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Stop signs in hippocampal insulin signaling: the role of insulin resistance in structural, functional and behavioral deficits

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Abstract

In peripheral tissues insulin activates signaling cascades to facilitate glucose uptake from the blood into tissues like liver, muscle and fat. While insulin appears to play a minor role in the regulation of glucose uptake in the central nervous system (CNS), insulin is known to play a major role in regulating synaptic plasticity in brain regions like the hippocampus. The concept that insulin regulates hippocampal neuroplasticity is further supported from animal models of type 2 diabetes (T2DM) and Alzheimer's disease (AD). The goal of this review is to provide an overview of these studies, as well as the studies that have examined whether deficits in hippocampal insulin signaling are amenable to intervention strategies.

Introduction

Insulin signaling in the CNS

Insulin is synthesized by pancreatic β cells and is released into circulation in response to increases in plasma glucose levels. Once released into circulation, insulin binds to and activates insulin receptors to promote glucose uptake and utilization in peripheral tissues such as liver, muscle and fat. While the central nervous system was once viewed as an insulin-insensitive organ, studies by Woods and coworkers demonstrated that intracerebroventricular administration of insulin suppressed food intake and body weight in a dose-dependent manner [1]. These seminal observations shed light on a role for insulin in the CNS and ultimately lead to a greater understanding of the role of hypothalamic peptide systems in the regulation of food intake, body weight and metabolism [2;3]. Beyond the hypothalamus, it is clear that the actions of insulin extend into other regions of the CNS including the hippocampus. Insulin receptors are expressed in the hippocampus [4;5] and activate similar signaling cascades as have been identified in peripheral tissues [6] In this

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regard, insulin crosses the blood-brain barrier (BBB) by a carrier facilitated process [7] and binds to insulin receptors expressed in the CNS, including the hippocampus. The insulin receptor is a heterotetrameric protein complex consisting of 2 α subunits that provide the insulin binding site and the membrane spanning β subunits that stimulate autophosphorylation of the β subunits. This initiates several signaling cascades, including the PI3-kinase/Akt pathway and MAPK/Erk signaling pathway (See Figure 1). It is important to note that these insulin-stimulated signaling cascades exhibit significant cross-talk and also that these signaling pathways are not the exclusive domain of insulin receptor activation. For example, leptin also facilitates hippocampal synaptic plasticity through activation of these pathways [8]. Conversely, hippocampal insulin resistance (i.e. 'stop signs' in insulin signaling; Figure 1) contributes to neuroplasticity deficits in T2DM, obesity and AD. The sections below will describe causes and consequences of this biphasic relationship between hippocampal insulin signaling and neuroplasticity, with a particular emphasis on how hippocampal insulin resistance contributes to the structural, functional and behavioral deficits observed in T2DM, obesity and AD.

Insulin, cognition and behavior

Clinical and preclinical studies support the hypothesis that insulin is a critical regulator of structural and functional plasticity in the hippocampus, including cognitive function. In this regard, studies by Alkon and co-workers demonstrated that spatial learning increases insulin receptor expression and signaling in the rat hippocampus [9]. In addition, a number of studies have reported that increasing hippocampal insulin levels increases behavioral performance in control rats. For example, intracerebroventricular insulin administration improves behavioral performance in the passive avoidance task [10], while intrahippocampal administration of insulin improves spatial learning and memory in control rodents [11-13]. Intranasal insulin administration also increases both short and long term memory retrieval in mice [14]. Interestingly, these studies also demonstrated that activation of hippocampal insulin signaling participates in the memory-enhancing properties of insulin [11] and that increasing brain insulin levels does not impact peripheral glucose metabolism [12;14]. These rodent studies correlate nicely with clinical studies demonstrating that the cognitive-enhancing effects of intranasal insulin are not associated with changes in peripheral glucose homeostasis in humans [15].

Stop signs in CNS insulin signaling

The accumulated data from both clinical and preclinical studies support the hypothesis that hippocampal insulin resistance contributes to neuroplasticity deficits in T2DM, obesity and AD. For example, deficits in hippocampal insulin receptor signaling (i.e. hippocampal insulin resistance) have been identified at each step in this cascade, including impairments in BBB transport of insulin [16-18], reduced insulin-stimulated phosphorylation events [19-22] and reduced trafficking of insulin sensitive glucose transporters [20;23;24]. In addition, increased serine phosphorylation of insulin receptor substrate 1 (IRS-1), which is a hallmark feature of peripheral insulin resistance, is also observed in the hippocampus of mice fed a high fat diet [22]. Collectively, these studies demonstrate that deficits in insulin receptor signaling can occur at all steps in the cascade, from the transport of insulin into the CNS to the level of transcription. More importantly, these results support the hypothesis that

hippocampal insulin resistance is a keystone mechanistic mediator of neuroplasticity deficits observed in experimental models of T2DM and obesity.

Cellular and Molecular underpinnings of hippocampal insulin resistance

Diabetes and obesity are characterized by a wide variety of metabolic and endocrine abnormalities, many of which may elicit hippocampal insulin resistance (Figure 2). This includes dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis that is characterized by elevated levels of glucocorticoids [23;25]. Our previous studies have demonstrated that exposure to glucocorticoids elicits peripheral insulin resistance, as well as hippocampal insulin resistance [20]. Additional support is provided by Stranahan and coworkers, who showed that deficits in hippocampal synaptic plasticity observed in *db/db* mice could be reversed by adrenalectomy and replacement with physiological levels of glucocorticoids [26]. In addition to HPA axis dysregulation, impairment in mitochondrial function leading to increased production of reactive oxygen species (ROS) and lipid peroxidation products is also suggested to contribute to the neurological complications associated with metabolic disorders [27], including the development of hippocampal insulin resistance [28]. Pro-inflammatory cytokines may also elicit hippocampal insulin resistance; indeed, chronic mild inflammation is a characteristic feature of metabolic disorders [29]. In metabolic disorders associated with increases in adiposity, it is proposed that macrophages infiltrate adipocytes thereby leading to increases in the production and secretion of pro-inflammatory cytokines. Increases in pro-inflammatory cytokines are proposed to transduce their signal across the BBB and induce neuroinflammation. In support of this hypothesis, immunohistochemical indices of increased microglial activation and increases in pro-inflammatory cytokines are observed in the hippocampus of experimental models of T2DM and obesity [30;31]. More recent studies have identified a critical role for IL-1 signaling in the behavioral deficits associated with obesity and diabetes phenotypes [32]. Interestingly, neuroinflammation-induced insulin resistance has also been proposed as a potential mechanism that links metabolic disorders with AD [33]. Amyloid β oligomers ($A\beta O$) may similarly link insulin resistance in T2DM with AD. In this regard, intrahippocampal $A\beta O$ administration decreases spatial memory performance [34] and mechanistically these impairments in spatial learning are proposed to result from $A\beta O$ -mediated decreases in hippocampal insulin receptor expression and signaling [34,35,36]. While it is likely that these factors also act more directly to impair hippocampal synaptic plasticity, these studies identify HPA axis dysregulation, mitochondrial dysfunction, neuroinflammation and $A\beta O$ as factors that elicit hippocampal insulin resistance.

Behavioral consequences of hippocampal insulin resistance

The concept that hippocampal insulin resistance contributes to neurobehavioral deficits is supported by rodent models of insulin resistance. This includes studies in rodents fed a high fat diet (HFD), experimental models of T2DM/obesity (such as Zucker rats, *db/db* and *ob/ob* mice) and molecular approaches to reduce brain insulin receptor expression. Behavioral deficits in hippocampal-dependent learning are consistently observed in these experimental models of T2DM and obesity [28], including deficits in spatial learning in the water maze [37-40], object recognition testing [26;41], discrimination testing [42;43], contextual fear conditioning [44] and the variable interval delayed alternation task [23;45-47]. In addition to

deficits in learning and memory tasks, increases in depressive-like behaviors and anxiety-like behaviors are observed in animal models of T2DM and obesity [48-51]. These findings are consistent with clinical observations that patients with metabolic disorders exhibit cognitive deficits [52] and also have increased risk of developing neuropsychiatric disorders like depressive illness [53;54]. Importantly, these studies support the concept that hippocampal insulin resistance contributes to deficits in hippocampal-dependent function.

Structural and functional consequences of hippocampal insulin resistance

Additional studies have begun to identify the structural and functional neuroplasticity deficits that may contribute to the behavioral deficits observed in experimental models of insulin resistance, including decreases in neurogenesis in the dentate gyrus [55;56], decreases in spine density [57], alterations in synapse formation [44] and decreased BBB integrity [58]. Importantly, these structural changes are associated with behavioral deficits in diabetes/obesity phenotypes [38;39;43;44]. Similarly, functional deficits in hippocampal synaptic transmission, specifically impairments in stimulus-evoked long term potentiation (LTP), are associated with spatial memory deficits in experimental models of insulin resistance, including Zucker rats [37;40], *db/db* mice [26;40] and rodents fed a high fat diet [38]. Insulin receptor haploinsufficient (i.e. *IR*^{+/-}) mice also exhibit deficits in LTP that are accompanied by spatial learning deficits [41]. These electrophysiological deficits are likely driven in part by alterations in glutamate receptor expression and subunit composition (For reviews see [59;60]). Histochemical features normally associated with AD-like pathology, such as hyperphosphorylated tau protein, are also observed in the hippocampus of rodents with insulin resistance [61-64], which provides another example of where the causes and consequences of insulin resistance may overlap in AD and T2DM.

Causal relationship for hippocampal insulin resistance and neuroplasticity deficits

While these studies involving experimental models illustrate that hippocampal insulin resistance is correlated with structural, functional and behavioral deficits, they cannot demonstrate a causal link between hippocampal insulin resistance and these neuroplasticity deficits. As noted above, experimental models of T2DM and obesity exhibit a wide array of metabolic and endocrine changes in addition to insulin resistance, including leptin resistance, glucose intolerance, HPA axis dysregulation and increases in pro-inflammatory cytokines. Moreover, the key loci of insulin resistance that mediate hippocampal neuroplasticity deficits in diabetes/obesity phenotypes remain unclear. More simply, does peripheral insulin resistance, CNS insulin resistance or a combination of peripheral and central insulin resistance contribute to hippocampal neuroplasticity deficits in metabolic disorders like T2DM? To address this issue, we recently developed an animal model of hippocampal-specific insulin resistance. Using virus-mediated gene transfer, we downregulated insulin receptor expression in the hippocampus without affecting hypothalamic insulin receptor expression. In addition, rats with hippocampal-specific insulin resistance did not exhibit changes in body weight, body adiposity or peripheral insulin sensitivity. However, rats with hippocampal-specific insulin resistance exhibited changes in glutamate receptor subunit expression, decreases in stimulus-evoked LTP and impairments in spatial learning [65••]. These results demonstrate that hippocampal insulin resistance may occur independent of peripheral insulin resistance and glucose dysregulation and supports

the concept that hippocampal insulin resistance contributes to the development of cognitive deficits observed in patients with metabolic disorders like T2DM and obesity.

Restoration of hippocampal insulin signaling

Restoration of insulin signaling has shown promise in reversing hippocampal neuroplasticity deficits in rodents with insulin resistance. For example, while insulin sensitivity was reduced in diet-induced obese rats provided a high fat diet, higher doses of intrahippocampal insulin effectively reversed spatial learning in this model of insulin resistance [11]. Several studies have also examined the ability of anti-diabetic drugs to reverse hippocampal synaptic plasticity deficits, with mixed results. Specifically, the PPAR- γ ligand rosiglitazone reversed HFD-induced deficits in spatial memory [66] while metformin administration did not rescue operant learning behavioral deficits in HFD rats [67]. Studies aimed at increasing CNS activity of the incretins (i.e. glucagon-like peptide and glucose dependent insulinotropic polypeptide) have yielded more consistent findings. In this regard, incretin analogs restore brain insulin activity and behavioral performance in experimental models of insulin resistance [68-70]. Similarly, inhibition of dipeptidyl peptidase-4 activity, which is responsible for incretin degradation, reversed HFD-induced decreases in hippocampal insulin signaling and impairments in spatial learning [71]. Collectively, these pharmacological approaches support the concept that restoration of behavioral performance in experimental models of insulin resistance involves enhancement of hippocampal insulin activity.

Conclusions and translational perspectives

While this review has focused on experimental models of diabetes and obesity, these findings provide insight into the observations in patients with metabolic disorders. Indeed, structural and functional deficits are observed in the hippocampus of patients with insulin resistance, including cognitive dysfunction [28]. These rodent studies also support the concept that activation of hippocampal insulin signaling contributes to the pro-cognitive effects of intranasal insulin administration in normal healthy adults [72;73] in T2DM patients [74;75••] and in AD patients [76;77]. Similarly, the pro-cognitive effects of the incretin analogs may result at least in part from the ability of these compounds to cross the BBB and activate hippocampal incretin signaling to promote cognition in patients with metabolic disorders [78;79]. Increased physical activity [57;80;81] and weight loss approaches [82-84] also restore behavioral performance in rodent models of T2DM and obesity, thereby supporting data indicating that lifestyle interventions enhance cognitive performance in patients with metabolic disorders. This includes aerobic exercise [85;86] and weight loss achieved through bariatric surgical procedures [87•]. While these lifestyle approaches improved peripheral insulin sensitivity in these patient populations, it remains to be determined whether the pro-cognitive effects of these interventions involves enhancement of hippocampal insulin signaling. However, if the preclinical studies are truly 'translatable', the rodent studies support the hypothesis that restoration of hippocampal insulin signaling is responsible for improved cognitive performance in these clinical settings. More importantly, these studies illustrate that pharmacological and lifestyle

approaches represent promising treatment strategies that have the potential to attenuate or reverse cognitive deficits in T2DM, obesity and AD.

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Highlights

- Insulin signaling in the central nervous system (CNS) facilitates cognition
- CNS insulin resistance (IR) reduces cognition and neuroplasticity
- Hippocampal IR impairs cognition and neuroplasticity independent of peripheral IR
- Restoration of hippocampal insulin activity improves cognition and neuroplasticity

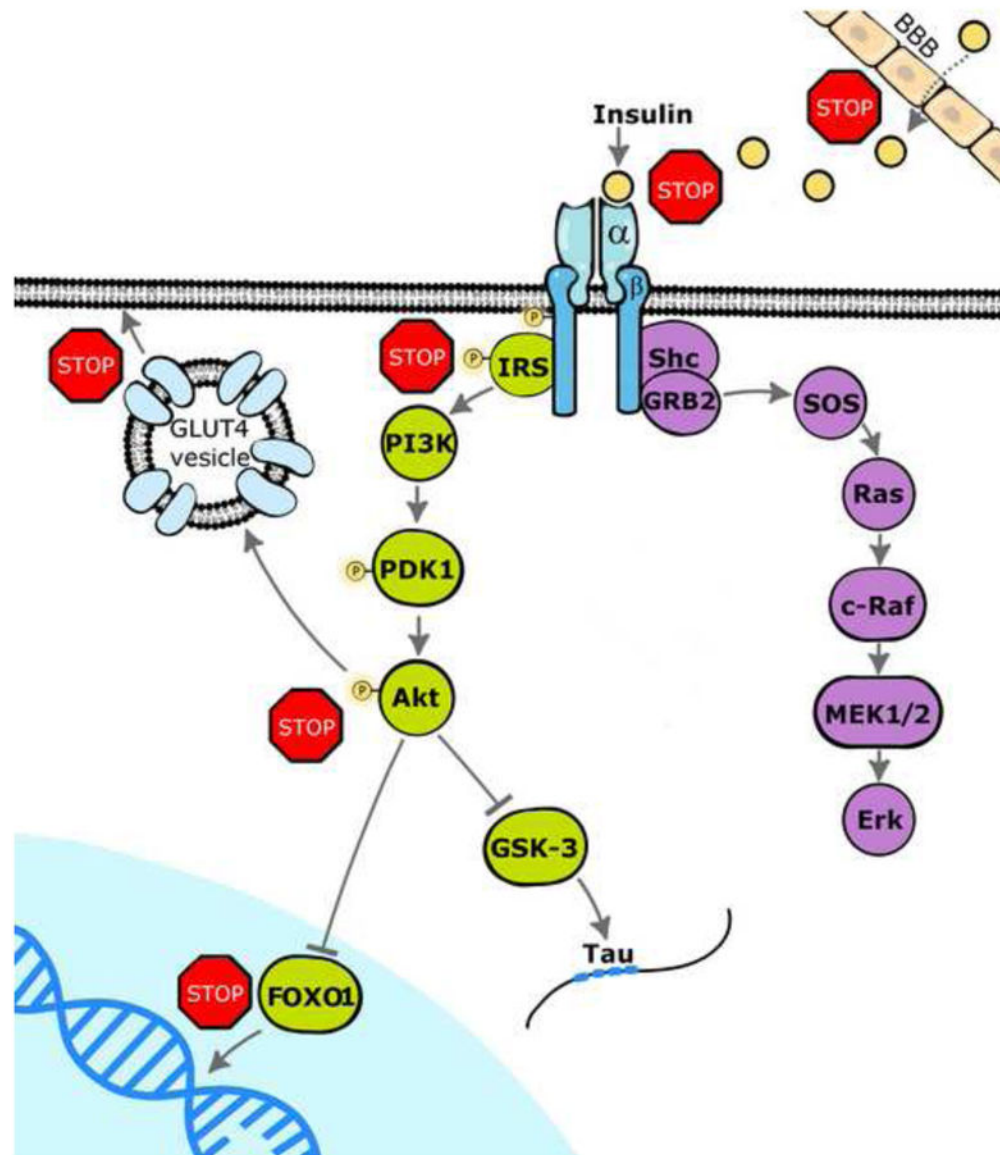


Figure 1. Insulin receptor signaling in the hippocampus

Insulin crosses the blood brain barrier (BBB) via a carrier facilitated process to activate insulin receptors in the CNS and stimulate similar signaling cascades as has been described in peripheral tissues such as skeletal muscle and adipose tissue. These insulin signaling cascades diverge following autophosphorylation of the β subunits of the insulin receptor and include the MEK/Erk pathway and the PI3/Akt pathway. Dysregulation of these pathways may occur at several sites (shown as Stop signs) and in doing so contribute to the development of hippocampal insulin resistance, including impaired BBB transport of insulin, decreased expression and/or activity of the insulin receptor, as well as modulation of the phosphorylation state of insulin receptor substrate (IRS) proteins. Decreased insulin-stimulated phosphorylation of Akt will also impact several downstream components of insulin signaling, including the trafficking of the insulin-sensitive glucose transporter GLUT4 and the activity of GSK-3 β , which regulates the phosphorylation state of the

microtubule associated protein Tau and the activity of FOXO1 family of transcription factors. Figure adapted from [28].

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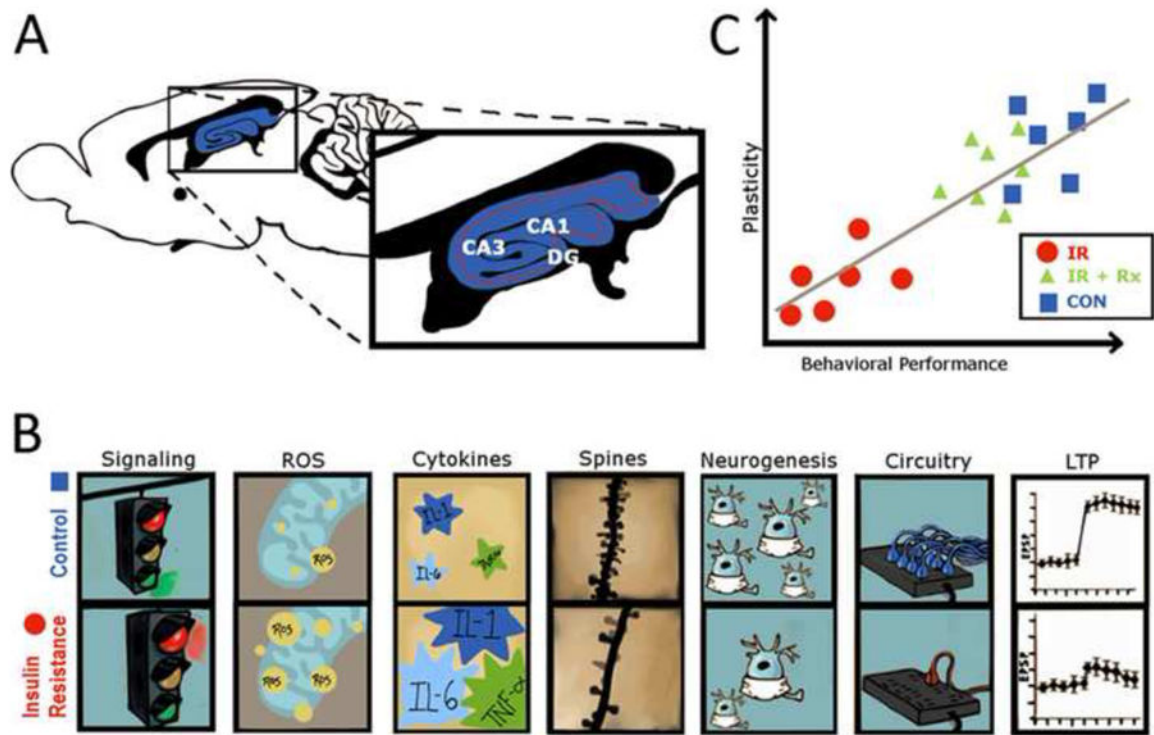


Figure 2. Hippocampal neuroplasticity deficits in experimental models of IR: causes and consequences

In experimental models, the complications of peripheral insulin resistance extend to the central nervous system and elicit neuroplasticity deficits in the hippocampus, including impairments in the dentate gyrus (DG) and the CA1 and CA3 regions of Ammon's Horn (Panel A). An important mechanism in hippocampal neuroplasticity deficits is the development of hippocampal IR, which results from a combination of decreases in BBB transport of insulin and insulin receptor signaling (Panel B). The cellular underpinnings of hippocampal IR are also likely to include mitochondrial dysfunction leading to increased production of reactive oxygen species (ROS) and neuroinflammation, including increased levels of pro-inflammatory cytokines. The consequences of hippocampal IR include morphological changes (decreases in spine density and neurogenesis and disruption of neuronal circuitry), as well as deficits in synaptic transmission (LTP). While these IR-induced hippocampal neuroplasticity deficits are associated with impairments in the performance of hippocampal-dependent behaviors (Panel C), a variety of intervention strategies are known to effectively restore neuroplasticity in models of hippocampal IR. See text for details.