Obesity: The Brain Disease

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Introduction

- Looking into evidence supporting the theory of obesity as a brain disorder:
- Obesity is a complex issue made up of several environmental, biological, and behavioral issues.
- Over-nutrition is a biological trap, not simply a willful choice
- OLD BELIEF: Animals can select food with precision for normal growth and survival;
- Stigma behind Obesity
- Evolution of environment vs. evolution of the human body
- This old theory is challenged in Galef., 1991 and Nakashima and Yokokura, 2010
Review Key Terms

- Leptin resistance- leptin regulates food intake; resistance to it is cells fail to respond to hormone leptin
- Hyperphagia- abnormally increased appetite for consumption of food
- Hypertensive- high blood pressure
- Hyperinsulinemia- excess levels of insulin circulating the blood
Over-nutrition is a biological trap, not simply a willful choice

- Galef et al., 1991; Nakashima and Yokokura., 2010
- Rats exposed to fatty foods earlier predisposes to favor high fat diet in adult life
- Vallerand et al., 1986
- Long term exposure to fat and sugar rich cafeteria feeding in turn increased energy intake in rats by 25%
Over-nutrition is a biological trap, not simply a willful choice

- Naim et al., 1985 - Set multiple choice cafeteria diet in rats --> it resulted in increase in hyperphagia and obesity
- Miesel et al., 2010 offered hypertensive rats a choice between cafeteria diet and regular chow ---+ the rats experienced increase body weight but also featured leptin and insulin resistance and higher blood pressure than control rats fed with regular chow.
Background: Brain structure and maturation not completed in-utero but extended into first phases of life

Boitard et al., 2012- exposure to high fat diet in adults and juvenile mice; but only juvenile - resulted in reduced hippocampal neurogenesis and reduction in rational memory flexibility

Tozuka et al., 2009- high fat diet from pre-mating to lactation led to offspring with increased hippocampal lipid peroxidation and decreased neurogenesis

Srinivasan et al., 2008- exposed rat pups to high-carbohydrate (HC) milk formula ---> develop chronic peripheral hyperinsulinemia and adult onset obesity despite replacement to regular rat chow.
Marconuterient dependent or caloric-related

- Srinivasan et al., 2008- Caloric restriction later in life reduce body weight but hyperphagia is irreversible
- Beck et al., 2012- macronutrient-dependent or caloric-related?
- Unnecessarily enriched nutrition imprints hypothalamic feeding
- example: comparing maternal high-fat, high carbohydrate diet resulted in lower arcuate nucleus POMC expression (This encodes at this site appetite curbing hormone alpha melanocyte-stimulating- hormone, alpha MSH) and higher paraventricular nucleus NPY and orexin peptide concentrations in their young adult rat offspring)
Oben et al., 2010 - Direct nutritional effects and maternal obesity are both dominant factors: Cross-fostering of offspring of lean rat dams by obese dams resulted in an exaggerated dysmetabolic, insulin-resistant, and NAFLD phenotype compared to offspring lean dams nursed by their natural mothers.

Non-alcoholic fatty liver disease (NAFLD)
Hypothalamus
Chronic high fat intake can lead to inflammatory changes in the brain cortex

What inflammation indicates? Why is it important?

Zhang et al. 2005- Revealed that high-fat diet (HF diet) induced cerebral oxidative stress, neural inflammation, and NF-κB activation in rat cerebral cortex, and provided novel evidence regarding the link between high dietary fat and increased risk of dementia.

1 month of age to 5 months

Low Fat Diet (LFD) or High Fat Diet (HFD)
Over-nutrition elicits brain disease: related to obesity

- Moroz et al., 2007:
- High Fat Diet (HFD) demonstrated in mice developed obesity
- HFD feeding $\rightarrow$ impaired insulin receptor binding in temporal lobe
- These mice did not exhibit Alzheimer’s disease with increases in Amyloid-B or phospho-tau, or impairment in insulin-like growth factor 1
- increased expression of Amyloid Precursor Protein (APP) in adipose tissue from obese human subjects and that plasma Amyloid-B is positively related to body fat, even in normal subjects Lee et al., 2008
Insulin resistance is a hallmark of obesity and caloric excess and can play an important role in brain dysfunction.

Insulin resistance- a condition in which the cells of the body fails to respond to the normal actions of the hormone insulin

Hyperinsulinemia- condition in where excess levels of insulin circulating in the blood than expected relative to the level of glucose

These two conditions develop rapidly with increase caloric intake and weight gain even prior to evolution of obesity Danielsson et al., 2009; Lee et al., 2011

<table>
<thead>
<tr>
<th>Short-term overeating</th>
<th>Lean Individuals</th>
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<tbody>
<tr>
<td></td>
<td>High caloric diet</td>
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<tr>
<td>weight gain</td>
<td>10%</td>
</tr>
<tr>
<td>Total Body Fat gain</td>
<td>19%</td>
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Musen et al., 2012

- Functional magnetic resonance imaging (fMRI) showed that homeostasis model of assessment (HOMA-IR), standard measure of insulin resistance derived by fasting.
- Elder subjects with insulin sensitivity was **positively related** to verbal fluency performance, brain size, and temporal lobe gray matter volume (Benedict et al 2012)

<table>
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<tr>
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<th>Connectivity in right inferior frontal gyrus</th>
<th>Peripheral insulin sensitivity</th>
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<tbody>
<tr>
<td>Type 2 Diabetes individuals</td>
<td>reduced connectivity</td>
<td>reduced functional connectivity in DMN</td>
</tr>
<tr>
<td>non-diabetic individuals</td>
<td>stronger connectivity as compared</td>
<td>functional connectivity with insulin sensitivity</td>
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Obesity is associated with at least some of insulin’s CNS effects: example, intra-nasally administered insulin acts through CNS and lowers food intake in normal weight but not obese men (Hallschmid et al., 2008)

Insulin enhanced cerebrocortical activity is controlled by hippocampus linked to locomotor activity and voluntary movement, but effects are not significant on obese subjects (Tshritter et al., 2009)
The Actual Culprit?

- Obesity is a condition brought about through the presence of a multitude of factors.
- Determining factors for obesity typically stem from imbalances in homeostasis such as leptin deficiency, poor regulation of caloric intake, or stress.
Problems with BMI

### BMI classification

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI Range</th>
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<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
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<tr>
<td>Normal range</td>
<td>18.5 - 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥ 25.0</td>
</tr>
<tr>
<td>Preobese</td>
<td>25.0 - 29.9</td>
</tr>
<tr>
<td>Obese</td>
<td>≥ 30.0</td>
</tr>
<tr>
<td>Obese class I</td>
<td>30.0 - 34.9</td>
</tr>
<tr>
<td>Obese class II</td>
<td>35.0 - 39.9</td>
</tr>
<tr>
<td>Obese class III</td>
<td>≥ 40.0</td>
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### Body Fat Pictures

<table>
<thead>
<tr>
<th>Description</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential fat</td>
<td>10-13%</td>
<td>2-5%</td>
</tr>
<tr>
<td>Athletes</td>
<td>14–20%</td>
<td>6-13%</td>
</tr>
<tr>
<td>Fitness</td>
<td>21–24%</td>
<td>14–17%</td>
</tr>
<tr>
<td>Average</td>
<td>25–31%</td>
<td>18–24%</td>
</tr>
<tr>
<td>Obese</td>
<td>32%+</td>
<td>25%+</td>
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Hyperglycemia

- Rats who consumed a large amount of fructose in their diet had memory impairment. (Gomez 2012)
- Individuals who had breakfasts low in the glycemic index tended to score better than their peers who had food higher in the glycemic index. (Cooper 2012)
- Decreased appetite suppression can result from large, continuous glycemic intake BEFORE the individual even gains weight.
### Cause and Effect

<table>
<thead>
<tr>
<th>Signals</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Gliosis detected in T2 from MRI</td>
<td>Gliosis found in hypothalamus, less BBB proteins.</td>
</tr>
<tr>
<td>Blunted hypothalamic response to insulin</td>
<td>Increase hepatic glucose output and peripheral lipolysis</td>
</tr>
<tr>
<td>Diminished brain volume</td>
<td>Neurodegeneration in hippocampus</td>
</tr>
<tr>
<td>Memory deficiency</td>
<td>High fat diets increase hippocampal TNF-alpha and microglia</td>
</tr>
<tr>
<td>Mitochondrial dysfunction</td>
<td>Loss of glucose sensing neurons, increases changes for type 2 diabetes</td>
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BMI and brain volume have an inverse relationship. Obese individuals have a lower quality of white matter (makes up the CNS and myelin sheath).
Actual Effectual Memory Loss

BMI Increase % Rate

Loss of Functional Memory
Obese individuals tend to have more brain activity in the presence of food. The startling fact is that this continues after they have already ate.

A theory postulated from this result claims that due to the fact obese people have more brain activity when presented with food they most likely have a greater reward value for it.

Evolutionary lag
A main reason why most people who lose weight gain it again is because this mechanism cannot be scaled back.

The dorsal prefrontal cortex had a significant difference between dieters who were successful and those who were not.

This can be attributed to its control of behavioral responses.
TNF (tumor necrosis factor)-alpha is a proinflammatory cytokine present in the hypothalamus during a short term surge of high fats in a diet. This leads to the impairment of insulin via the interference of insulin signals.

Kappa B kinase beta is involved with obesity because it can interrupt both insulin and leptin signaling.

Mediobasal hypothalamic inflammation is usually onset within a few days of high fat food intake and appears before a gain in weight. As a result it has been pinned as a mediator of obesity.

The inflammation of the hypothalamus leads to the increased base level of insulin as well as a decrease in the anorexogenic effects of leptin.
Local neuroprotective repair mechanisms are overwhelmed by the chronic overload resulting from obesity.

Since they have less repair mechanisms, obese individuals are much more susceptible to gliosis.
Hypothalamic Inflammation affects insulin

Calegari et al., 2011-Recent evidence indicates that hypothalamic inflammation results:

- impaired central regulation of energy and balance
- disruption of normal insulin secretion
- reduction peripheral insulin sensitivity
- ICV injection of low dose of TNF-alpha leads to dysfunctional increase in insulin secretion and activates the expression of a number of markers of apoptosis in pancreatic islets.
Hypothalamic Inflammation affects insulin release and action

- Milanski et al., 2012- In this recent study hypothalamic inflammation was reduced;
- resulted in attenuation of hypothalamic resistance to leptin
- Improved insulin signal transduction in the liver and lessening of liver steatosis-
- Steatosis- also called fatty change, fatty degeneration or adipose degeneration
Fotuhi et al., 2012- Obesity and obesity-related conditions are known to adversely influence hippocampal size

Later a direct study matching controls and hypertensive subjects failed to identify a role for hypertension hippocampal volume Gold et al., 2005; Raz et al., 2003
Tested the hypothesis that an AMP-activated protein kinase activator, resveratrol (RES), which is known to exert potent anti-inflammatory effects, would attenuate peripheral and central inflammation ---> Improve memory deficit in mice fed a high-fat diet (HFD)

- mice fed HFD and HFD with RES for 20 weeks
- used Western Blot analysis to test metabolic parameters
- used Morris water maze test to study role of RES on memory
- HFD fed mice hippocampus had protein levels of tumor necrosis factor-a and Iba-1 expression reduced by RES treatment
- Found RES to significantly improve memory deficit in HFD fed mice; The finding indicate RES reverses obesity-related peripheral and central inflammation and metabolic derangements and improves memory
Inflammation and cell damage

- Ho et al., 2011; Jagust et al., 2005; Raji et al. 2009; Whitmer et al., 2008
- HFD can induce local pro-poptotic signaling such as increased expression of caspase-3 and gliosis in the hippocampus, particularly in the dentate gyrus. These damages may eventually lead to loss of hippocampal tissue.
BMI and hippocampal atrophy

- (Jagust et al., 2005; Knopman, 2008; Raji et al., 2010; Taki et al., 2007)
- Cherbuin et al., 2012- Looked at glucose and its role in hippocampal volume shrinkage.

<table>
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<th>Mid-life</th>
<th>Later-life</th>
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<tr>
<td>Body Mass Index</td>
<td>hippocampal atrophy</td>
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Plasma glucose levels and hippocampal atrophy and amygdalar atrophy

- 266 cognitively healthy individuals free of T2D 60-64 yrs of age
- Used fMRI scans collected at wave 1 and at wave 2-4
- 6-10% in volume change after controlling for age, sex, BMI, hypertension, alcohol, and smoking
- These findings suggest that subclinical range and in the absence of diabetes, monitoring and management of plasma glucose levels could have impact on cerebral health
Direct hippocampal exposure to leptin reduces food intake (Kanoski et al., 2011)

Brain leptin resistance: Masaki et al., 2012

Hippocampal injury play a role in disrupting feeding behavior

Adiponectin-protein hormones, causes sensitivity peripheral tissues to insulin (Usually lower for obese individuals)

Adiponectin protects hippocampus neurons against excitotoxicity. Qui et al., 2011
During high fat diet, brain inflammatory damage and the associated cognitive decline may depend on the dietary formulation, not only on weight gain (Pistell et al., 2010)

Why would we consider that obesity can cause cognitive disadvantages?

Metabolic syndrome, a cluster of risk factors that include: large waist with excess belly fat, high blood sugar, high triglycerides, low levels of HDL (good cholesterol) and high blood pressure.

Obesity and Metabolic Syndrome (MetS) and cognitive impairment is strongly supported (Case et al., 2001; Yaffe et al., 2004)

MetS in early life (Maayan et al, 2011)

Matched gender, education, socioeconomic status

<table>
<thead>
<tr>
<th>lean individuals</th>
<th>obese individuals</th>
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<tbody>
<tr>
<td>lower disinhibition on TFEQ</td>
<td>higher disinhibition on TFEQ</td>
</tr>
<tr>
<td>higher cognitive test scores</td>
<td>lower cognitive test scores</td>
</tr>
<tr>
<td>higher orbitofrontal cortex volume</td>
<td>lower orbitofrontal cortex volume</td>
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</table>
Obesity and cognitive decline

- Yates et al., 2012; Pauli-Pott et al., 2010; Elias et al., 2003, 2005; Waldstein and Katzel, 2006
- Early deficits include reduction in executive functioning and attention, decreased global functioning or lesser IQ.
- Deficient executive function may play a role in development or persistence of obesity.
- Weak inhibitory control performance leads to overeating.
- Healthy obese have some deficits in learning, memory, and executive function relative to non-obese individuals.
Cognitive performance and physical activity

- Cognitive performance declines with decrease physical activity and aerobic fitness. (Donnelly et al., 2009)
- In more existing studies weight loss may result in improvement of cognitive functions (Gunstad et al., 2011; Siervo et al., 2011) and metabolic control (Ryan et al., 2006)
- Both peripheral inflammation and central inflammatory processes may affect the brain in the obese state: it is well accepted that expression of inflammatory cytokine can be induced in brain cells, which then leads to neuronal apoptosis and impaired cognition (Gemma and Bickford., 2007)
Hormonal Alterations and Cognitive Function in Obesity

- Leptin improves cognitive impairment and helps the protective mechanisms in obese individuals.
- GLP-1, a hormone obese individuals have a decrease amount of, increases insulin release and helps improve learning.
- GLP-1 has also had a beneficial effect against Parkinsons and Alzheimers since it has been linked to decreasing neurodegeneration.
This neurotrophin suppresses food intake, regulates neuronal development, and is involved in both learning as well as memory.

When activated by MCP-4 and leptin, it gradually reduced the weight of the rats.

People who have a genetic bias towards being overweight tend to have less BDNF than others.

All obesity phenotypes have some relation to BDNF.
A decrease in sleep leads to an increase in neuronal activity when presented with food.

Interestingly enough, obesity negatively affects sleep and as a result makes the individual more hungry so they want to eat more.

Rats who had their circadian rhythms affected grew gradually in weight. They also exhibited diminished memory and inflammation mechanisms.
The process an individual goes through when they are obese put them at risk for diabetes, hypertension, dysglycemia, and metabolic syndrome.

There are two ideas which try to classify obesity as a brain disease.

The first one claims that there is an anomaly which deregulates the individual’s diet.

Chronic brain damage evolves secondary to obesity.
Effects of Obesity

Overnutrition

- Weight gain, obesity

- Hypothalamic inflammation and insulin resistance

- Fat tissue lipolysis

- Hypothalamic gliosis

- Impaired energy and food intake control

- Impaired insulin secretion

- Brain structural changes

- Cognitive deficits

- Fat tissue expansion and inflammation; Amyloid β precursor

- Brain insulin resistance

- Inflammation/oxidative stress

- Hippocampal inflammation & atrophy

Executive function, Learning, Spatial navigation, Attention, Locomotion, Memory
Conclusion

- Overeating causes hypothalamic inflammation causing there to be a problem with homeostasis regarding energy and insulin.
- The structural changes they create further facilitate the anomaly the body is going through.
- Much of the problems from obesity can be attributed to genetics and an imbalance of hormones.