Metabolic Brain Disorders
Insulin is a pleiotropic peptide

- Neuroplasticity
- Neurotrophism
- Neuromodulation

One Hormone Can Have Multiple Effects

The term pleiotropy is derived from the Greek words *pleio*, which means "many," and *tropic*, which means "affecting."
Metabolic Disturbance & Cognitive Dysfunction:

- Disturbed neuronal signaling
- Abnormal cellular structure and function

Overlap: Abnormal central insulin-signaling \(\rightarrow\) impairs neuronal functioning.
Insulin-mediated effects of brain function:

- Brain function
- Insulin pathways
- Degeneration

Targeting insulin as a new approach for treatment
What is the relationship between peripheral glucose metabolism & psychiatric disorders?

"long sorrow"

Henry Maudsley 1874

Family history

Diabetic personality

Kety, S. (1950) American Journal of Medicine

Circulation and Metabolism of the Human Brain in Health and Disease

Seymour S. Kety, M.D.
Philadelphia, Pennsylvania

One important approach to the enigma of the human brain resides in a study of its circulation. A number of diseases produce serious cerebral manifestations and sometimes death by interference with the circulatory nutrition of the brain. Others are associated with a breakdown at some point or other in the complex series of metabolic processes which underlie normal cerebral activity. Measurement of the cerebral blood flow in man may afford not only some insight into these circulatory disturbances but also an opportunity to investigate the more abstruse problem of cerebral metabolism. Such studies are yet in their infancy and, compared to what is yet to be learned, our accumulated knowledge is modest indeed. From this point of view a summary of our knowledge at this time is warranted, if only to point out the great gaps which still exist.
Kety, S. (1950) American Journal of Medicine

**Table II**

**CONDITIONS INVOLVING ALTERATIONS IN MENTAL STATE OR CEREBRAL METABOLISM**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mental State</th>
<th>Mean Blood Pressure mm. Hg</th>
<th>Cerebral Blood Flow cc./100 gm./min.</th>
<th>Cerebral O₂ Consumption</th>
<th>Cerebrovascular Resistance mm. Hg/cc./100 gm./min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Alert</td>
<td>85</td>
<td>54</td>
<td>3.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Schizophrenics</td>
<td>Alert-inaccessible</td>
<td>95</td>
<td>54</td>
<td>3.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Schizophrenics, narcosynthesis</td>
<td>Alert-more accessible</td>
<td>95</td>
<td>54</td>
<td>3.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Cerebral arteriosclerosis</td>
<td>Confused</td>
<td>121</td>
<td>41</td>
<td>2.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Diabetic acidosis</td>
<td>Confused</td>
<td>86</td>
<td>45</td>
<td>2.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Insulin hypoglycemia</td>
<td>Confused</td>
<td>86</td>
<td>61</td>
<td>2.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>Comatose</td>
<td>122</td>
<td>34</td>
<td>2.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Pentothal anesthesia</td>
<td>Comatose</td>
<td>78</td>
<td>60</td>
<td>2.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Insulin coma</td>
<td>Comatose</td>
<td>93</td>
<td>63</td>
<td>1.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Diabetic coma</td>
<td>Comatose</td>
<td>66</td>
<td>65</td>
<td>1.7</td>
<td>1.1</td>
</tr>
</tbody>
</table>
Cerebral metabolism may be deranged by the presence of depressant agents of endogenous or exogenous origin. Among those originating within the body are the hydrogen ion and the products which accumulate in uremia and ketosis. In diabetic acidosis and coma the confusion and unconsciousness are well correlated with a considerable depression in cerebral oxygen consumption. This is not on the basis of inadequate supply to the cells of the brain since a normal or augmented cerebral circulation carrying adequate quantities of oxygen and glucose is maintained in this condition. The defect is probably intracellular and may be due to the acidosis or ketosis per se. The metabolism of brain tissue slices is quite sensitive to pH changes and the metabolic depression in diabetic acidosis does show some correlation with arterial pH. A better correlation, however, is found with blood ketone concentrations; and since at least one of these substances (acetoacetate) is capable of causing coma in itself when injected into animals, it seems reasonable to suppose that much of the coma and depressed cerebral metabolism in this condition is due to their presence in excessive amounts. The nature of the cerebral depression underlying uremic coma requires more investigation.
Relationship between depression and diabetes?

“Depression is associated with a 60% increased risk of type 2 diabetes. Type 2 diabetes is associated with only modest increased risk of depression.”

Mezuk, B et al. (2008) Diabetes Care, Vol 31, Number 12
Association between metabolic disturbances and neuropsychiatric disorders:

**Psychiatric disorders**
- Schizophrenia
- Bipolar disorder
- Depression
  - \( \uparrow 60\% \) higher risk of T2D

**Neurodegenerative diseases**
- Alzheimer’s Disease
- Vascular Dementia
- Parkinson’s Disease
- Huntington’s Disease

**Congenital neurodegenerative diseases**
- Prader-Willi
- Alstrom syndrome
- Bardet-Biedl syndrome
- Down’s syndrome
- Louis-Bar syndrome
- Niemann-Pick disease
- Werner syndrome
- Wolfer syndrome
- Woodhouse-Sakati syndrome

**Other congenital disorders**
- Glut I deficiency
- Familial hyperinsulinism
- Kearns-Sayre syndrome
- Klinefelter syndrome
- Feigenbaum syndrome
- Friedreich ataxia
- MELAS syndrome
- Myotonic dystrophy I
- Narcolepsy
- Thiamine responsive megaloblastic anemia syndrome
- Spinocerebellar ataxia 3
- Turner syndrome

\( \uparrow 20\% \text{ will develop metabolic complications} \)

**Bidirectional association!**

\( \uparrow \text{T2D with } \text{diabetes, obesity & insulin resistance} \)

\( \uparrow 7x \) T2D risk

**Antidepressant medication also \( \uparrow \) T2D risk!**

Table adapted from: Kaidanovich-Beilin, O., et al., (2012) F1000 Reports Biology
Prevalence and Correlates of Diabetes in National Schizophrenia Samples

by Lisa Dixon, Peter Weiden, Janine Delahanty, Richard Goldberg, Leticia Postrado, Alicia Lucksted, and Anthony Lehman

Abstract

People with schizophrenia may be at increased risk for Type II diabetes because of the side effects of antipsychotic medication, poorer overall physical health, less healthy lifestyles, and poorer health care. The present study uses data bases collected by the Schizophrenia Patient Outcomes Research Team (PORT) to assess the prevalence and demographic and clinical correlates of diabetes within large populations of persons receiving treatment for schizophrenia. In the Schizophrenia PORT, Medicaid and Medicare data from 1991 and more recent interview data were collected regarding the comorbidity of schizophrenia and diabetes: prevalence, quality of life, physical health, and services utilization and costs. The study found that rates of diagnosed diabetes exceeded general population statistics well before the widespread use of the new antipsychotic drugs. Risk factors for diabetes were similar to those observed in the general population. The linkage of diabetes to poor physical health, medical morbidity, and increased service use and cost requires attention. This study of diabetes in the early 1990s suggests that even before the widespread use of the atypical antipsychotic drugs, diabetes was a major problem for persons with schizophrenia.

Keywords: Schizophrenia, diabetes, antipsychotics, hyperglycemia, health services.


Persons with schizophrenia have a higher risk of T2D independent of antipsychotic medication.
Second Generation Antipsychotics drugs are associated with metabolic disturbances.

Therapeutic mechanism of action is unclear

SGAs
- clozapine
- olanzapine

Metabolic disturbances correlate with efficacy

Persons with schizophrenia have abnormal insulin signaling
Second Generation Antipsychotic Medication (SGAs)

Important Side Effects

Second Generation Antipsychotic Medications (SGAs) are a group of medications used to treat some psychiatric conditions. Some SGAs are FDA-approved for use in the treatment of schizophrenia, acute mania, bipolar disorder and bipolar mania and other mental illness conditions.

SGAs are also referred to as atypical antipsychotics. The term "atypical" refers to the fact that they generally do not cause the same degree of movement side effects that are common to the first generation, or so-called "typical" antipsychotics.

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOZAPINE</td>
<td>Clozaril</td>
</tr>
<tr>
<td>OLANZAPINE</td>
<td>ZYPREXA</td>
</tr>
<tr>
<td>QUETIAPINE</td>
<td>SEROQUEL</td>
</tr>
<tr>
<td>RISPERIDONE</td>
<td>Risperdal</td>
</tr>
<tr>
<td>PALIPERIDONE</td>
<td>Invega</td>
</tr>
<tr>
<td>ARIPIPAZAOLE</td>
<td>Abilify</td>
</tr>
<tr>
<td>ZIPRASIDONE</td>
<td>Geodon</td>
</tr>
</tbody>
</table>

An atypical antipsychotics compound was approved in 2009

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASENAPINE</td>
<td>Saphris</td>
</tr>
</tbody>
</table>

http://www2.nami.org/Content/NavigationMenu/Hearts_and_Minds/Second_Generation_Antipsychotic_Medications.htm
SGAs are not all equal in terms of their risk of heart-related side effects. People living with mental illness should evaluate these side effects when choosing a medication in partnership with their health care provider. First generation antipsychotic medications generally have higher rates of movement disorders (both short- and long-term) and relatively fewer risks of weight gain and diabetes than most of the SGAs.

Examples of first generation antipsychotic medications include:

Note: Brand patents have expired, but these medicines are referred to by both names at times.

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Trilafon</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>Stelazine</td>
</tr>
</tbody>
</table>

http://www2.nami.org/Content/NavigationMenu/Hearts_and_Minds/Second_Generation_Antipsychotic_Medications.htm
Cognitive effects of insulin in the central nervous system

C.R. Park\textsuperscript{a,b,}\textsuperscript{*}

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\textsuperscript{b}Department of Psychology, University of South Florida, Tampa, FL, USA

Received 6 October 2000; revised 4 April 2001; accepted 9 April 2001

Abstract

Evidence has been accumulating recently that the hormone insulin may modulate cognitive activity by acting in the central nervous system. Initially derived from the observation that insulin and insulin receptors are found in specific brain areas, this evidence also includes cognitive assessments of humans in insulin-deficient and insulin-resistant disease states and experimental manipulation of rodent models. Additional support is derived from in vivo and in vitro systems that are used to investigate the neurophysiological basis of learning and memory. This article is a brief review of the literature that suggests a connection between insulin and memory and draws together some of the findings relevant to possible physiological mechanisms for this cognitive effect. Published by Elsevier Science Ltd.

Keywords: Insulin; Memory; Learning; Brain; Diabetes; Neuromodulator; CNS disorders
Insulin is not just in the periphery

Ancient hormone

Invertebrates: neuromodulators

CNS: role in modulating behaviors

Insulin may have a functional role in the brain.
**Insulin sensitive?**

**YES** – they are sensitive to insulin!

The majority of glucose uptake by peripheral tissues is under the control of insulin via the insulin-sensitive glucose transporter, GLUT-4.

It *was* thought that CNS glucose uptake tissue is not dependent on insulin.

New information: hippocampus glucose metabolism is sensitive to application of exogenous insulin!

Some brain areas have insulin receptors that can promote glucose utilization.
What is the source of the insulin in the CNS?

CNS insulin source

Pancreas

Neural Tissue
Option 1: Peripheral insulin crosses BBB

plasma → Transendothelial transport across BBB → CSF

insulin specific transporter
**Option 2: Synthesis of insulin in CNS?**

- Insulin mRNA detected in neural tissue – during development
- Non-specific immunolocalization of insulin in CNS
- Evidence of synthesis may be species dependent