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REVIEW PAPER

Insulin and brain aging

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Abstract

The world's population is living much longer than in the past. It is crucial to find as many pathological factors that deteriorate the health condition and well-being of elderly people as possible. Loss of activity and functions over time is typical for elderly people.

Aging affects brain function, metabolism and structure in different ways, and these effects have multiple etiologies. Cognitive impairment, impaired neurotransmitter activity and reduction of brain volume are observed in the elderly population. The process of brain aging is associated with a decrease of central insulin concentration as well as impairment of insulin receptor binding ability, resulting in deterioration of glucose homeostasis in the brain.

Peripheral insulin resistance is a typical feature of older age. Data from the literature suggest that high circulating insulin and insulin resistance are important contributors to progressive cognitive impairment and neurodegenerative processes.

The maintenance of insulin sensitivity and proper insulin signaling may lead to preserved cognition that results in well-being of elderly people.

Key words: insulin, insulin resistance, brain, aging.

Introduction

Today, the world's population is living much longer than in the past. According to the World Health Organization, between 2015 and 2050, the proportion of people over 60 years old will nearly double from 12% to 22% [1]. These predictions of the future indicate that by 2050 the world's population aged 60 years and older is expected to reach a total of 2 billion, up from 900 million in 2015. Therefore, it is crucial to find as many pathological factors that deteriorate the health condition and well-being of elderly people as possible. On the other hand, loss of activity and functions over time is typical for the process of aging. Normally, the decline in physical and mental conditions is gradual and progressive. However, it is still under discussion whether this decline is a consequence of physiological or pathological processes. Nevertheless, aging affects the brain function, metabolism and structure in different ways, and these effects have multiple etiologies. Indeed, cognitive impairment, quantitative and qualitative changes in neurotransmitter activity and a reduction of brain volume, particularly in the frontal cortex area, are observed in the elderly population [2, 3]. In addition, it has been reported that older age is associated with peripheral insulin resistance [4]. On the other hand, the maintenance of insulin sensitivity has been reported in the oldest-old [2, 4].

Risk factors that have been considered with regard to the ageing brain include metabolic disturbances. Hypertension, diabetes, hyperhomocysteinemia, and dyslipidemia are amongst conditions that increase the possibility of stroke and ischemia or at least lead to development of white matter lesions [3]. It has also been suggested that impaired glucose metabolism or a reduced input of glucose into the brain may also influence the course of brain aging [5]. Moreover, insulin resistance at the central nervous system (CNS) level has been linked to increased risk for both cognitive decline and dementia including those of neurodegenerative origin, e.g. Alzheimer's disease (AD), and those of vascular origin [6].

Herein we present the current knowledge considering the role of insulin in the process of brain aging.

The physiological role of insulin in the central nervous system

Since 1983 when Dorn and co-workers reported that the human brain contains insulin in concentrations much higher than in the blood, insulin has been considered as an important factor in brain physiology [2, 4].

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Although insulin is a large peptide hormone and cannot passively pass through the blood-brain barrier (BBB), it is still found in the cerebrospinal fluid (CSF) [7]. Nowadays, three different sources of insulin in the brain are proposed. Firstly, insulin could be transported into the CNS by a saturable, insulin receptor-mediated pathway. Secondly, insulin could directly flow into the CSF without crossing the BBB as circumventricular regions are characterized by a lack of typical BBB structure and the presence of porous capillaries permitting plasma to freely diffuse [4]. Finally, experimental studies on an animal model indicated that insulin could be produced within the brain. Specifically, *in vitro* experiments showed the synthesis and release of insulin by cultured rat brain neuronal and astrocyte glial cells. Also *in vivo* research protocols revealed the presence of preproinsulin I and II mRNAs and insulin immunoreaction in the rat fetal brain [4]. However, it is still controversial whether human brain cells are able to produce insulin [2, 8].

After reaching the CNS insulin binds to the insulin receptor, which belongs to the family of tyrosine kinase receptors. Interestingly, insulin receptor subunits found in the brain are different to those of the periphery. The main difference is in the structure, as brain insulin receptor subunits have a lower molecular weight [4]. Moreover, it was found that brain insulin receptors can be exposed to hyperinsulinemia that does not cause down-regulation of the receptor. To date, two specific insulin receptors within the mammalian brain have been determined: the neuronal/neuron-specific type, and the non-neuronal/peripheral-like type [4]. After insulin binding to the insulin receptor, autophosphorylation of the receptor, which is essential for its activation, occurs. Then, the activated insulin receptor phosphorylates insulin receptor substrate (IRS) proteins. After that, signaling networks are recruited [2]. It is worth noting that IRS proteins are also activated upon binding of the IGF-1 ligand to its receptor. Thus, IRS proteins connect the insulin and IGF-1 signaling cascades [4].

Insulin receptors are widely distributed within the brain, with the highest concentration in the hypothalamus, hippocampus, in the olfactory bulb, cerebellum, amygdala, and cerebral cortex [9]. The wide spectrum of insulin receptors' location within the CNS indicates multifunctionality of insulin.

Central insulin plays a role in maintaining energy homeostasis, as it has the ability to increase blood glucose levels (acting in opposition to peripheral insulin), to decrease feeding and body weight and lower blood levels of insulin [6]. It has been reported that inside the brain, insulin exerts its effects on peripheral metabolism through the hypothalamic-pituitary-adrenal axis [6].

Insulin is suggested to have neuroprotective properties and to exert neurotrophic effects on CNS neurons. Moreover, it could positively influence emotion and higher cognitive processes including attention, executive functioning, learning and memory [4].

Data from previous studies indicate that glucose can enter the brain without the help of insulin-dependent mechanisms by diffusing across the BBB. Subsequently, glucose transporters, mainly insulin-insensitive, cause absorption of glucose by brain cells [2]. However, the presence of an insulin-sensitive glucose transporter, named GLUT-4, in the hippocampus, cerebellum and hypothalamus has also been reported. Moreover, central insulin is able to increase cerebral GLUT-4 expression and translocation [6].

Insulin and physiological brain aging

The process of brain aging is associated with a decrease of cortical insulin concentration as well as impairment of insulin receptor binding ability. These characteristic features were confirmed by Frolich and colleagues in their study on post mortem brains of elderly subjects [10]. Furthermore, aging contributes to reduced expression of the insulin receptor in the BBB, and this effect is augmented by prolonged peripheral hyperinsulinemia and insulin resistance [2].

The whole body sensitivity may be reflected by the ratio of CSF to serum insulin. A reduction in ratio in insulin-resistant individuals suggests altered transport of insulin across the BBB [10]. In addition, a decrease in insulin-dependent glucose transport with GLUT-4 in the CNS was also observed as a combined effect of aging and peripheral insulin resistance [7]. All those combined abnormalities may lead to the brain insulin resistance, deteriorated systemic control of glucose and impaired brain glucose uptake observed in the elderly.

Data from clinical studies also suggest a correlation between decreased brain glucose uptake and age-associated cognitive impairment.

For example, the results of a study conducted by Thambisetty and co-workers indicated that the cerebral blood influx declined much faster with age in individuals in whom impaired glucose tolerance was diagnosed [11]. Other clinical studies indicated that fluorodeoxyglucose (FDG) uptake is commonly reduced in specific brain regions that are vulnerable to Alzheimer's disease in older subjects with diabetes [12]. These data confirm glucose hypometabolism of the brain in DM patients.

Other mechanism that should be taken into account with regard to glucose-insulin metabolism and brain aging is inflammation caused by advanced glycation end products (AGE). In the case of peripheral and central insulin resistance, decreased accessibility of insulin and inadequate high glucose concentration cause the formation of glycated end products in the brain. As a result of AGE formation, inflammation and development of vascular dysfunction occur within the CNS [6].

Finally, it is worth noting that aging is characterized by an increase in oxidant production as the mitochondrial function is impaired. As a result of overproduction

of H_2O_2, insulin resistance is amplified [5]. Moreover, a switch to pro-inflammatory activity of microglia additionally enhances insulin resistance and leads to neurodegeneration [5].

Central and peripheral insulin resistance and brain pathological aging

Alzheimer's disease (AD) is the most common form of dementia. It belongs to a group of neurodegenerative disorders and is characterized by irreversible and progressive loss of memory and other cognitive functions.

Previous studies have reported that the risk of developing AD is increased by 50-60% in the case of type 2 diabetes [13]. Generally, lower brain glucose uptake and impaired glucose metabolism (hypometabolism) are associated with AD [5]. Moreover, a decrease in insulin signaling and lower insulin receptor activity were observed in AD brains when compared to healthy (non-demented) controls [2]. Furthermore, central insulin resistance results in functional hypoglycemia, a typical feature of AD [13].

Data from a clinical observation revealed that insulin resistance is accompanied by IGF-1 resistance and IRS dysfunction. This complex of receptor abnormalities was found to be an early and common characteristic of AD [14]. Due to the fact that insulin signaling has an impact on production of AD components (amyloid β accumulation and phosphorylation of tau protein [15]), it could be supposed that insulin signaling impairment in DM patients correlates with neurodegeneration processes observed in the course of AD. According to the findings from the studies, coexistence of type 2 diabetes and AD results in hyperphosphorylation of tau protein, abnormal regulation in the clearance process of amyloid β leading to deposition of amyloid β plaque, an increase in cortical IL-6 concentration, mitochondrial dysfunction and high frequency of microvascular infarcts in comparison to non-diabetic AD subjects [13]. Moreover, insulin and amyloid β are cleared by insulin-degrading enzyme (IDE), and while IDE is bound with insulin the availability of IDE for amyloid β clearance is reduced [15].

Interestingly, peripheral insulin resistance assessed by HOMA-IR correlated with increased CSF levels of AD biomarkers [7]. Furthermore, increased CSF levels of insulin correlated with decreased cognitive ability in patients with diabetes and AD [7].

As there is a confirmed close correlation between impaired insulin homeostasis and cognitive decline, the researchers created the term "type 3 diabetes" (T3D) for type 2 diabetes-induced AD, and therefore type 3 diabetes was defined as a critical situation of insulin resistance that eventually induces AD [7].

Conclusions

Data from many studies indicate that insulin may play a key role in brain aging. The maintenance of insulin sensitivity and proper insulin signaling may lead to preserved cognition that result in well-being of elderly people.

Disclosure

Authors report no conflict of interest.

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