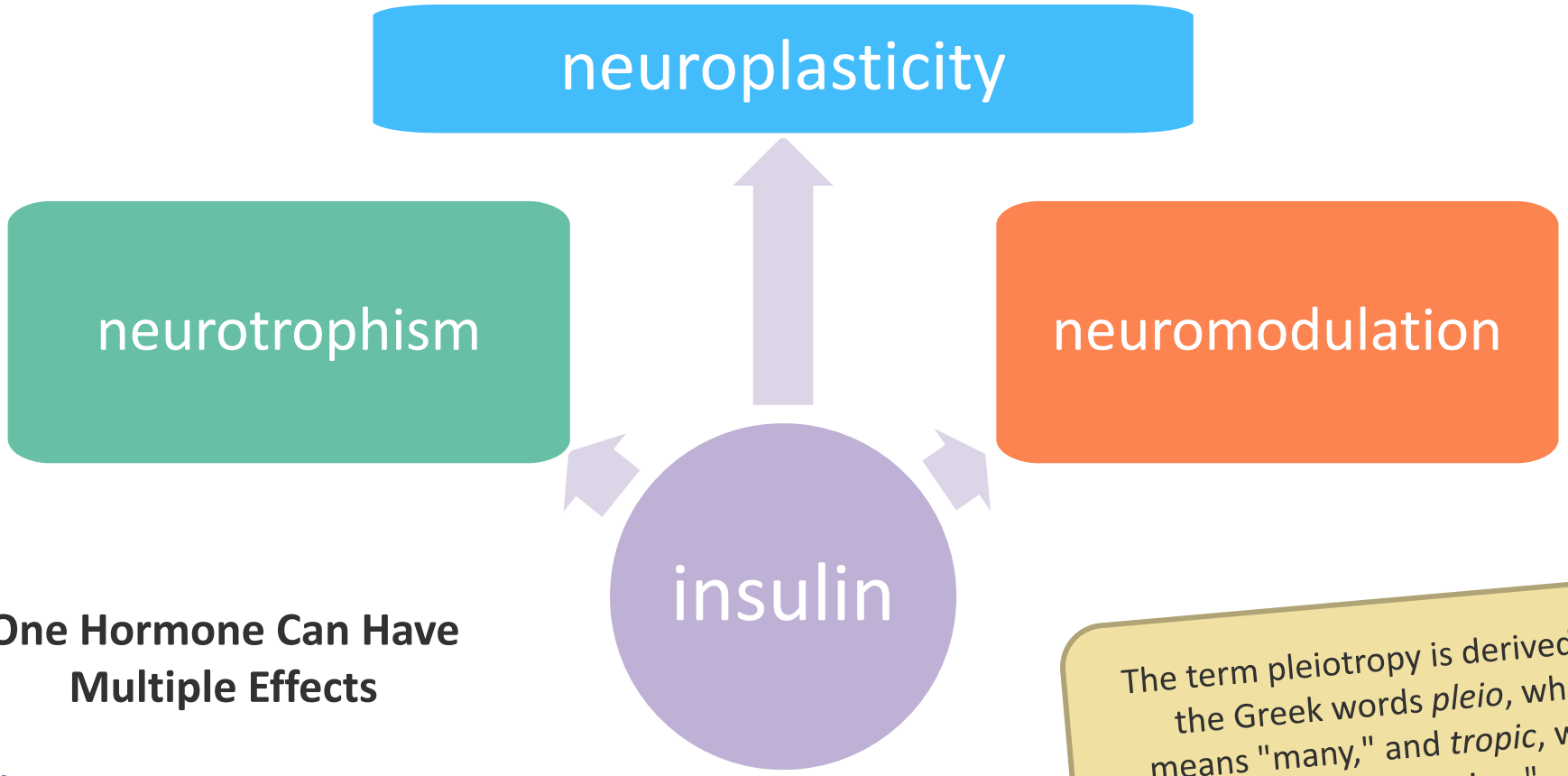
Metabolic Brain Disorders

Mary ET Boyle, Ph.D. -- Department of Cognitive Science -- UCSD

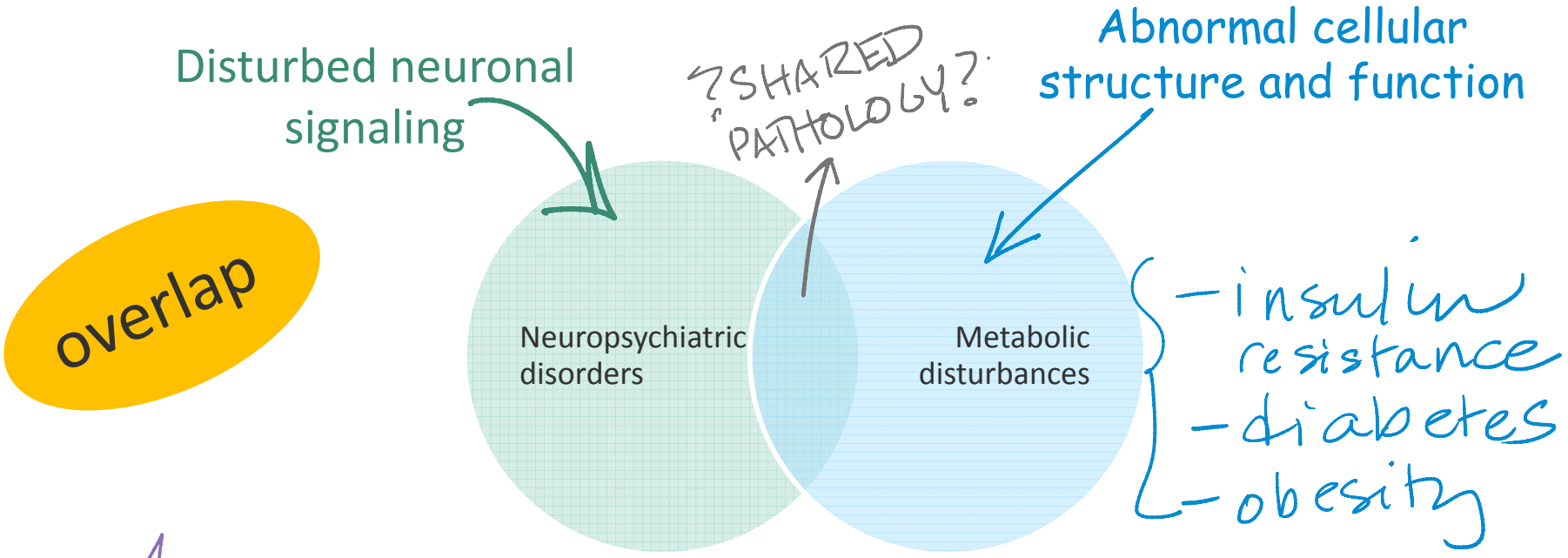
Insulin is a pleiotropic peptide



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:



Abnormal central insulin-signaling → impairs neuronal functioning.

Insulin-mediated effects of brain function:

- Brain function
- Insulin pathways
- Degeneration

What is the relationship between

peripheral glucose metabolism &

psychiatric disorders?

Henry Maudsley 1874

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

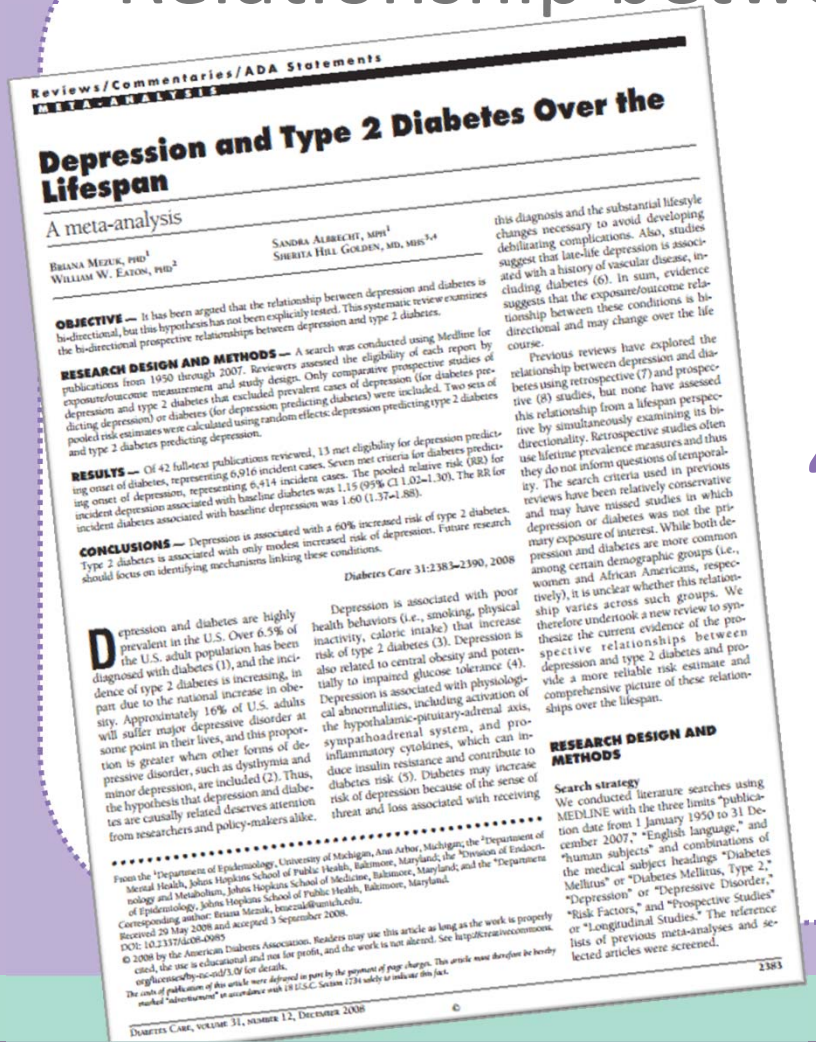
Condition	Mental State	Mean Blood Pressure mm. Hg	Cerebral Blood Flow	Cerebral O_2 Consumption	Cerebrovascular Resistance mm. Hg/cc./100 gm./min.
			cc./100 gm./min.		
Normal[31]	Alert	85	54	3.3	1.6
Schizophrenics[34]	Alert-inaccessible	95	54	3.3	1.7
Schizophrenics, narcosynthesis[34]	Alert-more accessible	95	54	3.3	1.8
Cerebral arteriosclerosis[6]	Confused	121	41	2.8	3.0
Diabetic acidosis[28]	Confused	86	45	2.7	2.1
Insulin hypoglycemia[27]	Confused	86	61	2.6	1.4
Brain tumor[33]	Comatose	122	34	2.5	3.6
Pentothal anesthesia[24]	Comatose	78	60	2.1	1.3
Insulin coma[27]	Comatose	93	63	1.9	1.5
Diabetic coma[28]	Comatose	66	65	1.7	1.1

Kety, S. (1950) American Journal of Medicine

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.[28] 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.

Kety, S. (1950) American Journal of Medicine

Relationship between depression and diabetes?



Reviews/Commentaries/ADA Statements
META-ANALYSIS

Depression and Type 2 Diabetes Over the Lifespan

A meta-analysis

Briana Mezuk, PHD[1]
William W. Eaton, PHD[2]
Sandra Albrecht, MPH[1]
Sherita Hill Golden, MD, MHS[3,4]

OBJECTIVE — It has been argued that the relationship between depression and diabetes is bi-directional, but this hypothesis has not been explicitly tested. This systematic review examines the bi-directional prospective relationships between depression and type 2 diabetes.

RESEARCH DESIGN AND METHODS — A search was conducted using Medline for publications from 1950 through 2007. Reviewers assessed the eligibility of each report by exposure/outcome measurement and study design. Only comparative prospective studies of depression and type 2 diabetes that excluded prevalent cases of depression (for diabetes predicting depression) or diabetes (for depression predicting diabetes) were included. Two sets of pooled risk estimates were calculated using random effects: depression predicting type 2 diabetes and type 2 diabetes predicting depression.

RESULTS — Of 42 full-text publications reviewed, 13 met eligibility for depression predicting onset of diabetes, representing 6,916 incident cases. Seven met criteria for diabetes predicting onset of depression, representing 6,414 incident cases. The pooled relative risk (RR) for incident depression associated with baseline diabetes was 1.15 (95% CI 1.02–1.30). The RR for incident diabetes associated with baseline depression was 1.60 (1.37–1.88).

CONCLUSIONS — Depression is associated with a 60% increased risk of type 2 diabetes. Type 2 diabetes is associated with only modest increased risk of depression. Future research should focus on identifying mechanisms linking these conditions.

Diabetes Care 31:2383–2390, 2008

Depression and diabetes are highly prevalent in the U.S. Over 6.5% of the U.S. adult population has been diagnosed with diabetes (1), and the incidence of type 2 diabetes is increasing, in part due to the national increase in obesity. Approximately 16% of U.S. adults will suffer major depressive disorder at some point in their lives, and this proportion is greater when other forms of depressive disorder, such as dysthymia and minor depression, are included (2). Thus, the hypothesis that depression and diabetes are causally related deserves attention from researchers and policy-makers alike.

Depression is associated with poor health behaviors (i.e., smoking, physical inactivity, caloric intake) that increase risk of type 2 diabetes (3). Depression is also related to central obesity and potentially to impaired glucose tolerance (4). Depression is associated with physiological abnormalities, including activation of the hypothalamic-pituitary-adrenal axis, sympathoadrenal system, and pro-inflammatory cytokines, which can induce insulin resistance and contribute to diabetes risk (5). Diabetes may increase risk of depression because of the sense of threat and loss associated with receiving this diagnosis and the substantial lifestyle changes necessary to avoid developing debilitating complications. Also, studies suggest that late-life depression is associated with a history of vascular disease, including diabetes (6). In sum, evidence suggests that the exposure/outcome relationship between these conditions is bi-directional and may change over the life course.

Previous reviews have explored the relationship between depression and diabetes using retrospective (7) and prospective (8) studies, but none have assessed this relationship from a lifespan perspective by simultaneously examining its bi-directionality. Retrospective studies often use lifetime prevalence measures and thus they do not inform questions of temporality. The search criteria used in previous reviews have been relatively conservative and may have missed studies in which depression or diabetes was not the primary exposure of interest. While both depression and diabetes are more common among certain demographic groups (i.e., women and African Americans, respectively), it is unclear whether this relationship varies across such groups. We therefore undertook a new review to synthesize the current evidence of the prospective relationships between depression and type 2 diabetes and provide a more reliable risk estimate and comprehensive picture of these relationships over the lifespan.

RESEARCH DESIGN AND METHODS

Search strategy

We conducted literature searches using MEDLINE with the three limits "publication date from 1 January 1950 to 31 December 2007," "English language," and "human subjects" and combinations of the medical subject headings "Diabetes Mellitus" or "Diabetes Mellitus, Type 2," "Depression" or "Depressive Disorder," "Risk Factors," and "Prospective Studies" or "Longitudinal Studies." The reference lists of previous meta-analyses and selected articles were screened.

From the [1]Department of Epidemiology, University of Michigan, Ann Arbor, Michigan; the [2]Department of Mental Health, Johns Hopkins School of Public Health, Baltimore, Maryland; the [3]Division of Endocrinology and Metabolism, Johns Hopkins School of Medicine, Baltimore, Maryland; and the [4]Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, Maryland.
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META-ANALYSIS

Depression and Type 2 Diabetes Over the Lifespan

A meta-analysis

"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:

Bidirectional association!

Psychiatric disorders	Neurodegenerative diseases	Congenital Neurodegenerative diseases	Other congenital disorders
Schizophrenia Bipolar disorder Depression	Alzheimer's Disease Vascular Dementia Parkinson's Disease Huntington's Disease	Prader-Willi Alstrom syndrome Bardet-Biedl syndrome Down's syndrome Louis-Bar syndrome Niemann-Pick disease Werner syndrome Wolfram syndrome Woodhouse-Sakati syndrome	Glut I deficiency Familiar 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

2-4X CO-OCCUR WITH DIABETES, OBESITY & INSULIN RESISTANCE

↑ 60% HIGHER RISK OF T2D

associated with T2D & obesity

Metabolic disturbance might be linked to treatment (Clevadopa)

T2D 7X ↑↑

★T2D is an independent risk factor for DEMENTIA!

★ANTIDEPRESSANT MEDICATION ALSO ↑↑ 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

Persons with schizophrenia have a higher risk of T2D independent of antipsychotic medication.

Abstract

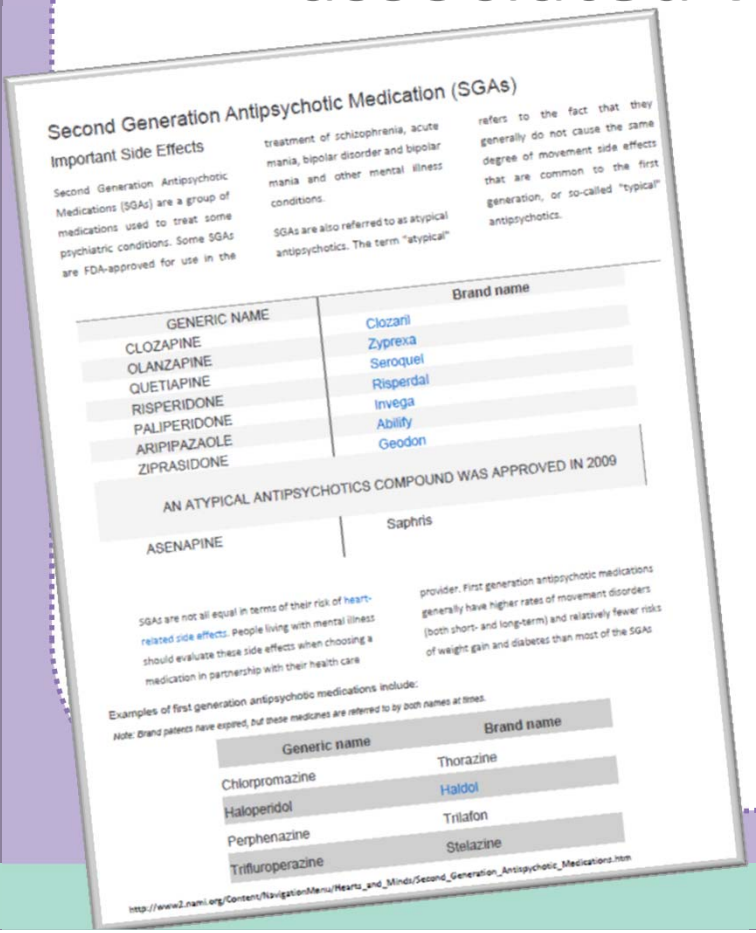
People with schizophrenia may be at increased risk for Type II diabetes because of the side effects of antipsychotic medication, poorer overall physical health, less healthy lifestyles, and poorer health care. The present study uses data bases collected by the Schizophrenia Patient Outcomes Research 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.

***Schizophrenia Bulletin*, 26(4):903–912, 2000.**

Dixon, L., et al , (2000) *Schizophrenia Bulletin,* Vol. 26, No. 4

Second Generation Antipsychotics drugs are associated with metabolic disturbances.



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.

GENERIC NAME	Brand name
CLOZAPINE	Clozaril
OLANZAPINE	Zyprexa
QUETIAPINE	Seroquel
RISPERIDONE	Risperdal
PALIPERIDONE	Invega
ARIPIPAZOLE	Abilify
ZIPRASIDONE	Geodon
AN ATYPICAL ANTIPSYCHOTICS COMPOUND WAS APPROVED IN 2009	
ASENAPINE	Saphris

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.

Generic name	Brand name
Chlorpromazine	Thorazine
Haloperidol	Haldol
Perphenazine	Trilafon
Trifluroperazine	Stelazine

http://www2.nami.org/Content/NavigationMenu/Hearts_and_Minds/Second_Generation_Antipsychotic_Medications.htm

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)

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Generic name	Brand name
Chlorpromazine	Thorazine
Haloperidol	Haldol
Perphenazine	Trilafon
Trifluroperazine	Stelazine

http://www2.nami.org/Content/NavigationMenu/Hearts_and_Minds/Second_Generation_Antispychotic_Medications.htm

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PERGAMON

Neuroscience and Biobehavioral Reviews 25 (2001) 311–323

NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS

www.elsevier.com/locate/neubiorev

Review

Cognitive effects of insulin in the central nervous system

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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.

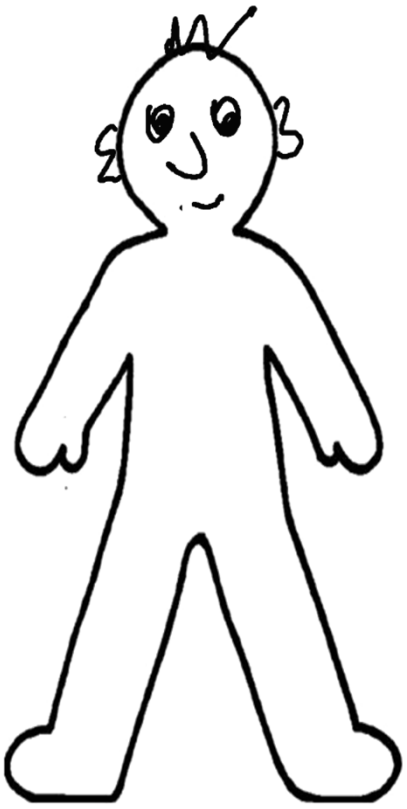
Keywords: Insulin; Memory; Learning; Brain; Diabetes; Neuromodulator; CNS disorders

Insulin is not just in the periphery

Ancient hormone

Invertebrates: neuromodulators

CNS: role in modulating behaviors

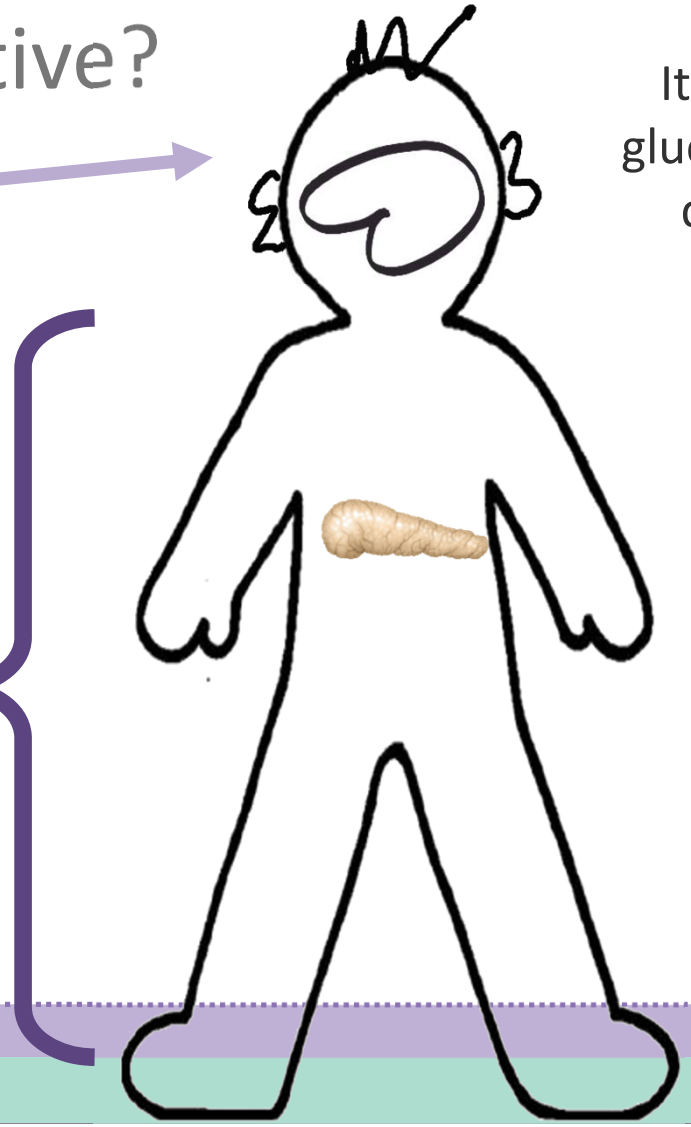


Insulin may have a functional role in the brain.

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

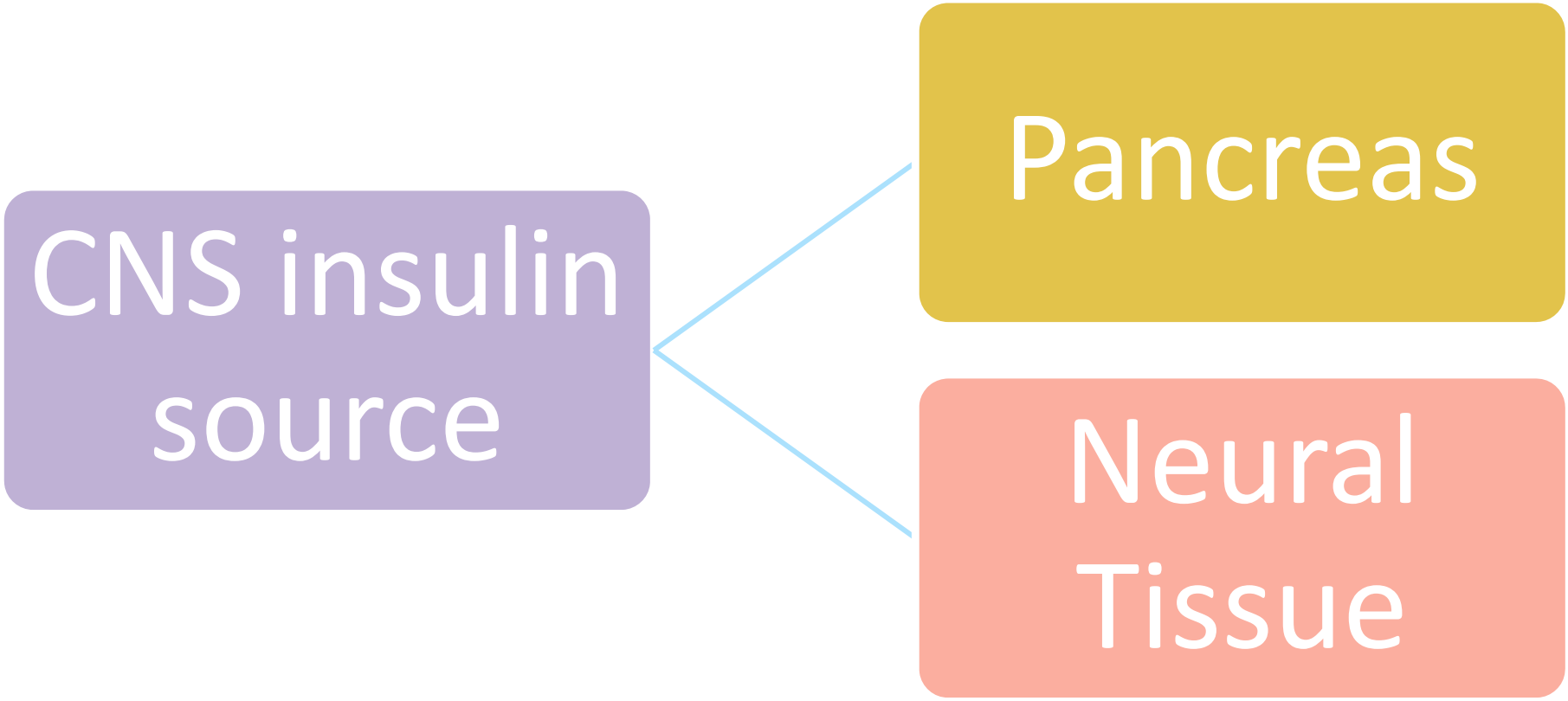


It *was* thought that CNS glucose uptake tissue is not dependent on insulin.

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?



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