Glucose and Its Discontents

The Emerging Role of Metabolic Abnormalities in Stress, Psychosis, and Neurodegeneration
Neuropsychiatric Disorders and Metabolic Disturbances

- Insulin is a pleiotropic peptide involved in:
  - Neurotrophism
  - Neuroplasticity
  - Neuromodulation
- Abnormal central insulin signaling mediates alterations in neuronal integrity and functioning
- “Moreover, refining disease models for neuropsychiatric disorders, by evaluating the phenotypic and neurobiological overlap between neuropsychiatric disorders with metabolic disturbances, is an essential step in the development of personalized, preventative, and/or pre-emptive treatments.” (1)
Thomas Willis (1621 - 1675)

- Founding member of the Royal Society
- As had many before him, correctly observed that the urine of diabetic patients was sweet
- First to describe a possible association between diabetes and stress
- From his work, coined the term *mellitus*, which is Latin for “honey” or “sweet” (*Diabetes* is Greek for “siphon”)
Henry Maudsley (1835 - 1918)

- Found that diabetes and schizophrenia were often co-expressed in families
- “Diabetes is a disease which often shows itself in families in which insanity prevails,” (2)

“I look like a creep.”
Insulin Coma Therapy

- Developed by psychiatrist Manfred Sakel between 1928 and 1933
- Sakel began by using large doses of insulin to treat symptoms of opiate withdrawal
- Found that patients became calm and more cooperative, in addition to gaining weight
- Repeated experiments on schizophrenic patients and found similar results
- For context, insulin had only just been discovered and was being hailed as a miracle drug
- Announcement of Sakel’s discovery came at a time when there was no clear treatment for schizophrenia - patients and their families were desperate
Insulin Coma Therapy

- No standardized procedure
- Insulin was prescribed at increasing doses daily, until comas were induced
- Patients remained in a coma for up to an hour or more, and were revived with a glucose shock
- A full treatment course could consist of up to 50 to 60 insulin induced comas
- Reintroducing glucose en masse to hypoglycemic patients is extremely dangerous
- Efficacy can largely be traced to the complete lack of glucose in brain
- Without a proper energy substrate, psychosis of patients largely replaced by a general stupor
- Therapeutic benefits of ICT eventually disproven
Brain disorders associated with an increased prevalence of insulin resistance/diabetes and/or obesity

<table>
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<th>Psychiatric disorders</th>
<th>Other congenital Disorders</th>
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<td>Schizophrenia</td>
<td>Glut1 deficiency</td>
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<tr>
<td>Bipolar disorder</td>
<td>Familiar hyperinsulinism</td>
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<tr>
<td>Major Depressive Disorder</td>
<td>Kearns-Sayre syndrome</td>
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<tr>
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<td>MELAS syndrome</td>
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<td>Bardet-Biedl syndrome</td>
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<td>Niemann-Pick disease</td>
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<td>Wolfram syndrome</td>
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- Schizophrenia
- Bipolar disorder
- Major Depressive Disorder

- Alzheimer's disease
- Vascular Dementia
- Parkinson's disease
- Huntington's disease

- Prader-Willi
- Alstrom syndrome
- Bardet-Biedl syndrome
- Down's syndrome
- Ataxia-telangiectasia (Louis-Bar syndrome)
- Niemann-Pick disease
- Werner syndrome
- Wolfram syndrome
- Woodhouse-Sakati syndrome

Other congenital Disorders
- Glut1 deficiency
- Familiar hyperinsulinism
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- Spinocerebellar ataxia 3 (Machado-Joseph disease)
- Spinocerebellar ataxia 6
- Turner syndrome
Correlations

- Depression is associated with a 60% greater risk for T2D
- Metabolic disturbances are found at a 2x to 4x greater rate in schizophrenic patients
  - The primary cause of death in schizophrenia is cardiovascular disease
- T2D is considered an independent risk factor for dementia
- Impaired glucose tolerance is found in 80% of those with Parkinson’s Disease (PD)
- In Huntington’s Disease, 7x increased likelihood of developing T2D
Correlations (cont.)

- Both antidepressants and antipsychotics (eg. neuroleptics) can influence metabolism
- Research suggests that more than 20% of those affected by congenital neurodegenerative disorders will develop metabolic complications
- Insulin signaling dysfunctions have been implicated in pathophysiological mechanisms for anorexia and bulimia nervosa
- Starvation is also capable of inducing depression, anxiety, psychosis, and/or suicide
Sources

Stress and Metabolism

--- Stress has been implicated in the pathogenesis of obesity, addiction, and other psychiatric disorders
--- Exogenous administration of glucocorticoids is associated with hyperinsulinemia and insulin resistance
--- Mice overexpressing CRH are characterized by increased food intake, weight gain, insulin resistance, increased anxiety, impaired learning, and altered adaptations to stress
Cortisol = Chronic stress hormone

Stimulus for release:
- ACTH is the direct stimulus
- Indirect factors include stress, hypoglycemia, the circadian rhythm (released during late stages of sleep and increases every few hours due to lack of meals hypoglycemia), caffeine, and sleep deprivation.

Actions:
- Liver: Increase glucose levels by increasing gluconeogenesis. However during last stage fasting/starvation, it also increases glycogen synthesis as well.
- Pancreas: decrease insulin synthesis.
- Adipocytes: increases lipolysis, increases the hormone sensitive lipase activity, increases sensitivity to glucagon.
- Brain: a stimulant that causes euphoria and agitations. Also causes decrease in sleep duration and quality. (if you are stressed, you have trouble sleeping)
- Suppresses immune response. This is why steroids are used as anti inflammatory agents. And this is why stressed out people have bad immunity towards common things.
Stress Hormone

Pro-opiomelanocortin (POMC)

ACTH, γ-lipotropin, β-endorphin, Fragments

Pituitary

α-MSH, γ-MSH, Fragment

Non-pituitary tissues

Melanin synthesis, Immune response, Food intake

CRH, ACTH, Cortisol

Hypothalamus, Anterior pituitary

Adrenal cortex

Immune system, Liver, Muscle, Adipose tissue

Function suppressed, Gluconeogenesis, Protein catabolism, Lipolysis

Circadian rhythm, Stress

long-loop negative feedback
Neuroinflammation

**Acute inflammation**

- Immediate and early response to an injurious agent
- A defensive response that paves the way for repair of the damaged site being typically short-lived
- Unlikely to be detrimental to long-term neuronal survival
  
i.e. stroke and injury

**Chronic inflammation**

- Occurs when the harmful stimulus persists over time
- A long-standing and often self-perpetuating neuroinflammatory response which in the end, results in detrimental consequences for neurons
  
i.e. multiple sclerosis or Alzheimer disease (AD)
Inflammation and Metabolism

-----Changes in levels of many cytokines including increased levels of IL-1\(\alpha\), IL-1\(\beta\), IL-6, TNF-\(\alpha\), and GM-SF

-----Current evidence suggests that administration of exogenous TNF-alpha to animals can induce insulin resistance, whereas neutralization of TNF-alpha can improve insulin sensitivity
What do Schizophrenia, Parkinson’s, Huntington’s, and Drug Addiction have in common?
Dopamine

Not just the “pleasure molecule”

Binds to DA receptors in the pancreas, lungs, kidneys, and gastrointestinal tract

Also works to suppress prolactin secretion in the pituitary
Dopamine Receptors

There are five

D1-like = D1 and D5 receptors

D2-like = D2, D3, and D4 receptors
Dopamine Synthesis

L-Tyrosine

Tyrosine hydroxylase

L-Dihydroxyphenylalanine (L-DOPA)

DOPA decarboxylase

Aromatic L-amino acid decarboxylase

Dopamine

Dopaminergic Neuron

Tyrosine

L-DOPA

Dopamine

VMAT

DAT

Dopamine Receptors

D1

D2
Dopaminergic Systems

Mesolimbic
Mesocortical
Nigrostriatal
Tuberoinfundibular (not pictured)
Dopaminergic Systems

- Mesolimbic
- Mesocortical
- Nigrostriatal

Tuberoinfundibular (not pictured)
The Nigrostriatal System

Projections from the substantia nigra to the dorsal striatum

The substantia nigra deteriorates in Parkinson’s Disease

Implicated in reward and voluntary movement
The Mesolimbic System

Often called the “reward circuit”

Projects from the ventral tegmental area to the nucleus accumbens

Responsible for “liking” and “wanting”

Palatable foods, sex, drugs, and rock n’ roll trigger DA release in these areas
<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Mechanism for DA increases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulant drugs (cocaine, methamphetamine, amphetamine)</td>
<td>DAT</td>
<td>Blocks DAT on the terminals of DA projecting neurons from VTA to NAc (cocaine) or releases DA from the vesicles of DA terminals (methamphetamine, amphetamine)</td>
</tr>
<tr>
<td>Opioids (heroin, opioid analgesics)</td>
<td>MOR</td>
<td>Disinhibits VTA DA neurons by inhibiting GABA interneurons that contain MOR in the VTA or directly activates NAc neurons that contain MOR</td>
</tr>
<tr>
<td>Nicotine (cigarettes and other tobacco products)</td>
<td>Nicotinic receptors (predominantly α4β2 subtype)</td>
<td>Directly activates VTA DA neurons by stimulating their nicotine receptors and indirectly activates them by stimulating the nicotine receptors in glutamatergic terminals to VTA DA neurons</td>
</tr>
<tr>
<td>Alcohol and inhalants</td>
<td>Multiple targets, including GABA and glutamate receptors</td>
<td>Facilitates GABAergic neurotransmission, which may disinhibit VTA DA neurons from GABA interneurons or may inhibit glutamate terminals that regulate DA release in Nac</td>
</tr>
<tr>
<td>Cannabinoids (marihuana)</td>
<td>Cannabinoid CB1 receptors</td>
<td>Regulates dopaminergic signaling through CB1R in NAc neurons and in GABA and glutamate terminals to NAc</td>
</tr>
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</table>
The Lateral Hypothalamus

The LHA is responsible for hunger

It manufactures and secretes orexin and melanin-concentrating hormone

Lesions cause rats and mice to starve

Stimulation causes eating en masse

*The LHA shares connections with the mesolimbic system*
The Hunger-Pleasure Axis

Hunger increases mesolimbic dopamine secretion in response to food anticipation and consumption.

Satiation decreases the amount of mesolimbic dopamine secretion in response to food anticipation and consumption.

Certain foods don’t do this. They instead trigger the release of orexin and melanin-concentrating hormone to make us want more food.
Molecular Basis of the Hunger-Pleasure Axis

The lateral hypothalamus and the mesolimbic system all express leptin and insulin receptors.

Leptin and insulin tell us we are full.

The binding of leptin and insulin to the lateral hypothalamus is inhibitory.

The binding of leptin and insulin to the mesolimbic system is inhibitory.
So What?

The dopaminergic systems are interconnected with those responsible for food consumption.

The dopaminergic systems go awry in many neuropsychiatric disorders.

Perhaps the metabolic disturbances we see in many neuropathologies could be due in part to malfunctions in dopaminergic signaling.
Huntington’s, Parkinson’s, and Dopaminergic Systems

Parkinson’s Disease is a neurodegenerative disease characterized by resting tremors, rigid muscles, slow movements, and bent posture. Other behavioral and cognitive impairments develop later on, with dementia and depression appearing most frequently.

No known cause, although genetic and environmental factors do contribute.

Most heavily affects the basal ganglia/substantia nigra, with many dopaminergic cells and astrocytes dying off, as well as formation of Lewy bodies (alpha-synuclein buildup). Costs an estimated 23 billion dollars annually in the U.S.
“Aggregated α-synuclein in Lewy bodies resembles the changes in cooking an egg,”
Dr. Frank Church
Parkinson’s and Dopamine

L-DOPA is the precursor to dopamine and is used as a treatment for early stages of PD. However, these medications lose efficacy over time and in fact contribute to the development of dyskinesia, as well as other physical side and behavioral side effects.

Other dopamine agonists are also used as initial treatments, along with MAO-B inhibitors which slows dopamine breakdown in the basal ganglia.
The Substantia Nigra

It’s an area in the midbrain that appears darker than surrounding tissue due to high concentrations of neuromelanin in the dopaminergic neurons.

Composed of the pars compacta and pars reticulata, the substantia nigra plays a key role in motor planning, reward pathways, and learning.

The pars compacta is particularly affected by Parkinson’s, losing its ability to mediate the striatum through dopaminergic signaling and thus impairing motor control in patients.
Dopaminergic Systems, Hormones, and Feeding

Leptin decreases the firing rate of dopaminergic neurons found in the midbrain, including those of the SN and VTA. Leptin and ghrelin administration further affect high-order feeding behavior via the mesolimbic system.

Past studies have found dopamine is released in areas that receive projections from the SN/VTA during eating, particularly in response to novel rewards.

Patients with dopamine depletion or impairment in the SN have shown body weight deficits related to eating. Nigrostriatal projections consistently reduce feeding levels when their dopamine is depleted or the VTA is legioned.

However, research is complicated by other factors, including non-dopaminergic signaling and the complex nature of dopamine signaling itself.

*Narayanan, Guarnieri, DiLeone*
Huntington’s, Parkinson’s, and Dopaminergic Systems

- **Huntington’s Disease** is a genetic, fatal neurodegenerative disease affecting 30,000 Americans today with no available cure.
- Symptoms usually appear in late 30’s and 40’s and worsen over a 10 to 20 year period. These include:
  - Physical symptoms: involuntary jerking movements (chorea), rigid muscles, difficulty swallowing and speaking, fatigue.
  - Cognitive impairments with thinking, impulse control, and attention, behavioral and personality changes, heavy atrophy in substantia nigra.
- Individuals only need to inherit a single copy of the mutated Huntingtin gene from either parent to develop the disease.
\( h \) = normal allele
\( H \) = Huntington’s allele

**Parent 1:**
- \( Hh \)

**Parent 2:**
- \( hh \)

- **Possible gametes:**
  - \( H, h \)

- **Possible combination of alleles in offspring:**
  - \( Hh, Hh, hh, hh \)

- **Outcomes:**
  - Huntington’s
  - Huntington’s
  - Normal
  - Normal
Huntington’s and Dopamine

The nigrostriatal dopaminergic pathway transmits dopamine from the substantia nigra to the caudate nucleus and putamen and is mainly linked to motor control.

Dopamine plays a critical role in brain signaling. Too much or too little DA reduces brain function and leads to abnormal “cognitive inflexibility.” Additional evidence suggests that increased DA induces chorea while insufficient DA also reduces control over voluntary movements. Rat models imply either impaired DA/vesicle interactions or depleted DA reserves in late stage-HD.

Imaging studies have found systemic striatal and cortical loss of DA receptors in early stages of HD which also affects executive function and learning.

*Delphine Charvin, Peter Vanhoutte, Christiane Pagès, Emiliana Borelli, and Jocelyne Caboche*
The kicker:

Abnormal DA signaling was first proposed as an underlying cause of HD symptoms in 1970 after L-DOPA treatments led to dyskinesias.

Excess excitatory neurotransmitters, like glutamate, have proven to be particularly toxic to dorsal striatal cells. Not only can DA accelerate neurodegeneration through production of free radicals, but studies suggest DA is closely intertwined with glutamate transmission and both work to exacerbate toxicity.

DA research could lead to a definitive treatment for HD’s pathology. We understand much more about DA’s role in Parkinson’s than HD.

(Klawans HC et al.)
Schizophrenia and Metabolism

Obesity occurs twice as often in populations with schizophrenia

- Two-thirds will die of heart disease
- 20% shorter than average lifespan
- One in five schizophrenic patients have diabetes

Possible factors include:
- Antipsychotic medication
- Lifestyle
- HPA axis abnormalities
- Shared genetic diathesis
Antipsychotics and Metabolism

Obesity is 2-4x higher in patients taking antipsychotic medication

Atypical antipsychotics induce significantly more weight gain than their conventional predecessors

Clozapine has the highest efficacy of the atypical antipsychotics, but is also associated with the greatest weight gain

- Weight gain is highly correlated with degree of symptom reduction
- Patients who gained >10% of their body weight in a 16 week trial saw the greatest decrease in positive and negative symptomatology
Antipsychotics and Metabolism: Possible Mechanisms

D2 antagonism - inhibiting the “brakes” on the dopamine system
- Linked to increased striatal activation in anticipation of reward
- Administering a D2 agonist reduces feeding in rats treated with atypical antipsychotics
- Receptor polymorphisms correlated with weight in healthy populations

Serotonin antagonism
- Serotonin agonists suppress appetite
- Other psychotropic medications with antagonistic effects are linked to weight gain and carbohydrate craving
- Lithium affects serotonin transmission and is associated with reduced weight gain

Sedative effects also decrease physical activity, making increases in caloric intake particularly detrimental
Schizophrenia, Obesity, and Lifestyle Factors

Drug-naive patients have a poor diet and low rates of physical activity
- Difficult to determine whether this is due to shared risk factors like low socioeconomic status or a direct result of the illness

Direct neural mechanisms have yet to be elucidated, but may potentially include:
- Aberrant dopamine signaling leads to decreased salience of non-psychosis related stimuli and in turn poor dietary choices
- Hypofunctionality of the prefrontal cortex leads to lack of inhibitory behavioral control
Schizophrenia and the HPA Axis

Those with schizophrenia have hyperactivity of the HPA Axis

- Heightened cortisol secretion
- Cortisol levels correlated with symptom severity
- Abnormal cortisol levels across 24 hour period indicating circadian disturbances

Genetic variants affecting CRH and glucocorticoid signaling are associated with suicide attempts in schizophrenia
Glucocorticoids and Appetite

Interfere with insulin signaling leading to insulin resistance
- Impairs GLUT4 activation in response to insulin
- Interferes with insulin binding

Upregulation of serum leptin levels
- High circulating leptin ultimately leads to leptin resistance

Increased reward sensitivity and in turn palatable behaviors
- Increased reward stimulus salience
- Resistant to normal satiety signals (insulin and leptin) that reduce hedonic value of food via inhibition of dopamine
- Opioid release in response to reward decreases HPA axis activity, thereby driving reward-seeking behaviors as self-medication
Schizophrenia and T2D - Genetic Link

Drug-naive patients have elevated rates of insulin resistance and impaired glucose tolerance

- Seen even when compared to BMI-matched controls
- First degree relatives of psychotic patients show similar elevations in metabolic disturbances

This suggests a possible shared genetic diathesis for both schizophrenia and diabetes
Schizophrenia and DISC1

DISC 1 (disrupted in schizophrenia gene) aberrations associated with schizophrenia, bipolar, depression, and autism

- Translocation leads to 50x increased risk of these disorders
- Implicated in a wide range of functions including neural development, cAMP signaling, cytoskeleton regulation, and translational regulation
DISC1 and Type 2 Diabetes

- Aberrations in DISC1 disrupt inhibition of GSK3β
- Result in cell death and decreased insulin secretion
- This leads to hyperglycemia and type 2 diabetes

 Jurczyk, Nowosielska, Przewozniak, Aryee, Dilorio, Blodgett (2015). Beyond the brain: Disrupted in schizophrenia 1 regulates pancreatic β-cell function via glycogen synthase kinase-3β. The FASEB Journal 30(2).
The mechanisms of schizophrenia are not well understood so it is difficult to know what underlies the association with obesity and diabetes.

Lifestyle and antipsychotic medication use are likely the largest contributors to obesity in schizophrenic populations.

Newer research suggests that the pathology of schizophrenia may have a direct link to metabolic dysfunction:

- Elevated glucocorticoid levels affect appetite.
- Abnormal reward response and inhibitory control may drive unhealthy food choices.
- New evidence points to a shared genetic risk for both diabetes and psychosis.