Fight against glucose rescues Age-Related cognitive decline

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Aging is commonly associated with dysfunctions of various systems, especially the cognitive decline that seriously diminishes the independence and life quality of old individuals. Exploring the approaches for maintaining a healthy brain is now a critical public health concern. Calorie restriction (CR) has been known to extend longevity, promote metabolic health, and delay the progress of aging and the risk of age-related diseases, such as type 2 diabetes and Alzheimer’s disease (AD). Studies have shown that CR improves the insulin sensitivity. Moreover, defected insulin signaling in individuals with or without diabetes is related to a higher risk of age-related cognitive deficits or AD. Evidences suggest that treatment of diabetes mimics the activity of CR, modulating the metabolism of glucose and lipid and the function of insulin system, thus may has the anti-aging potential. In this paper, we reviewed the laboratory experiment and clinical data that focused on the protective role of CR, and that investigated the effect of several types of common agents for diabetes treatment on aging or cognitive ability. The progress in recent years inspires researchers to explore the mechanisms of age-related cognitive decline, and search for safe and effective therapeutic strategies. In the future, more high-quality studies are required to optimize the application of CR or diabetes therapies on the prevention or treatment of brain aging.

Keywords: acarbose; brain aging; calorie restriction; GLP-1; insulin; thiazolidinediones

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Introduction

Aging is characterized by the recession of body structure and biological functions. In the aging process, human shows progressively limited mobility and adaptability, decreased resistance to stress, loss of independent living skills, and increased risk of diseases such as hypertension, obesity, cardiovascular and neurodegenerative diseases. There has been a rapid increase in the population aged 60 years or over, showing that the world population is rapidly aging, which poses a series of new challenges to the society [1]. The long-term burden of cognitive impairment will lead to disability and greatly diminish the quality of life in the older people [2]. In addition, the prevalence of age-related neurodegenerative diseases, such as Alzheimer’s disease (AD), is rising [3]. However, currently, no effective treatment is available to delay or reverse their progression. Therefore, the development of therapeutic strategies to optimize brain health and prevent or ameliorate the age-related cognitive decline is urgently needed.

Calorie restriction

Currently, calorie restriction (CR) is the most promising intervention shown to decrease the aging process with numerous health benefits, including reduced fat stores and
proinflammatory cytokines, and increased insulin sensitivity [4]. CR has shown effect on extension of longevity and the maintenance of more youthful-like function states in rodents and primates [4].

In humans, several studies have observed beneficial metabolic adaptations that occur in experimental animal models, providing solid supports for CR to improve the brain health and potentially extend the lifespan [5]. CR has been shown to decrease the incidence of many age-related diseases (such as cancer, cardiovascular disease, diabetes mellitus, and neurodegenerative diseases) [6]. Existing epidemiological studies indicates that restricted calorie intake is associated with a reduced risk of developing AD [7]. CR diets or intermittent fasting can rescue the cognitive deficits in the transgenic mouse models of AD [8]. The effect is associated with alleviated hippocampal atrophy, β-amyloid burden and hyperphosphorylation of tau protein in the brain [8, 9]. In a study of model of accelerated aging, CR attenuated the deficits of learning and memory in middle-aged senescence-accelerated mouse strain P 8 (SAMP8) mice in a passive avoidance task [10]. For healthy elderly humans, significantly increased verbal memory scores after CR has been reported, which is correlated with improved insulin sensitivity and suppressed inflammatory activity [11]. These interventional trials demonstrate beneficial effects of CR on memory ability.

The mechanism of CR delaying aging is a mystery that is becoming clearer with the progress in the researches in this area. CR induces mild neuron stress responses, which can further facilitate the synaptic plasticity and neurogenesis. In the obese rat, a 10-week CR diet increased the hippocampal levels of the NR2A and NR2B subunits in N-methyl-D-aspartic acid receptor (NMDAR), essential for synaptic plasticity and hippocampal-dependent learning and memory [12]. In addition, a variety of neuroprotective functions are involved in the anti-aging effect of CR, such as the suppression of the age-related excessive inflammatory reaction and oxidative stress, the activation of the ubiquitin-proteasome [13] and the enhancement of the cell ability to repair DNA damage [14]. CR also modulates the neuroendocrine system. Old people that underwent twelve months of CR show improvements in glucose tolerance and insulin sensitivity [15]. The upregulation of brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor is another important neuroprotective response to CR [4]. During normal brain aging and AD, a declined expression of brain-derived neurotrophic factor and its receptor tyrosine receptor kinase B has been found, and this decline is correlated with impaired cognitive functions and decreased dendritic spine density in hippocampus [16]. What’s more, evidence from genetic studies has demonstrated that after a 4-month CR, the genes related to neurogenesis and synaptic plasticity become upregulated, while the genes associated with inflammation become downregulated in the hippocampus of transgenic AD mice [9].

The improved health and postponed aging process under CR are based on the long-term adherence to this lifestyle intervention. However, many individuals lack the adherence to CR regimens over the long-term [14]. Therefore, finding new methods that mimic the effect of CR may be a feasible way.

**Insulin treatment**

During aging, a decrease in the levels of insulin, C-peptide and insulin receptors, and impaired insulin signaling in the brain have been observed in the animal studies [17]. A recent research of adults without diabetes has examined the effects of age on homeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-B). The results show that the HOMA-B decreases in both genders and the HOMA-IR increases in men and postmenopausal women with increasing age [18]. Age-related increase in plasma glucose levels has a close association with impaired insulin secretion rather than insulin resistance [18]. Epidemiological studies have suggested an increased risk of developing AD in the diabetes patients [19]. The animal models and patients of AD exhibit lower insulin level in the cerebro-spinal fluid and/or ratio of cerebro-spinal fluid insulin/plasma insulin, and a decrease expression of insulin receptors and their tyrosine kinase activity, which is associated with the cognitive decline [20]. Therefore, impaired insulin signaling has been proposed to be an underlying pathogenic mechanism in AD.

The insulin signaling in the brain plays a protective role in the glucose metabolism and neuronal function. Studies have shown that intracerebroventricular infusion of insulin displays an anorexigenic effect, markedly decreasing food intake and weight gain [21]. Most importantly, insulin is essential in the cognitive function by regulating synaptic plasticity, including the synapse number, dendritic plasticity, visual circuit function, long-term potentiation, and long-term depression [21, 22]. Insulin induces the membrane recruitment of NMDAR in excitatory synapses, and contributes to the development of long-term potentiation in the hippocampus. Besides, insulin triggers the clathrin-dependent endocytosis of alpha-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid receptors, regulating the long-term depression [21]. A recent report indicates that the improved memory recall in rats after intranasal insulin administration may due to the amelioration of the age-related increase of Ca2+-dependent hippocampal after hyperpolarization, a well-characterized
neurophysiological indicator of aging [23]. In AD, insulin action has been shown to decrease the burden of β-amyloid and hyperphosphorylation of tau, thus alleviate the pathological hallmarks (i.e., amyloid plaques and helical neurofibrillary tangles) [24].

There is abundant evidence that peripherally administering insulin improves memory in word recall and enhances attention in AD patients. Healthy adults received infusion of insulin also show increased cognitive performance and enhanced neuronal activity within the medio-temporal lobe [25]. Nevertheless, the induction of systemic hypoglycemia limits the application of peripherally insulin infusion. Fortunately, intranasal insulin is proved a better administration route that provides an efficient delivery to the brain and easily achieves clinically relevant concentrations of insulin with much less risk of hypoglycemia [26]. Clinical trials have shown that an intranasal insulin therapy (both 20 and 40 IU) for 4 months improves memory performance and brain glucose metabolism in adults with amnestic mild cognitive impairment or AD [27]. Even in healthy adults, 8-week intranasal insulin has been reported to improve delayed recall of words and emotional health [26]. Nevertheless, there are concerns about the unwanted adverse effects of intranasal insulin, including elevated blood pressure, promoted tissue degeneration and potential risk of proliferation of neoplastic cells [28]. Therefore, experimental research and larger clinical trials of longer duration are necessary to better understand the safety of intranasal insulin therapy and explore an optimized dosing strategy.

**Metformin**

Metformin is a first-line antidiabetic drug, in particular, for overweight and obese patients of type 2 diabetes. Metformin significantly decreases the serum glucose level by multiple mechanisms, including inhibiting the glucose intake from the gastrointestinal tract, increasing glucose utilization in peripheral tissue, and suppressing hepatic gluconeogenesis. The most common adverse effects of metformin are gastrointestinal, including diarrhea, nausea, vomiting, and flatulence, etc. Evidence has suggested that metformin helps to reduce low-density lipoprotein and triglyceride levels, promotes weight loss, and may prevent the cardiovascular complications of diabetes [29]. High-fat diet Wistar rats received metformin treatment display attenuation of learning and memory deficits on Morris water maze test. The protective effect may link to the decreased peripheral and cerebral oxidative stress, and improved peripheral insulin sensitivity and brain mitochondrial function [30]. A recent study of 365 older adults with diabetes shows that long-term treatment with metformin associated with lowest risk of cognitive decline [31]. In addition, metformin has been shown to inhibit mammalian target of rapamycin complex 1 signaling and increase longevity in mice [32]. In an in-vitro study of neuronal insulin-resistant model with hallmark AD-like changes, treatment with metformin alleviates neuronal insulin resistance and prevents the appearance of molecular and pathological characteristics of AD [33]. The administration of both insulin and metformin can provide significant neuroprotection against AD pathology, including β-amyloid neuritic plaques and down-regulation of the insulin receptor, thus improving cognitive function. The mono-therapy of metformin, however, is not recommended as it was observed to increase the generation of intra- and extracellular β-amyloid [34]. Moreover, it has been reported that in the older people with diabetes metformin is associated with worse cognitive performance, which may be the result of metformin-induced vitamin B12 deficiency [35]. Taking vitamin B12 and calcium supplements can ameliorate the vitamin B12 deficiency and promote better cognitive performance [35].

**Alpha-glucosidase inhibitors**

Alpha-glucosidase inhibitors, including acarbose, miglitol and voglibose, are oral anti-diabetic drugs used for type 2 diabetes mellitus. Alpha-glucosidase inhibitors are saccharides that work by competitively inhibit the enzymes needed to digest carbohydrates, lead to less glucose absorbed through the intestine and decrease circulating glucose level. The ameliorated post-prandial hyperglycemia reduces insulin resistance, leading to improved atherogenic dyslipidemia. The beneficial effects of alpha-glucosidase inhibitors also include the prevention from age-related weight gain, the protection on endothelial function or oxidative stress, which reduce the risk of diabetes and cardiovascular events [36]. The common side effects are gastrointestinal discomforts such as flatulence and diarrhea, which can be avoided by starting with a low dose and gradually increase it.

Acarbose is the most widely used alpha-glucosidase inhibitor. It favorably affect blood pressure, serum lipids and endothelial function, thus decrease the risk for microvascular and macrovascular complications in type 2 diabetics. Acarbose has been reported to reduce the stress of pancreas islet β-cells in the advanced stage of diabetes, probably alleviating the decrease in insulin secretion [37]. In mice, acarbose has been reported to increase the median and maximal lifespan [38]. The promoted metabolic health and prolonged longevity by acarbose may be associated with the stimulated production of glucagon-like peptide-1 (GLP-1) production in intestine [39]. However, the effects of acarbose on neural function and cognitive ability have not been evaluated.
In our recent published research, we use the SAMP8 mice, a model with characteristics of accelerated aging, to explore the effect of long-term treatment with acarbose on the age-related behavioral and biochemical changes. The mice in the acarbose group are administered acarbose by drinking water (20mg/kg/d) from 3 to 9 months of age. The old blank mice exhibit age-related deficits of behavioral performance and alteration of serological and hippocampal histochemical indicators. The acarbose-treated mice exhibit enhanced sensorimotor ability, open field anxiety, and spatial and non-spatial memory abilities, compared to the same-age controls. Besides, the acarbose mice show higher levels of serum insulin, hippocampal insulin receptor, brain-derived neurotrophic factor and presynaptic protein syntaxin 1, and lower levels of insulin-like growth factor-1 receptor and presynaptic protein synaptotagmin 1 in most hippocampal layers relative to the same-age controls. The age-related behavioral performance is closely related to the serological and histochemical data. These results indicate that the acarbose treatment can alleviate the age-related behavioral and biochemical changes in SAMP8 mice. The research provides the first laboratory evidence that acarbose has the potential in the treatment of cognitive decline and the prevention of brain aging. As the drug has been withdrawn before the behavioral tests, and the biochemical tests are not undertaken until 15 days after finishing the behavioral tests, the results indicate a long-term effect of acarbose on the age-related decline of cognition and epigenetic alterations of age-related genes may be involved, which requires more research in the future. Currently, there are no clinical trials of acarbose in the treatment of dementia. No study has examined the effects of miglitol and voglibose on cognitive ability.

Thiazolidinediones

Thiazolidinediones (TZDs), such as rosiglitazone and pioglitazone, are anti-diabetic drugs that function by enhancing insulin sensitivity. TZDs bind and activate peroxisome proliferator-activator receptors, inducing the alteration in the expression of genes associated with glucose uptake and disposal, ultimately improving glucose homeostasis. Besides, TZDs have other neuroprotective activities, including preventing adipogenesis, reducing β-amyloid accumulation and suppressing neuroinflammation through peroxisome proliferator-activator receptor-3 expression, and enhances the learning and memory performance and synaptic plasticity in middle-aged Wistar rats. Therefore, rosiglitazone and pioglitazone may be potential therapeutics for the treatment of mild cognitive impairment or AD. In clinical trials, rosiglitazone has shown protective effect on the cognitive function in older individuals with type 2 diabetes and mild cognitive impairment. In a six-month random-control trial at 15~30 mg doses, pioglitazone treatment can alleviate the cognitive decline tested by the Alzheimer’s Disease Assessment Scale in AD or mild cognitive impairment patients with diabetes. However, there is also contrast report that the long-term use of TZDs is not associated with the risk of developing AD. In some clinical trials, TZDs failed to show any improvements on cognitive performance in the patients with mild-to-moderate AD. In addition, the use of TZDs is limited by the increased risk of hepatic impairment. Especially, the rosiglitazone is associated with an increased incidence of coronary heart disease and heart attacks. No clinical trials have examined the effects of TZDs on people with normal aging.

GLP-1

GLP-1 is an incretin made in the intestine, inducing glucose-dependent stimulation of insulin secretion. GLP-1 is known to restore the glucose sensitivity and the proliferation of pancreatic β-cells, as well as inhibit pancreatic β-cell apoptosis and increase insulin gene expression. GLP-1 helps protect against the age-related impairment of pancreatic β-cell function. The treatment of (Val18) GLP-1(GluPAL), a stable GLP-1 receptor agonist, for 20 days reverses the deficits of long-term potentiation and improves the performance of learning and memory in the high fat mice, linking to the decreased oxidative stress and neuroinflammation in hippocampus. The treatment also reduces circulating glucose and increases insulin levels, and enhances glucose tolerance and glucose-mediated insulin secretion.

Since GLP-1 in the circulation has a very short half-life. Degradation-resistant analogs, the GLP-1 receptor agonists have been developed and used for the treatment of type 2 diabetes. The GLP-1 receptor agonists exenatide, liraglutide, lixisenatide, albiglutide and dulaglutide have been approved for clinical use as adjunct therapy in diabetes, with a lower risk of hypoglycemia than the classic insulin secretagogues such as sulfonylureas or meglitinides. In transgenic mice model of AD, liraglutide prevents memory deficits in object recognition and water maze tasks, and the hippocampal synapse loss and deterioration of synaptic plasticity, accompanied by reduced β-amyloid oligomers and plaques, as well as suppressed inflammation response as indicated by
activated microglia numbers. Exendin-4 also decreases the neuronal pathologies of AD in the hippocampus. In addition, exendin-4 alleviates the defective insulin signaling, indicated by the suppressing of the increased serine phosphorylation of insulin receptor substrate-1 and activated c-Jun N-terminal kinase, commonly observed in AD. Lixisenatide also shows neuroprotective effect and improves memory and synaptic plasticity in the rodent models of diabetes or AD. These evidences support that exenatide, liraglutide or lixisenatide prevent or alleviate the age-related neurodegeneration and AD progression, thus have the potential to be novel agents for the treatment of dementia. Whether albiglutide and dulaglutide provides protection against age-related cognitive decline still needs research. In 2013, a study reported that exenatide improves cognitive outcome in patients with Parkinson's disease, signifying the first steps of the GLP-1 receptor agonist into the clinic use in neuroprotection. The first clinical trial of GLP-1 analogs on mild cognitive impairment cases in the USA and the UK is ongoing. More clinical trials are needed to determine the safety and efficacy of the GLP-1 receptor agonists for the treatment of cognitive decline in AD patients or normal elderly.

**Conclusions**

As the global population aging rapidly, the brain aging and cognitive decline is becoming a serious issue needed to be solved. Currently, no curative treatment for cognitive impairment and dementia is available. Epidemiologic data have shown that diabetes and impaired glucose tolerance are related to a higher risk of AD and other demenias. CR has been proven to be effective in promoting longevity and brain health, and decreasing the incident of AD. Insulin and common anti-diabetic medicines (including the metformin, alpha-glucosidase inhibitors, TZDs, and GLP-1 analogs) have shown the protective effect against age-related cognitive decline. However, some anti-diabetic medications, such as metformin and TZDs, show inconsistent results. In addition, how to improve the safety and to minimize the side effects of the anti-diabetic drugs should be considered in exploring their application for the treatment of brain aging. Therefore, more researches are required for better understanding of the aging mechanisms and for exploring effective ways to maintain brain health. Especially, the researches that study the effect of anti-diabetic drugs on the cognitive ability in normal elderly are needed. As more and more promising information has been collected, feasible and effective therapies will be developed for the prevention of brain aging in the future.

**Conflict of interest**

The authors declare no conflict of interest.

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