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Alzheimer's & Dementia 10 (2014) S3–S11

Alzheimer's & Dementia

Review Article

The paradox of neuronal insulin action and resistance in the development of aging-associated diseases

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Abstract During past decades, ever-increasing life expectancy, despite the development of a sedentary lifestyle and altered eating habits, has led to a dramatic parallel increase in the prevalence of age-related diseases such as type 2 diabetes mellitus (T2DM) and neurodegenerative disorders. Converging evidence from animal and human studies has indicated that insulin resistance in the central nervous system (CNS) is observed in both T2DM and neurodegenerative disorders such as Alzheimer's disease (AD), leading to the hypothesis that impaired neuronal insulin action might be a unifying pathomechanism in the development of both diseases. This assumption, however, is in striking contrast to the evolutionary conserved, protective role of impaired insulin/insulin-like growth factor 1 signaling (IIS) in aging and in protein aggregation-associated diseases, such as AD. Thus, this review summarizes our current understanding of the physiological role of insulin action in various regions of the CNS to regulate neuronal function, learning, and memory, and to control peripheral metabolism. We also discuss mechanisms and clinical outcomes of neuronal insulin resistance and address the seeming paradox of how impaired neuronal IIS can protect from the development of neurodegenerative disorders.
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Keywords: Insulin; Brain; Insulin resistance; Diabetes; Aging; Dementia; Alzheimer's disease

1. Action of insulin within the central nervous system in control of metabolism and neurodegenerative diseases

During past decades, considerable progress in advanced modern medicine combined with greater quality of life in developing countries has extended one's life span markedly, and the elderly are expected to live even longer in the future [1]. Improvement of life expectancy is associated inevitably with a subsequent escalation in the prevalence of age-related diseases. Among them, type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) are considered to be part of the leading health threats in old age [2,3].

Historically, T2DM and AD were considered unrelated disease entities, being characterized as either a metabolic disorder affecting primarily glucose homeostasis in skeletal muscle, liver, and fat, or a degenerative disease of the central nervous system (CNS), respectively. However, recent studies have raised the possibility that these diseases share similar molecular roots; recently, both diseases have been associated with impaired insulin action within the CNS. This notion is supported further by epidemiologic studies, which have uncovered an association between T2DM and AD [4]. However, other studies have failed to reveal this association [4]. Postmortem analyses of brain from patients with AD have demonstrated that insulin receptors (IRs) are downregulated [5], as is observed during aging [6,7]. This led to the hypothesis that neuronal insulin resistance may contribute to the etiology of AD. Thus, the close correlation between T2DM and AD is believed to originate mainly from the establishment of insulin resistance (i.e., one of the main hallmarks of T2DM) and the associated alterations of the pleiotropic effects of insulin on core physiological functions.

The authors have no conflicts of interest to report.

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1552-5260/$ - see front matter © 2014 The Alzheimer's Association. All rights reserved.
http://dx.doi.org/10.1016/j.jalz.2013.12.008

Nearly one century after the discovery of insulin as a pancreatic-secreted peptide [8], the classic view of insulin as one of the principal regulators of glucose homeostasis by promoting glucose uptake in muscle and fat, and by suppressing hepatic glucose production has been expanded to a large range of physiological and cellular effects, including its neuroprotective role and the regulation of learning and memory. After describing the molecular basis of insulin action in the CNS, this review provides an overview of the key regulatory roles of insulin in the CNS-dependent control of glucose and energy homeostasis, as well as cognition, both under physiological and pathological conditions. Last, we address the seeming paradox of the neuroprotective effect of insulin and the role of inflammatory signaling pathways that causes neuronal insulin resistance and are activated both in obesity/T2DM and AD.

2. CNS insulin signaling: Regional distribution and molecular mechanisms

IRs are distributed extensively throughout the CNS [9–11]. The expression of IRs in the brain displays a widespread but selective regional pattern, because the intensity of IRs varies in different regions of the CNS [9–11]. In rodents, the highest density of IRs is found in the olfactory bulb, hypothalamus, cerebral cortex, cerebellum, hippocampus, thalamus, and midbrain [9–11]. Thus, IRs are present abundantly in brain areas involved in both glucose and energy homeostasis as well as cognitive processes (i.e., the hypothalamus and the cortical/hippocampal regions, respectively) [9–11].

After its transport into the brain via a saturable transporter expressed in the blood–brain barrier, insulin binds and activates its receptors [12]. IRs are tetrameric membrane receptors composed of two extracellular α subunits and two transmembrane β subunits, which constitute the binding region and tyrosine kinase activity, respectively [13–15] (Fig. 1). Insulin actions are mediated through a complex signaling profile that requires numerous second messengers that can be simplified into two major branches: the phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT) pathway and the mitogen-activated protein kinase pathway (MAPK)/extracellular signal-regulated kinase cascade (for more details, see Kahn and Suzuki [15]). Binding of insulin to the IRs triggers a conformational change of the receptor, leading to activation of tyrosine kinase activity and, consequently, autophosphorylation of the receptor and phosphorylation of the insulin receptor substrate (IRS) protein family (mainly IRS-1 and IRS-2 in the CNS) [15]. Phosphorylation of IRSs induces the activation of various effector molecules, such as PI3K, which in turn activates the serine/threonine kinase AKT through phosphoinositide-dependent kinase 1 (Fig. 1). Once activated, AKT inhibits glycogen synthase kinase 3. Phosphorylated IRS also induces the activation of Ras, the initiator of the MAPK pathway, which results in the activation of extracellular signal-regulated kinase 1/2 (Fig. 1). One of the main targets of these pathways is the modulation of transcription and, therefore, gene expression. More important, based on their ability to form hybrid receptors, as well as their shared ligands and intracellular pathways, signaling of insulin and insulin-like growth factor 1 (IGF-1) are generally considered homologous as insulin/IGF-1 signaling (IIS) [16].

3. Insulin actions in neuronal control of energy and glucose homeostasis

Insulin action in the regulation of body weight, food intake, and glucose homeostasis is fine-tuned by its controlled secretion from pancreatic β cells via both short- and long-term regulation (i.e., acutely in response to hyperglycemia and directly proportional to adiposity in the long term). Intracerebroventricular (ICV) insulin administration leads to decreased food intake and body weight [17] (Fig. 2). The anorexigenic effect of insulin has been attributed primarily to its action in the two major antagonistic neuronal populations in the arcuate nucleus of the hypothalamus (ARH): the orexigenic neurons coexpressing neuropeptide Y (NPY) and agouti-related peptide (AgRP), and the anorexigenic neurons that produce proopiomelanocortin (POMC) and cocaine and amphetamine related-transcript (CART) [13,18,19]. Both NPY/AgRP neurons and POMC/CART neurons express IRs [20–22]. ICV insulin administration decreases the expression level of NPY/AgRP and increases that of POMC/CART, resulting in a decreased ratio of orexigenic-to-anorexigenic signals. ARH neurons then relay the signals to second-order neurons (for review see Vogt and Bruning [13] and Elmquist and colleagues [18]). More important, activation of these downstream pathways is dependent of the melanocortin system; co-infusion of insulin and melanocortin receptor (i.e., activated by the POMC-derived peptide α-melanocyte-stimulating hormone and inhibited by AgRP) antagonist blunts these effects [20]. Of note, in parallel to the insulin-induced reduction of food intake, the reduction in body weight after central infusion of insulin may also be linked to greater energy expenditure and locomotor activity, which is attributed to the action of insulin on POMC neurons [23,24].

In addition to its anorexigenic effect, insulin is a main player in CNS-dependent regulation of peripheral glucose fluxes (for a detailed review, see Grayson and colleagues [25]). Central insulin infusion results in suppression of hepatic glucose production (HGP) [21,26,27]. Accordingly, insulin fails to suppress HGP in CNS-restricted IR knockout mice (named NIRKO mice) [15,19] (Fig. 2). These defects are recapitulated by ablating the IR specifically in AgRP neurons, but not in POMC neurons [21], demonstrating that only 3000 AgRP neurons are required for insulin-induced suppression of HGP. In contrast to its anorexigenic effect, the antigluconeogenic effect of central insulin is not dependent of the melanocortin pathway [26].

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