IL-1β in hippocampus
  - exacerbated TNF-α, IL-6, IFN-γ, IL-1β in response to high sugar Western diet (Bilbo and Tsang, 2010).
  - DIO selectively increases IL-6 in cerebral amyloid angiopathy mice, while decreasing levels of TNF-α in non disease control mice.
  - Diet induced obesity shows higher levels of CNS macrophage infiltration/activation adipose tissue from ceramide & saturated fatty acid palmitate.
Factors linking obesity with neurodegeneration:

1. Proinflammatory Cytokines

2. Insulin/IGF-1 Resistance
1. Proinflammatory Cytokines

What are proinflammatory cytokines and what do they do?

- Cytokines and Chemokines: molecular mediators of inflammation

What are the types of cytokines?

- Types of Cytokines: tumor necrosis factor alpha (TNF-α), interleukin (IL)-6 and (IL)-1B.
2. Insulin/IGF-1 Resistance
Review of Insulin and IR

What is insulin?

What is insulin resistance?
Role of IGF-1

What is IGF-1?

Why is IGF-1 important?
Role of IGF-1 Resistance

How does IGF-1 resistance happen?
Role of Insulin and IGF-1 in inflammation

What does insulin and IGF-1 have to do with inflammation?
Pathophysiological Mechanisms
What are the effects of Insulin and IGF-1 Resistance in obesity and neurodegeneration?

1. Excess molecular mediators cross the BBB and trigger neuroinflammation which aggravates the possibility of neurodegeneration.
2. Irregularities of insulin and IGF-1 hormone levels contribute to neurodegenerative diseases like Parkinson’s, Alzheimer’s and Huntington's.
Parkinson's Disease
Introduction to Parkinson’s

What is it? What impact does it have on society?

Definition:
- A neurodegenerative disease, seen in middle age to elderly people, that causes muscle stiffness, slow and imprecise movement, and often tremors.

Stats:
- Nearly one million will be living with Parkinson's disease (PD) in the U.S. by 2020.
- Approximately 60,000 Americans are diagnosed with PD each year

Economic impact:
- Nearly $25 billion per year in the United States alone.
Structure to Investigating PD:

1. OBESITY + INSULIN/IGF-1 RESISTANCE
2. BRAIN STRUCTURES
3. PATHWAYS
The Brain Structures Affected:

1. Cerebellum
2. Thalamus
3. Hypothalamus
4. SNpc

And more....

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5052937/?report=printable
1. Cerebellum

Key Function:

- A hindbrain structure that is involved primarily with guided and timed movements.

Implications with PD:

- Has reciprocal connections with the basal ganglia. Changes were observed that were related to PD.
- These changes may be a result of the degeneration of dopaminergic (DA) neurons as the basal ganglia projects these neurons into the cerebellum.
2. Thalamus and Hypothalamus

Key Function:

- Thalamus: A forebrain structure that is a principal stop along sensory, motor and arousal pathways. It projects into the cortex.
- Hypothalamus: Controls the 4 F’s, maintains homeostasis.

Implications with PD:

- Volume of the Thalamus decreases
- Changes of white matter of the thalamus leads to depression in most PD patients.
- The hypothalamus is involved with sleep, so with the loss of grey matter (that melatonin levels are associated with), sleep disorders may develop.
3. Substantia Nigra pars compacta (SNpc) - Within the basal ganglia

Key Function:

- Plays a key role in both movement and reward. The name is latin for ‘black substance’ as it appears darker compared to the surrounding area because of the neuromelanin within the dopaminergic neurons.
- It is the main focus within this presentation, as the pathology leading to PD impacts this area the most. More to come in later slides.

Implications with PD:

- Reduction in neuromelanin, neuron death, and Lewy Bodies are observed within the SNpc.
- In the basal ganglia, PD patients may undergo atrophy.
In PD patients, the basal ganglia undergoes atrophy.
   A) True or B) False

Development of sleep disorders associated with PD may be due to the loss of grey matter in the hypothalamus.
   A) True or B) False
Key Players in the Pathways:

1. \(\alpha\)-synuclein - Abundant in the brain while smaller amounts are found in the heart, muscles, and other tissues.
2. Lewy Bodies - Abnormal deposits of \(\alpha\)-synuclein in the brain.
3. Microglia - Primary immune cells in the CNS
4. NADPH - Coenzyme used in reduction reactions, seen in anabolic pathways of organisms.
5. ROS - Formed as a natural byproduct of the normal metabolism of oxygen and have important roles in cell signaling and homeostasis.
6. T Lymphocytes - Essential type of leukocyte (like a white blood cell) in the immune system.
7. \(K_{\text{atp}}\)
8. INSR- Insulin Receptor
Epidemiological Evidence:

Obesity contributing to Parkinson’s

Linking Obesity & Parkinson’s

- In the SNpc

α-Synuclein [NADPH + Ros] → Microglia↑

Microglia summon T-Lymphocytes

T-Lymphocytes may become toxic
Pathophysiological Evidence:
Insulin/IGF-1 receptors contributing to Parkinson’s

Obesity, Insulin/IGF-1 Resistance

- SNpc Region -

*Insulin Receptors ↓

Could contribute

Contributes to PD

Lewy Bodies ↑

Reducing beneficial growth & proliferation
Pathophysiologiical Evidence:

- Insulin Receptors ↓
- Absence of Insulin causes depolarization of Mitochondria
- Generates excess ROS
- Contributes to PD

SNpc Region SPECIFIC

- Insulin ↓ → Glucose uptake ↓
- Impacts ratio of ATP / ADP
- $K_{ATP}$
Parkinson's Pathology Pathway:

1. **Obesity**
   - EFA
   - IL-6
   - IL-1β
   - TNFα

2. **Blood-brain barrier**
   - Insulin/IGF-1 signaling

3. **CNS**
   - DA synthesis
   - DA clearing
   - α-Synuclein aggregation
   - Lewy Bodies

4. **Promotion of Parkinson's Disease Pathology**
   - JNK, IKKβ, PKC
   - Mitochondrial Dysfunction
   - Neuroinflammation
   - ROS

5. **Growth factors of Insulin**
   - SNpc
   - InsR in SNpc

6. **Mitochondrial Dysfunction**
   - IL-6
   - IL-1β
   - TNFα
Alzheimer's Disease (AD)
Outline to Alzheimer’s Disease:

1. Overview of AD

2. Brain structures affected in AD

3. Epidemiological Evidence Linking Obesity and Insulin/IGF-1 Resistance in AD

4. AD as a Type 3 Diabetes

5. Molecular Key Players in AD

6. Obesity induced insulin/IGF-1 resistance contribution to Alzheimer’s Disease Pathology
Overview of AD:

- Neurodegenerative disease
- Most common form of Dementia
- Progressive decline of memory, cognitive functions, and changes in behavior and personality
- AD affects close to 6 million Americans
- 6th leading cause of death among adults.
- With aging, the brain shrinks to some degree, but does not lose large number of neurons like AD.
The Brain Structures Affected in AD

Cerebral Cortex:
1. Frontal Lobe
2. Temporal Lobe
   a. entorhinal cortex
   b. hippocampus.
3. Parietal Lobe

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Epidemiological Evidence Linking Obesity and Insulin/IGF-1 Resistance in AD

- 2 hallmark characteristics of AD at the cellular level:
  - 1) amyloid beta (AB) plaques
  - 2) neurofibrillary tangles (NFTs)
Epidemiological Evidence Linking Obesity and Insulin/IGF-1 Resistance in AD

Obesity and Alzheimer’s Disease:

- Obese individuals exhibit altered insulin/IGF-1 signaling.
- Increased expression of cytokine levels with high adiposity.
  - NOTE: not all obese individuals exhibit an increase in cytokine levels.
- Inflammation acts as pathogenic force.
- Neuroinflammation characterized by overactive glial cells.
- Obese males scored significantly lower than non-obese males in a variety of cognitive ability tests.
- Exact mechanisms are currently unclear.
Epidemiological Evidence Linking Obesity and Insulin/IGF-1 Resistance in AD

Insulin/IGF-1 resistance: Alzheimer’s Disease as a Type 3 Diabetes

- Insulin receptors (IR) are expressed both in neurons and glia of the brain.
- In a healthy brain, insulin signaling stops the formation of Amyloid Beta Plaques and abnormal phosphorylation of tau protein.
- Some experts consider AD to be a direct result of brain insulin resistance, naming it “Type 3 Diabetes” and here is why:
  - Defective insulin signaling is associated with decreased cognitive ability and the development of dementia, including Alzheimer's disease.
    - More than 20 neurological syndromes associated with insulin/IGF-1 signaling malfunctions and obesity.
- Having T2D significantly increases the risk of developing T3D/AD.
Key Players in the Pathways:

1. **Insulin/ IGF-1**
2. **Phosphatidylinositol 3-Kinase (PI3K)/ AKt pathway imbalance** can lead to obesity and Type 2 diabetes
3. **β-Amyloid** - naturally occurring deposits of protein fragments that build up in the spaces between nerve cells
4. **TAU** - proteins that stabilize neuron’s microtubules
5. **Neurofibrillary tangles** - abnormal accumulations of TAU that collects inside neurons

- **Microglia** - primary immune cells in the CNS

6. **Src homologous/collagenous protein (Shc)** - proteins are thought to participate in signaling through both receptor tyrosine kinases, such as the insulin receptor and the EGF (epidermal growth factor) receptor,
7. **Mitogen activated protein kinase (MAPK):** Involved in directing cellular responses to a diverse array of stimuli, such as mitogens, osmotic stress, heat shock and proinflammatory cytokines
8. **Pro-inflammatory cytokines:**
   - Interleukin-6
   - Interleukin-1β
   - Tumor Necrosis Factor-α
Obesity induced insulin/IGF-1 resistance contribution to Alzheimer’s Disease Pathology
5 Key Characteristics of The Promotion of Alzheimer’s Disease

1. Synaptic Plasticity = Memory/Learning Impairment
2. β-Amyloid & TAU
3. Cell death
4. Cell growth, proliferation, differentiation
5. Neuro-inflammation

Obesity results in downregulation of the PI3K pathway, leading to Alzheimer’s disease pathologies.
Obesity $\rightarrow$ synaptic signaling $\rightarrow$ A.D pathogenesis

- Obesity $\rightarrow$ decrease insulin/IGF-1 levels $\rightarrow$ INSR/IGF-2R activity $\rightarrow$ IRS-1 & IRS-2

This decrease in ligand activity causes

- less activation of PI3K pathway $\rightarrow$ synaptic plasticity $\rightarrow$ Learning/Memory Impairment

Promotion of Alzheimer's Disease Pathologies
Obesity $\rightarrow$ β-Amyloid / TAU $\rightarrow$ A.D Pathogenesis

- Obesity
  \[\downarrow\text{decreased Insulin/IGF-2 levels}\]
  \[\downarrow\text{less activation of PI3K pathway}\]
  \[\uparrow\beta\text{-Amyloid & TAU}\]

- INS & IGF-1R activity $\downarrow$

- IRS-1 & IRS-2 $\downarrow$

- Decrease in synaptic plasticity $\rightarrow$ Memory / Learning Impairment

- Promotion of Alzheimer's disease pathologies
Obesity \rightarrow \text{Cell death} \rightarrow \text{A.D Pathogenesis}

\text{Obesity} \rightarrow \downarrow \text{insulin, IGF-2 levels} \rightarrow \downarrow \text{INSR & IGF-1R activity} = \downarrow \text{IRS-1 & IRS-2}

\downarrow \text{less activation of PI3K pathway} \rightarrow \downarrow \text{cell death}

\downarrow 1 \rightarrow \downarrow \text{decrease synaptic plasticity}

\downarrow 2 \rightarrow \uparrow \beta\text{-Amyloid} \& \text{Tau}

\text{Promotion of Alzheimer's Disease Pathologies}
Obesity $\rightarrow$ decreased insulin/IGF-1 levels $\rightarrow$ decreased INSR IGF-1R activity $\rightarrow$ decreased SHC proteins $\rightarrow$ less activation of MAPK $\rightarrow$ decreased cell growth, proliferation, differentiation $\rightarrow$ Promotion of Alzheimer's Disease Pathologies
Obesity → Neuroinflammation → A.D. pathogenesis

- Obesity
- ↑ TNF-α
- Activated Microglia
- Pro-inflamm. cytokines: IL-6, IL-1β, TNF-α
- Neuroinflammation

Promotion of Alzheimer's Disease Pathologies
Obesity induced insulin/IGF-1 resistance contribution to Alzheimer’s Disease Pathology
Huntington's Disease

Subtitle
Introduction to HD

1. Overview of Huntington’s Disease

2. Brain Structures affected by HD

3. Stages and Symptoms

4. How Huntington’s is Inherited

5. Key players and pathways of Huntington’s
What is Huntington’s Disease?

Definition:

- Huntington’s Disease is a rare, progressive, genetic disorder with onset typically occurring between age 30 - 50

- This Neurodegenerative Disorder is characterized by dementia, chorea, and behavioral manifestations that are the result of the damage done to neurons and brain cells.

Statistics:

- The worldwide service-based prevalence of Huntington’s Disease, based on meta-analysis (n = 13 studies) was 2.71 per 100,000.

- Today, there are approximately 30,000 symptomatic Americans and more than 200,000 at risk of inheriting the disease.
How Does HD affect the Brain?

Huntington’s Disease affects the whole brain but certain areas are more vulnerable than others.

- Basal Ganglia - a group of nerves cell clusters called nuclei

Striatum (caudate nucleus and putamen), Globus Pallidus, Subthalamic Nucleus, Substantia Nigra

These nuclei play a key role in movement and behavior control and are parts of the brain most prominently affected in early onset of Huntington’s.
Full List of Symptoms

Movement Disorders associated with Huntington’s
- Chorea
- Dystonia
- Slow abnormal eye movement
- Impaired gait, posture, balance
- Difficulty with the physical production of speech or swallowing

Cognitive Disorders Associated with Huntington’s
- Dementia
- Difficulty organizing, prioritizing or focusing on tasks
- Tendency to get stuck on a thought, behavior or action
- Lack of impulse control
- Lack of awareness of one’s own behaviors and abilities
- Slowness in processing thoughts or “finding” words
- Difficulty in learning new information

Psychiatric Disorders associated with Huntington’s
- Depression
- Feelings of irritability, sadness or apathy
- Social withdrawal
- Insomnia
- Fatigue and loss of energy
- Frequent thoughts of suicide
Stages and Symptoms of HD

Early Stage:
- Early stage HD usually includes subtle changes in coordination, perhaps some involuntary movements (chorea), difficulty thinking through problems and often a depressed or irritable mood.

Middle Stage:
- In the middle stage, the movement disorder may become more of a problem. Diminished speech and difficulty swallowing also typically occurs.

Late Stage:
- In the late stage, a person with HD is totally dependent on others for care. At this stage, the person with HD can no longer walk and will be unable to speak. However, he or she is generally still able to comprehend language and retains full awareness of family and friends which is to be contrasted with Alzheimer’s Disease.
- When a person with HD dies, it is typically from complications of the disease such as choking or infection rather than from the disease itself.

In all Stages:
- Weight loss
How Is It Inherited

Huntington’s Disease is typically inherited and is caused by an autosomal dominant mutation in either of an individual’s two copies of a gene called Huntingtin.

A child of an affected person typically has a 50% chance of inheriting the disease.

HD is typically inherited but 10% of causes are due to a new mutation in the Huntingtin gene.
Pathway

IL-6 = Pro-inflammatory cytokines
Adipocytes = source of IL-6
Pathway

Obesity → ↓ Insulin/IGF-2 → ↓ regulation of HTT genes → Promotion of Huntington's Disease Pathologies

↓ Insulin/IGF-1 → ↓ clearing of HTT aggregates → ↑ cell death → promotion of HD pathologies

Huntington's affected neuron

Normal brain vs. HD brain

SGRA - Secreted which prevents a movement so if you want to step wind your legs

Urine PD HD has excess dopamine neurotransmitters

Lack of gamma

Uncontrolled movements
Down regulated in HD (Early onset of HD)

Obesity

↓ Insulin/IGF-1

↓ Akt (Kinase)

↓ Synaptic plasticity and signal 1

↓ Learning and memory

↓ Promotion of Huntington's disease pathologies
Periphery

- Obesity
  - Decrease in IGF-1
  - Decrease in Akt (Phosphorylation)
  - Decrease in synaptotagmin and Sigma 1
  - Decrease in learning and memory

Blood Brain Barrier (BBB)

- Increase in IL-6

↑ Regulation of HTT Gene
- Clearing of HTT aggregates
- Cell death

Neuroinflammation

Promotion of Huntington’s Disease Pathologies

Central Nervous System
There is compelling evidence that shows how obesity contributes to neurodegenerative disease such as AD, PD, and HD. We reviewed two mechanisms (obesity related insulin resistance and reduced insulin signaling) and showed how these can exacerbate chronic peripheral and CNS inflammatory responses.