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The Role of Insulin Resistance and Glucose Metabolism Dysregulation in the Development of Alzheimer´s Disease

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ABSTRACT

Alzheimer´s disease is a chronic neurodegenerative disorder affecting millions of people worldwide, characterized by a progressive decline in cognitive functions. Factors involved in the pathogenesis of Alzheimer´s disease include metabolic alterations such as insulin resistance and hyperglycemia, both of which are also hallmarks of type-2 diabetes mellitus. The accumulation of β-amyloid peptides in the brain of Alzheimer´s patients is responsible in part for the neurotoxicity underlying the loss of synaptic plasticity that triggers a cascade of events leading to cell death. A large number of studies revealed the key role of the hippocampus and cerebral cortex in the memory and learning deficits of Alzheimer´s disease. Although ample evidence suggests a link between altered insulin action, the dysregulation of glucose metabolism, and β-amyloid accumulation in animal models and humans with Alzheimer´s, no supporting evidence was available. In this article, we review the potential toxic effects of β-amyloid in the hypothalamus, a brain center involved in the control of insulin action and glucose metabolism. Furthermore, we discuss our recent studies unraveling a novel neurotoxic action of β-amyloid that perturbs hypothalamic glucoregulation, leading to increased hepatic glucose production and hyperglycemia. These findings provide evidence for a link between β-amyloid toxicity and altered glucose metabolism. (REV INVES CLIN. 2016;68:53-8)

Key words: Alzheimer´s. Diabetes. Amyloid peptide. Glucose metabolism. Insulin resistance. Hypothalamus. Liver.

THE ROLE OF β-AMYLOID PEPTIDES IN ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia in elderly people. It is characterized by a progressive loss of cognitive abilities including a pronounced memory deficit. Neuropathological analysis of AD brains shows extensive cortical atrophy caused by severe neuronal loss. At the histological level, hallmarks of the disease are the presence of neurofibrillary tangles and neuritic plaques surrounded by extensive areas of inflammation (astrogliosis and microglial activation), mainly the cerebral cortex and hippocampus[1]. The

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principal constituent of the neurofibrillary tangles is the cytoskeletal protein tau in its hyperphosphorylated form. Neuritic plaques instead, consist of abnormal depositions of β-amyloid (Aβ) peptides of varying length, predominantly the 40 and 42 amino acid residue peptides known as $A\beta_{1-40}$ and $A\beta_{1-42}$, respectively, surrounded by dystrophic neurites. Aβ peptides are produced after proteolytic cleavage of the Aβ precursor protein (AβPP) through the action of the β- and γ-secretases in the so-called amyloidogenic pathway. In contrast, in the non-amyloidogenic pathway the action of α- and γ-secretases on AβPP prevents the production of Aβ peptides[2-4] (Fig. 1).

Extensive evidence has demonstrated the neurotoxic effect of Aβ peptides on synaptic transmission and neuronal plasticity in experimental models *in vitro* and *in vivo*. For example, overproduction of Aβ in dendrites and axons not only reduces the number of synapses but also their plasticity[5,6]. Transgenic mouse models of AD revealed a marked decrease in the density of dendritic spines as well as severe disturbances in neurotransmission, resulting in altered neuronal plasticity[7,8]. These alterations in dendritic spines clinically correlate with symptoms in AD patients[9]. The neurotoxic effects of Aβ peptides are more severe and harmful when they are caused by Aβ soluble oligomers since these block long-term synaptic potentiation, producing severe damage of synaptic plasticity with the consequent negative impact on memory and learning[10,11]. The accumulation of abnormal fibrillary deposits of Aβ or their soluble forms leads to permanent synaptic alterations in the brain thus impacting AD progress.

In vivo rodent experimental models have been widely used to understand the neurotoxic mechanisms of Aβ peptides and their key role in the neurodegenerative damage leading to dementia in AD[12,13]. Studies of chronic infusions of Aβ into the cerebral ventricles of rats showed a pattern of extensive neuronal degeneration and death[14], alterations in hippocampal synaptic transmission and plasticity[15], and a deficit in the levels of neurotransmitters, including acetylcholine, dopamine, and certain neuropeptides[16,17]. These changes are similar to those observed in AD patients and are highly associated with behavioral alterations. Studies on the effects of co-infusing Aβ in the hippocampus of rodents have demonstrated a severe behavioral deficit of spatial memory[18-20]. These pharmacological interventions have been useful in the study of the effects of Aβ peptides on memory and learning, similar to those observed in AD patients.

THE HYPOTHALAMUS AND ALZHEIMER'S DISEASE

The neuropathology of AD affects cortical as well as subcortical structures of the central nervous system (CNS). Neuritic plaques observed in AD patients are distributed predominantly in the hippocampus and neocortex where dense deposits of Aβ peptides are observed[21]. Morphological studies using immunohistochemical methods have identified a kind of neuritic plaque called diffuse or amorphous plaque in the hypothalamus of patients with AD. Diffuse plaques are formed by deposits of fine fibers of Aβ, where dystrophic dendrites around the plaques and an Aβ dense center are not present as observed in the classical form of neuritic plaques[22]. However, the presence of neuritic plaques with a much lower density than those found in the hippocampus or entorhinal cortex have been observed in the hypothalamus of humans affected with AD[23]. In the hypothalamus, the distribution of diffuse plaques is wider than that of neurofibrillary tangles. Postmortem studies in the brains of AD patients have shown that diffuse plaques are distributed from the caudal region of the pre-optical area to the pre-mammillary region of the hypothalamus, including the medial and lateral region. This is in contrast with the distribution of neurofibrillary tangles whose distribution is restricted to the lateral and posterior region of the hypothalamus[24,25]. Only the region of the supraoptic nucleus and the magnocellular part of the paraventricular nucleus of the hypothalamus appears to be free of diffuse plaques and neurofibrillary tangles[25].

THE ROLE OF THE MEDIOBASAL HYPOTHALAMUS IN THE REGULATION OF INSULIN ACTION

The regulation of insulin action and glucose metabolism is an extremely complex function that requires the synchronized communication between various systems in order to integrate biochemical, hormonal, and neurogenic signals arising in peripheral tissues and organs such as the liver, skeletal muscle, or adipose tissue. These signals are relayed to the brain

areas responsible for the control of food intake, body weight, and energy metabolism[26,27]. Circulating nutrients are derived from two main sources: (i) exogenous, produced by the digestion of ingested food, and (ii) endogenous, carbohydrates and lipids produced by the liver. Circulating nutrients, such as glucose, lipids and amino acids, increase the plasma levels of leptin and insulin. These hormones activate efferent pathways in the hypothalamus, which then send signals to inhibit food intake and the production of glucose by the liver[28,29]. Insulin or leptin administration in the hypothalamus induces rapid changes in glucose mobilization from peripheral tissues, mainly the liver and skeletal muscle[30,31]. The ability of systemic insulin to suppress hepatic glucose production is due in part to the activation of insulin receptors located specifically in the arcuate nucleus of the mediobasal hypothalamus (MBH)[31].

The MBH has been proposed as a key neuronal center in the control of glucose metabolism. Perturbations of the homeostatic hypothalamic circuits are sufficient to produce obesity and insulin resistance[29]. Activation of insulin signaling in the MBH, including the insulin receptor and phosphoinositide-3-kinase (PI3K) as well as the activation of ATP-dependent potassium (K_{ATP}) channels constitutes a strong direct stimulus to trigger neurogenic signals to the liver, via the efferent vagus nerve, to suppress hepatic glucose production[32]. Other studies in this direction implicate the interleukin-6/signal transducer and activator of transcription 3 (IL-6/STAT3) signaling pathway in the inhibition of gluconeogenic enzyme transcription in the liver[33]. All these studies revealed a key role of the MBH in the fine-tuning of insulin action for the control of glucose metabolism.

RELEVANCE OF INSULIN IN ALZHEIMER'S DISEASE

The presence of insulin and the insulin receptor (IR) in the CNS suggests that the brain is a target for the action of insulin. Indeed, insulin exerts multiple effects in the brain, including neurotrophic, neuromodulatory, and neuroendocrine actions. Insulin reaches the brain via the blood brain barrier (BBB) or, in some instances, through its local production in the brain[34]. IR has been found in high concentrations in several areas of the brain, including the olfactory bulb, hypothalamus, hippocampus, and cortex of rodent and human brains[35]. Some of the effects of IR activation on food intake regulation, energy metabolism, and reproductive function have been studied in genetically modified mice models that do not express the IR in the brain. These animals display a phenotype characterized by increased food intake; diet-induced obesity; increased body adiposity; elevated circulating insulin, leptin, and triglycerides; mild insulin resistance; and altered reproductive function[36,37]. On the other hand, abundant evidence suggests a role for IR in the modulation of synaptic activity in the CNS through its effects on the release and re-uptake of neurotransmitters[38-40]. The presence of functional IRs in the hippocampus and cerebral cortex are important for cognitive function[41,42]. To demonstrate the effects of insulin on cognition, rats were treated with streptozotocin (a diabetogenic toxin) in the third cerebral ventricle, causing a deficit in energy metabolism, memory, and learning[43]. The molecular mechanisms by which insulin affects cognitive functions have been examined in studies of insulin signaling in AD. For instance, it has been reported that IR expression is increased, while its tyrosine kinase activity is decreased, in the brain of patients with AD, suggesting defects of insulin signaling[44]. More recent studies have indicated that insulin regulates the metabolism of the proteins Aβ and tau, the main components of senile plaques and neurofibrillary tangles, respectively, and constituents of the characteristic neuropathological lesions in AD. The association of tau with the microtubules is regulated through protein phosphorylation by protein kinases including glycogen synthase kinase 3β (GSK-3β). The GSK-3β is a main component of the insulin signaling pathway, and its activity is controlled by the binding of insulin and insulin-like growth factor 1 (IGF-1) to the IR[45]. Studies in neuronal cultures demonstrated that insulin and IGF-1 decreases tau phosphorylation and promotes its binding to microtubules via GSK-3β inhibition by PI3K[46]. It has also been reported that insulin and IGF-1 transiently increase tau phosphorylation on specific residues as a consequence of GSK-3β activation by Fyn tyrosine kinase[47]. In the case of interaction of Aβ peptides with insulin signaling, some studies have proposed that insulin may promote the accumulation of Aβ peptides through the stimulation of AβPP processing after activation of the mitogen-activated protein kinase (MAPK) pathway[48] (Fig. 1). Other studies have proposed a role for the insulin-degrading enzyme (IDE) in the molecular cascade leading to the abnormal accumulation of Aβ in the brain of people with AD. IDE is a metalloproteinase that degrades insulin and other small peptides, including Aβ.

Figure 1. Schematic representation of the role of insulin signaling in the metabolism of β-amyloid and the impact of hyperglycemia and hyperinsulinemia in the activity of the amyloidogenic pathway. High insulin and glucose levels are proposed to promote the abnormal accumulation of toxic β-amyloid peptides as a result of the stimulation of β-amyloid precursor protein processing mediated by insulin-dependent activation of the mitogen-activated protein kinase pathway. Conversely, high insulin and glucose block the activation of the non-amyloidogenic pathway, decreasing the production of non-toxic soluble peptides that promote neuronal survival. MAPK: mitogen-activated protein kinase; Aβ: β-amyloid; APP: Aβ precursor protein.

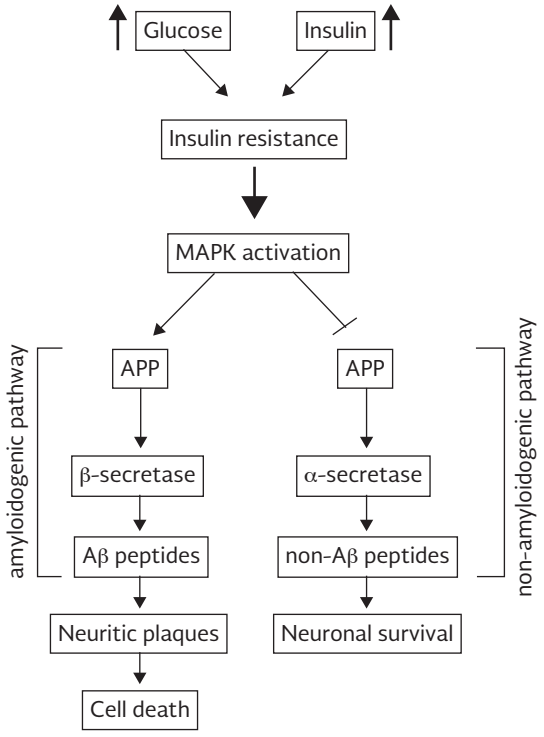
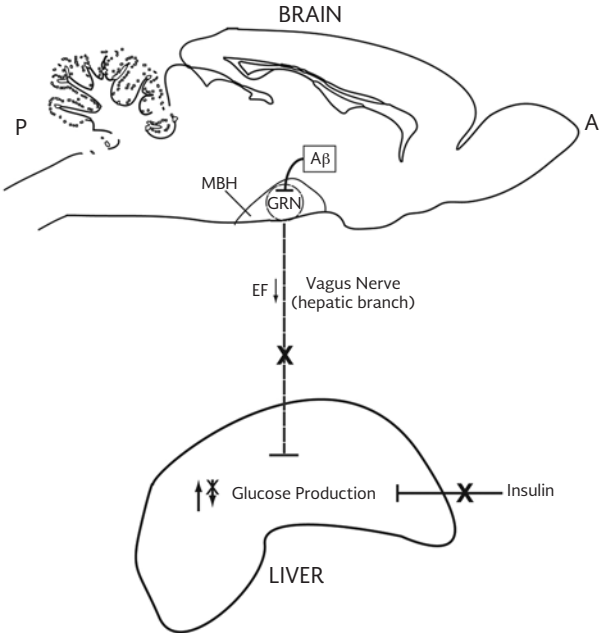


Figure 2. Schematic representation of the brain-liver interaction proposed to mediate the central toxic effect of $A\beta_{25-35}$ on liver glucose metabolism. Acute exposure of the mediobasal hypothalamus to $A\beta_{25-35}$ (shown in this rat sagittal brain middle section) blocks the glucoregulatory neuronal activity that normally sends appropriate neurogenic inhibitory signals through the hepatic vagal efferent innervation. The net result is an increase of liver endogenous glucose production and hyperglycemia. Aβ: $A\beta_{25-35}$ peptide; MBH: mediobasal hypothalamus; GRN: glucoregulatory neurons; EF: efferent flow; A: brain anterior face; P: brain posterior face.



It has been hypothesized that the binding of insulin to IDE not only stimulates the degradation and disposal of Aβ during hyperinsulinemia, but also promotes the formation of Aβ plaques[49].

Recently, we have shown that an Aβ short fragment, the amino acid sequence 25-35 ($A\beta_{25-35}$) participates in the dysregulation of the glucose metabolism in a non-diabetic animal model. We tested the hypothesis that $A\beta_{25-35}$ may have a toxic action in the MBH that perturbs central glucoregulation. To this aim, we first determined whether short-term exposure of the hypothalamus to $A\beta_{25-35}$ alters the circulating levels of both glucose and insulin by infusing $A\beta_{25-35}$ in the MBH of young rats. We observed that the acute intrahypothalamic infusion of $A\beta_{25-35}$ increased plasma glucose and insulin levels in comparison with the control peptide animal group. To gain insight into the mechanisms by which $A\beta_{25-35}$ increased glucose levels, we examined its effect during the course of pancreatic basal insulin clamps designed to maintain fixed and basal circulating insulin levels. Glucose kinetics measurements performed during the clamps showed that $A\beta_{25-35}$ caused a marked increase of endogenous glucose production, reflected by the decrease in the glucose infusion rate to maintain normal glucose levels and by the failure of the system to efficiently suppress glucose production by the liver. Furthermore, we did not observe changes in glucose utilization by peripheral tissues in the animals infused with $A\beta_{25-35}$ in the MBH[50]. These results unraveled a novel neurotoxic action of Aβ that perturbs hypothalamic glucoregulation, leading to increased hepatic glucose production and hyperglycemia. Furthermore, our findings provide a previously lacking piece of experimental evidence for a direct link between Aβ toxicity and altered glucose metabolism (Fig. 2).

DIABETES AND ALZHEIMER'S DISEASE

Type 2 diabetes mellitus (DM2) is one of the most common metabolic disorders and its prevalence and incidence has increased worldwide. Several epidemiological studies have suggested that DM2 is involved in the development of dementia in AD[51-53]; however, the factors linking DM2 with AD are largely unclear. Some of the risk factors proposed to play a role in the neurodegenerative process and the progression of dementia in AD include: hyperglycemia, insulin resistance, oxidative stress, activation of inflammatory cytokines, and damage to the micro/macrovascular system[54]. Clinical studies of patients with AD have yielded intriguing results. For example, high fasting blood insulin accompanied by low insulin levels in the cerebrospinal fluid (CSF) has been reported in patients with AD[55]. In contrast, studies of AD patients with varying degrees of severity of the disease display different profiles since individuals with milder forms of AD display high fasting plasma glucose and insulin, while in individuals with severe AD the hyperglycemia is not accompanied by hyperinsulinemia[56]. Prospective studies of patients with milder forms of AD and dementia progression revealed that low circulating insulin was associated with a decrease of memory facilitation, suggesting a cause-effect relationship between levels of plasma insulin and cognitive function. In this respect, short-term follow-up studies have demonstrated that hyperinsulinemia improves memory as long as circulating glucose is maintained at fasting levels. Conversely, hyperglycemia does not affect cognitive function as long as circulating glucose remains within normal basal limits[57,58]. The study of individuals with a diagnosis of AD that showed alterations of circulating insulin and dementia progression suggested that insulin was involved in the regulation of cognitive function. Consequently, it is clear that insulin may play a relevant role in the pathophysiology of AD.

CONCLUSIONS

In conclusion, studies on the molecular and cellular mechanisms involved in the pathophysiology of AD and its relationship with insulin and glucose metabolism support the idea that the metabolic alterations of DM2 are strongly associated to the development of AD. Importantly, our recent studies in rodents provided a piece of evidence supporting the novel concept that Aβ toxic action in the hypothalamus causes a dysregulation of glucose metabolism directly linking altered insulin action with AD. Further studies are required to better understand the details of this relationship and its causal role, if any, in the onset and progression of AD.

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