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Review article

Potential effects of current drug therapies on cognitive impairment in patients with type 2 diabetes

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ABSTRACT

Type 2 diabetes mellitus is a complex metabolic disease that can cause serious damage to various organs. Among the best-known complications, an important role is played by cognitive impairment. Impairment of cognitive functioning has been reported both in type 1 and 2 diabetes mellitus. While this comorbidity has long been known, no major advances have been achieved in clinical research; it is clear that appropriate control of blood glucose levels represents the best current (although unsatisfactory) approach in the prevention of cognitive impairment. We have focused our attention on the possible effect on the brain of antidiabetic drugs, despite their effects on blood glucose levels, giving a brief rationale on the mechanisms (e.g. GLP-1, BDNF, ghrelin) that might be involved. Indeed, GLP-1 agonists are currently clinically studied in other neurodegenerative diseases (i.e. Parkinson's and Alzheimer's disease); furthermore, also other antidiabetic drugs have proven efficacy in preclinical studies. Overall, promising results are already available and finding new intervention strategies represents a current need in this field of research.

Contents

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1. Introduction

Increasing evidence suggests that cognitive impairment and dementia might be complications of type 2 diabetes mellitus (T2DM) (Li and Huang, 2016; Strachan et al., 2011). T2DM is a complex metabolic disease that can cause serious damage to various organs. It is a chronic disease due to an altered homeostasis of glucose and lipid metabolism characterized by insulin resistance and often followed by progressive insufficient production of insulin by the pancreatic β cells (Esser et al., 2014). Recent studies suggest that chronic inflammation due to excessive adipose tissue contributes to the pathogenesis of diabetes. Fat cells' excess induces an increased release of proinflammatory cytokines (e.g. IL-6, TNF-α), which determine a chronic inflammation state leading to insulin resistance and T2DM (Richardson et al., 2013). T2DM has a significant impact on patients' quality of life and is associated with high mortality and morbidity. Among the best-known complications (i.e. retinopathy, nephropathy and vascular disease), an important role is played by cognitive impairment (Dash, 2013). Literature data suggest a correlation between T2DM and cognitive decline, and particularly between T2DM and mild cognitive impairment (MCI) (Luchsinger et al., 2007; Strachan et al., 2011). T2DM is associated with a slowly progressive brain damage (Brundel et al., 2014). Mild to moderate impairments of cognitive functioning has been reported both in type 1 and 2 diabetes mellitus (DM) (Koekkoek et al., 2014).

MCI is a pathological entity with heterogeneous cognitive characteristics. The transition to dementia might depend on different associated risk factors such as comorbidity, genetic predisposition and/or environmental factors (Campbell et al., 2013). The concept of MCI involves a state of subclinical cognitive deficit with a potential risk of developing Alzheimer's disease (AD) (Petersen, 2009). The exact pathophysiological mechanism(s) of cognitive dysfunction(s) and cerebral damage in DM is not completely understood, but different causes such as hyperglycemia, vascular disease, hypoglycemia, and insulin resistance seem to play significant roles. Poor glycemic control (measured as an increased glycated hemoglobin; HbA1c) and microvascular complications contribute to the anatomical and functional alterations on the central nervous system (CNS), with increased cortical atrophy and microstructural abnormalities that lead to cognitive impairment associated to attention deficit, impaired executive function, ideomotor movements, and verbal memory damage. Both hypoglycemia and hyperglycemia have been implicated as major causes of cognitive dysfunction. DM accelerates brain-aging process causing cerebral atrophy, furthermore, it seems to interfere with cerebral β-amyloidogenesis resulting in tau hyper-phosphorylation through a mechanism related to insulin resistance, neuroinflammation and disruption of synaptic plasticity (Roriz-Filho et al., 2009).

This review summarizes the link between DM and cognitive impairment focusing on the possible role played by antidiabetic drugs. To the best of our knowledge, there are no specific, well-designed, clinical studies considering potential positive or negative effects of drug treatment on cognitive function in diabetic patients (Patrone et al., 2014); we, therefore, review the most valuable data concerning this matter both obtained in clinical and preclinical studies also highlighting the most relevant molecular mechanisms involved.

2. Insulin and related signals function(s) in the brain

This section is meant to briefly highlight the importance of insulin and some related signaling pathways (GLP-1, Ghrelin, CREB, BDNF, SIRT1) for brain function in relation to cognition. Several studies pointed out the major role played by these systems in the CNS and identified such pathways as suitable targets for the development of effective therapies for the treatment of cognitive decline. Several reviews describing in details the role of each of them are currently available summarizing the current knowledge coming out from *in vitro* and in vivo studies; however, only few of them can be directly linked to cognitive decline as a comorbidity of diabetes and even less is known about the effects of antidiabetic drugs on these signaling pathways in the brain. Further studies in the future will hopefully shed light on their real relevance for therapeutical usefulness.

2.1. Insulin

Insulin, produced by pancreatic β-cells, regulates glucose utilization in the periphery and the metabolism of fat and proteins. The action of insulin is mediated by the insulin receptor (IR). The IR is a membrane protein of tyrosine kinase receptor family comprised of two α and two β subunits that is also largely expressed in the brain (Schulingkamp et al., 2000; Zhao and Alkon, 2001). IRs in the brain are mainly localized in the hippocampus (one of the most relevant areas involved in memory and learning), olfactory bulbs, cerebral cortex, hypothalamus, cerebellum and choroid plexus (Zhao et al., 1999). Insulin and IRs play important roles in learning and cognitive processes by modification of the activities of both excitatory and inhibitory postsynaptic receptors and the activation of specific signaling pathways (Plum et al., 2005; Zhao et al., 2004). Insulin is required to facilitate long-term potentiation (LTP) in the hippocampus of immature rats (Zhao et al., 2010). Brain insulin infusions improved spatial memory in aged and young rats (Haas et al., 2015). Intrahippocampal injections of insulin enhanced memory in healthy male rats (Babri et al., 2007). Mice with neural tissue-specific knockout (KO) of the IR (NIRKO) showed a complete loss of insulin-mediated activation of phosphatidylinositol 3-kinase and inhibition of neuronal apoptosis (Schubert et al., 2004). Furthermore, it has been shown that significant decreases in IR substrate 1 (IRS-1) and 2 (IRS-2) levels were identified in neurons from AD patients leading to resistance to IGF-1 and insulin signaling (Moloney et al., 2010). Recently, it has been observed that neuronal deficiency of the IR in AD mouse models leads to delayed Aβ accumulation (Zemva and Schubert, 2014). However, contrasting results on the role of IRS-2 have been reported; data suggested that IRS-2 is a negative regulator on memory formation by restricting dendritic spine generation, in particular IRS-2 KO mice showed enhanced hippocampal spatial reference memory (Irvine et al., 2011) while in mice lacking IRS-2, hippocampal synaptic plasticity and metaplasticity were disrupted (Costello et al., 2012) as well as LTP formation (Martin et al., 2012).

Insulin can cross the blood-brain barrier (BBB) by a receptor-mediated transport mechanism (Baura et al., 1993). Insulin resistance is characterized by reduced responsiveness of target tissues to insulin signaling. It causes decreasing insulin permeation

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