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Your Brain on Insulin: From Heresy to Dogma

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Abstract

As recently as 1988, the idea that insulin might regulate cognitive and neural functions was, if not quite heretical, still seen as unlikely. As our ability to measure metabolic and molecular changes in the brain has improved, the hippocampus in particular has been revealed as a primary target for insulin. Today insulin is established as a key regulator of hippocampal fuel supply and a critical component of memory formation and storage within the hippocampus. Brain insulin signaling is a target for therapeutic intervention in patients with neuropsychological conditions such as Alzheimer's disease.

A quarter century covers almost the entirety of some fields—the role of insulin in the brain is one of those. Insulin is a peptide hormone secreted from the pancreas as the primary regulator of blood glucose levels. Despite the brain relying on glucose as its sole fuel, insulin was long thought to play no role in the brain: early studies suggested that insulin did not affect brain glucose use and might not even get into the brain at all. In fact, insulin turns out to be central both to hippocampal glucose metabolism and to memory formation, which are them-selves linked.

The first measurements of insulin crossing the blood–brain barrier were reported in the mid 1980s (Woods et al., 1985); in retrospect, around 1988 a slow but now complete shift began away from the traditional view of the brain as insulin-insensitive. Receptors for insulin were identified in several brain regions, especially in the olfactory bulb and hypothalamus but also throughout the limbic system. Initial studies focused on a role for insulin in regulation of feeding via action as a satiety signal in the hypothalamus (Baskin, Figlewicz, Woods, Porte, & Dorsa, 1987). However, the last decade has seen a shift in attention to insulin's role in the hippocampus and cognitive function (McNay & Recknagel, 2011; Sherwin, 2008).

Methodological Improvements

Increased understanding of insulin's role in the brain, and particularly in enhancement of hippocampal memory processing, has been accompanied and made possible by improvements in analysis in two areas: measurement of brain glucose metabolism and identification of specific proteins upregulated by insulin within the brain.

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Brain glucose metabolism

Twenty-five years ago, the seminal work of Louis Sokoloff had begun the first measurements of brain glucose metabolism (Sokoloff et al., 1977). At the time, the brain was still believed to have a continuous excess of glucose supply (Lund-Andersen, 1979), and the first demonstration that glucose could be an endogenous memory enhancer had only just been reported (Gold, 1986). It would not be until 2000 that animal studies would directly show that hippocampal memory formation is constrained by glucose supply: Difficult hippocampally mediated cognitive tasks cause local glucose depletion in the fluid surrounding hippocampal neurons that correlates with impaired task performance (McNay, Fries, & Gold, 2000). Moreover, provision of additional glucose both reverses this depletion and improves memory performance.

Data from human studies are consistent with this finding: Providing additional glucose enhances memory task performance when the participant finds the memory task to be difficult, so that additional fuel will benefit the active hippocampal neurons. Thus, mechanisms potentially able to stimulate brain glucose metabolism have assumed increased importance as enhancers of memory processing. Insulin is just such an effector. Outside the brain, insulin acts to move glucose from the blood into fat and muscle cells for storage, using a specific insulin-regulated glucose transport protein (glucose transporter 4, or GluT4). Inside the brain, this same protein is found on neurons in the hippocampus, and insulin uses it to move glucose into neurons and provide extra fuel when needed (i.e., when hippocampal neurons are more active because they are encoding memories into patterns of potentiated synapses). Although early whole-brain measurements of glucose uptake failed to show any effect of insulin, more recent work with better resolution has confirmed that glucose metabolism increases in response to insulin in specific brain regions where GluT4 is found, such as the hippocampus.

Other mechanisms: Protein and synaptic measurements

Beyond glucose metabolism, insulin was already known in 1988 to be able to alter neuronal firing rates, albeit with data only *in vitro* or, at best, in anesthetized animals. As methods improved, subsequent studies confirmed that insulin in the hippocampus directly regulates both excitatory and inhibitory neuronal transmission and can also modulate synaptic plasticity—thus acting as a direct regulator of both GABAergic (inhibitory) and glutamatergic (excitatory) receptors at the synapse. Further, metabolism of glucose produces adenosine triphosphate (ATP), which binds to and closes ATP-gated potassium channels on hippocampal neurons, thus depolarizing them and making them more easily triggered to fire. Overall, insulin not only provides fuel for neurons but also modulates some neurons' firing rate and likely enhances memory formation by increasing hippocampal plasticity.

Insulin as Cognitive Enhancer

Two studies in the late 1990s helped to bring a potential role for insulin in hippocampal cognitive processes to the foreground. First, prescient work showed that memory impairments in human patients with Alzheimer's disease might be improved by combined insulin-glucose treatment (Craft et al., 1996)—the first demonstration that insulin could

improve memory performance. A couple of years later, water-maze memory training in rats was shown to specifically increase hippocampal insulin receptor activity (Zhao et al., 1999), which confirmed insulin signaling as a mechanism involved in memory processing in the hippocampus. At the same time, evidence was accumulating for insulin production and release within the brain, an idea that had been suggested well before 1988 and then discarded but turned out to be likely correct (McNay & Recknagel, 2011). Taken together, the data strongly suggested that brain insulin might be an endogenous enhancer of hippocampal and/or memory processes.

This possibility was confirmed in a series of behavioral studies. In 2000, delivery of insulin into the brain's ventricles was shown to enhance memory in rats (Park, Seeley, Craft, & Woods, 2000). Then, insulin given intranasally was shown to improve memory in humans (Benedict et al., 2004). By 2010, we showed that direct intrahippocampal insulin administration enhanced both memory and local metabolism. Perhaps more important, specific pharmacological blockade of endogenous hippocampal insulin markedly impaired both metabolism and spatial memory (McNay et al., 2010).

The overall conclusion is that insulin signaling, via regulation of hippocampal glucose metabolism and neuronal firing, is a vital component of hippocampal memory processes.

Disease States: Type 2 Diabetes and Alzheimer's Disease

Confirming the importance of brain insulin signaling, animal models of diet-induced insulin resistance show marked cognitive impairment accompanied by impaired hippocampal glucose metabolism (McNay et al., 2010). In humans, clinical studies from 1997 (Leibson et al., 1997) onwards have shown that insulin-resistant, Type 2 diabetes (T2DM) causes cognitive impairment, especially for hippocampally mediated tasks. This finding was initially controversial, but was clearly established by the mid 1990s (Biessels, Kappelle, Bravenboer, Erkelens, & Gispen, 1994). Moreover, T2DM patients have an increased risk of Alzheimer's disease (de la Monte, 2009). The link between T2DM and Alzheimer's disease has been the focus of much recent work. Brains of patients with Alzheimer's disease have impaired insulin signaling that likely explains much of both the hippocampal hypometabolism and cognitive impairment that characterize Alzheimer's disease—some have dubbed Alzheimer's disease as “Type 3 diabetes” (Steen et al., 2005). Drugs that improve insulin signaling have been used in clinical trials for Alzheimer's disease (Watson et al., 2005) and intranasal insulin is currently being tested in similar trials.

Summary

Twenty-five years ago, insulin was believed to be mostly unimportant to the brain, with perhaps a small role in hypothalamic hunger sensing. Today, there is wide acceptance of insulin as a central regulator of neural function and hippocampal metabolism and as a key player in multiple neuropsychological conditions. As APS hits the quarter century, it is a fitting time to look back on this paradigm shift.

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