Insulin signaling effects on memory and mood

(Review)

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Introduction

Diabetes mellitus is a chronic disease resulting from defects in insulin secretion, insulin action, or both

Long-term diabetes

\[ \text{discrete functional and structural disorders in the central nervous system} \]

Clinical evidence suggests that patients with diabetes have impaired cognitive functions

- cognitive functions \( \rightarrow \) Hippocampus

The hippocampus is an important integration center for learning and memory in the mammalian brain

Hippocampal long-term potentiation (LTP) is the cellular correlate of learning and memory

The goals of this review will be

1. To discuss the impact of hyperglycemia and insulin resistance upon the structure and function of the hippocampus

2. Describe how deficits in hippocampal synaptic plasticity in diabetic subjects may adversely affect cognitive performance and increase neuronal vulnerability for stress-related disorders like depressive illness

Is accelerated brain aging a consequence of diabetes?

- chronic hyperglycemia
  \[ \text{neuroanatomical alterations} \]
  \[ \text{neurochemical changes} \]
  \[ \text{impairments in HPA axis activity} \]
  \[ \text{deficits in plasticity and insulin signaling} \]

- cognitive/behavioral deficits

HPA = hypothalamic-pituitary-adrenal
• Streptozotocin (STZ) diabetic rats (type 1 model) rapidly exhibit dendritic remodeling in the CA3 region of the rat hippocampus.

• Hyperglycemia-mediated morphological changes are more widespread in the hippocampus of STZ rats and redistribution of synaptic proteins that may affect neurotransmission and plasticity.

In the hippocampus of diabetic rodents under conditions of uncontrolled hyperglycemia,

Neuronal apoptosis and suppression of cell proliferation/neurogenesis.

Previous studies

Diabetes-induced

Morphological changes in the hippocampus

Deficits in hippocampal synaptic plasticity

Reversed with insulin replacement.

Insulin receptor expression and signaling: correlation with cognitive function

Hippocampus is a region with high insulin receptor density as well as insulin sensitive glucose transporters (GLUT4).

Insulin improves cognitive performance in humans and animals.

Increases in plasma insulin levels.

Translocation of the GLUT4 to the plasma membrane in the rat hippocampus.

These data support the hypothesis that activation of insulin receptor signaling cascades improves cognitive/behavioral performance.

The relationship between insulin receptor activity and behavioral performance.

In experimental models of diabetes less consistent.

Type 1 diabetes, STZ diabetic rats exhibit behavioral deficits in the water maze task.

Impairments in hippocampal long-term potentiation (LTP).

Other studies have failed to demonstrate deficits in water maze performance in hypoinsulinemic Akita mice.

These different findings may be related to the type of analyses performed.
STZ diabetic rats performed as well as non-diabetic controls in some aspects of water maze performance but more poorly in others.

STZ diabetic rats

Hippocampal IR expression ↓
plasma membrane association of GLUT4 ↓

Impairments in hippocampal IR expression and signaling

deficits in hippocampal-dependent tasks

Behavioral training → ↑ IR signaling in the diabetic rat hippocampus

At least some of the neurological complications of hyperglycemia represent plastic, not permanent, changes.

Behavioral performance & Hippocampal synaptic plasticity in experimental models of type 2 diabetes

Inconsistent findings

→ water maze performance and hippocampal LTP ↓

→ others report that these measures are unaffected

Performance in the water maze is dependent upon locomotor activity

- ↓ muscle mass (type 1 models)
- ↑ adiposity (type 2 models)

Evaluation of learning and memory performance in a task that is less dependent upon locomotor activity such as:

The variable interval delayed alternation (VIDA) task

Type 2 Zucker diabetic rats effectively learn the VIDA task when inter-trial intervals (ITI) are short

When the ITI is lengthened
which is dependent upon intact hippocampal function

Behavioral performance deteriorates in the type 2 rats when compared with their lean littermates

Decreases in IR signaling

Support the hypothesis that

↓ hippocampal IR activities

behavioral deficits in type 2 rodents
Translation of animal studies to the clinical setting

The advent of imaging technologies has confirmed and extended these previous observations.

For example, Magnetic Resonance Imaging (MRI) techniques have not identified cerebral or hippocampal atrophy in type 1 patients. Voxel-Based Morphometry (VBM) revealed decreases in gray matter density in type 1 patients.

Imaging studies in type 2 patients

MRI analyses have identified structural atrophy, particularly in the limbic structures such as the hippocampus and amygdala. Decreases in hippocampal formation volume in type 2 patients have also been identified using a combined MRI/VBM approach. These structural changes are often associated with neuropsychological deficits in type 2 patients.

The complexity of the pathophysiological causes and consequences of diabetes may contribute to the dissimilar findings in clinical studies.

For example, a variety of factors negatively influence the structural and functional integrity of the brain in diabetes patients, including:

- the degree of glycemic control
- the number and severity of hypoglycemic episodes
- the age of onset and the duration of diabetes

Impairments in HPA axis function

In experimental animals, severe prolonged stress or GC administration leads to brain damage associated with hippocampal neuronal loss. Clinical studies have yielded inconsistent findings: HPA axis activity in diabetic patients.

The lifelong complications of hyperglycemia predispose diabetic patients to co-morbidities such as dementia, Alzheimer’s disease (AD), and recurrent depressive illness.

There are striking similarities between the neurological consequences of diabetes and depressive illness:

Decreases in hippocampal formation volume

HPA axis dysfunction, hypercortisolemia, and variety of other endocrine factors may predispose diabetic patients to depressive illness.
Conclusions

The growing obesity and diabetes patient populations

While clinical and pre-clinical studies have failed to reach a consensus

The accumulated data suggest that the neurological complications of diabetes include
• deficits in hippocampal synaptic plasticity
• structural and cognitive deficits

The increased incidence of co-morbidities in diabetic patients, including increased risk for Alzheimer’s disease and depressive illness are less debated

good news for diabetic patients

innovative transplantation strategies

pharmacological treatments

have the potential to significantly reduce or eliminate diabetes related complications

pancreatic islet cell transplantation strategies

for type 1 patients

The advancement of novel drug strategies such as insulin mimetics and incretin mimetics

for the treatment of type 2 diabetes and obesity