

Moieties in antidiabetic drugs as a target of insulin receptors in association with common neurological disorders (Review)

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Abstract. Insulin is a peptide that can be harmful with regards to neuroplasticity, neuroprotection and neuromodulation. Furthermore, the role of insulin highlights its relevance in the progress of diverse clinical disorders as well as in the mechanisms associated with certain pathogenesis and their evolution towards diabetes, obesity and neurodegenerative diseases. The precise molecular mechanisms by which these diseases are induced remain to be elucidated. The benefits in knowing/discovering these mechanisms in animal models and humans cannot be undermined. An in depth understanding of the principal risk factors leading to obesity and their management is vital in the implementation of early-life strategies of intervention and prevention, with a view to avoid adverse late-life outcomes. Therefore, the aim of the present study was to review their possible association with antidiabetic drugs.

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1. Introduction

Certain regions of the brain, particularly the brainstem as well as the hypothalamus, are known to be the homeostatic control centers of feeding, glucose homeostasis and energy consumption. Such brain spaces are composed of neurons and neuronal circuits, which may directly or indirectly be activated or inhibited by lipids, glucose or amino acids. An imbalance in the ability of the neurons to detect the signals emitted by such nutrients could provoke metabolic diseases such as obesity and diabetes (1). The brain is responsible for the two poles of glycemia (hyperglycemia and hypoglycemia) and the cells that detect glucose are located in numerous anatomical regions, such as the central nervous system (CNS). The regulation of glucose homeostasis and the sum of energy reaching the neurocircuits of the hypothalamus and those of higher brain regions, such as the dopaminergic system, is the function of the insulin-sensing cells of the CNS. Hyperinsulinemia of a fetus is principally in response to bad maternal nutritional habit that could lead to obesity and/or diabetes. This could cause a disturbance in the neurocircuit development in the fetus thereby disposing the fetus to metabolic diseases later in life (2).

2. Insulin and obesity

Obesity has been described as a New World Syndrome (3). It is characterised by an excess of glucose and body fat, which, the majority of the time, results in an increase in body weight. Obesity is defined as a body mass index ≥ 30 kg/m² in adults (4). Changes in glucose levels mobilize the neuroendocrine response in charge of preventing and correcting glycemia. The hypothalamus is the main area of the brain responsible for regulating glycemic homeostasis. Consequently, metabolic diseases such as diabetes and obesity arise principally as a result of imbalance in this control (5). Zeng *et al* (6), in a study of fatty acid metabolism using Yhhu981, a powerful novel compound that functions to stimulate oxidation of fatty acid and to exert pleiotropic effects on lipid metabolism (by activating 5' adenosine monophosphate-activated protein kinase), suggested that defects in the metabolism of fatty acid contributed to the pathogenesis of insulin resistance and obesity. Similarly, maternal obesity present during pregnancy

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could modify the development of certain specific fetal brain cell-networks. These defects can produce pathologies, such as metabolic syndrome and possibly certain neurological diseases, in the offspring at a later age (7).

In epidemiological studies, the level of adiposity is linked to dementia and Alzheimer's disease (AD). Overweight and obesity in mid and late-life may increase the risk of dementia (8). Currently, these disorders are considered as potential risk factors that could lead to several neurodegenerative failures (9).

Environmental factors existing during pregnancy and the postnatal period could have an impact on stress factors, susceptibility genes and brain development in a structural and functional manner, giving rise to disorders that could manifest later in life. Aging produces a desynchronization of biological systems which critically worsens brain entropy/decline. In AD, this imbalance may affect cortisol, noradrenaline, stress components and reactive oxygen species (ROS), the result of which is membrane damage and an insulin-resistant brain state leading to a decrease in glucose/energy metabolism (10). Presently, it has been discovered that treatments with cancer therapeutic agents such as glucocorticoids, chemotherapy, hormonal therapies and targeted drugs can induce insulin resistance (11).

The neurological systems responsible for the identification and response to salient stimuli are important for the survival in difficult and unsteady environmental conditions. Differences among humans, such as variations in genetics, and hormonal as well as metabolic status involve behavioral strategies and neuronal responses to changes in the environment. Certain investigators suggest that the capacity of leptin in promoting stress-induced dopaminergic function is crucial in the production of pathological states including mood, disorders in the use of drugs and eating promoting obesity, where dopamine has an important role (12). The study by Ariaans *et al* (11) indicates that diabetes is associated with reduced basal dopamine levels in the nucleus accumbens. Possibly, the free radicals in the CNS are responsible for the induction of these disorders (13).

3. Pathogenesis of oxidative stress in the brain

The amount of free radicals generated should be in equilibrium with the antioxidant system. Disruption of this equilibrium would give rise to cell damage, elicit disorders in the physiological state and foster pathological process such as neurodegenerative disorders, and DNA 8-oxo-7,8-dihydroguanine accumulation due to the integration of oxidized nucleotide resulting from replication or due to the oxidation of DNA guanine (14). Similarly, the mitochondrial respiratory chain becomes the principal site of superoxide radical production. However, the precise mechanism as well as the exact location for the generation of ROS within the mitochondrial respiratory chain, is yet to be elucidated. Oxidative stress has been shown to constitute a key factor for the onset of neurodegenerative diseases (15). Excessive production of ROS or reactive nitrogen species (RNS) is proposed as detrimental to target cells, and may be responsible for diverse degenerative processes of certain human diseases in the CNS. Depending on the species or target cells, ROS or RNS may be beneficial or harmful in neuronal signaling pathways concerned with the pathophysiology of the neurodegenerative diseases (16).

By contrast, neurodegeneration is characterized by selective neuron loss. In the brain regions, the loss of neurons in the hippocampus and substantia nigra sites are known to be extremely vulnerable to cell damage, and this is attributed to AD (17). In sporadic AD, disorders of metabolism such as atherosclerosis, diabetes or obesity [products of hypercholesterolaemia (Hpc)] constitute an important risk factor. Hpc is associated with an increment in immunoglobulin G that acts against oxidized lipoproteins. The Fc region of the immunoglobulin G has specific receptors and it has been found that in AD, autoantibodies against these receptors and non-brain antigens are produced. The γ -chain is the principal subunit that activates Fc receptors and it has been found that in rats, deletion of this chain has a protective effect against learning and memory disorders and does not increase cholesterolaemia nor affect the level of brain serum immunoglobulin G. Such protective effects are due to a decrease in tau hyperphosphorylation, loss of synapsis and accumulation of intracellular amyloid β ($A\beta$) not only in the neurons of the cortex but also in the hippocampal pyramid. The receptors of the Fc region of immunoglobulin G has an important role in the development of AD-hpc-associated features suggesting a new potential target in the prevention of AD in patients with Hpc (18).

Adult neural stem cells (NSCs) exist in few regions of the brain. In adult rats, the multipotent version of this cell, the htNSCs, are found in the mediobasal hypothalamus. Consumption of high fat-containing food in the chronic form is capable of reducing these cells, as well as activating I κ B kinase β (IKK β)/nuclear factor- κ B (NF- κ B) linked to htNSCs. It has been proposed that adult htNSCs are crucial in the regulation of metabolic physiology and that IKK β /NF- κ B-mediated impairment of adult htNSCs is an important neurodegenerative mechanism for the development of obesity and associated diabetes (19).

Epidemiological data suggests an increased risk of developmental dementia in individuals with obesity and type 2 diabetes and also in those with poor insulin sensitivity without diabetes, which causes a mechanistic link between adiposity, insulin sensitivity and dementia. Diabetes can cause neurodegenerative diseases due to its effect on the actions of insulin in the neurons (20).

4. Obesity and Alzheimer's disease

Insulin resistance by the central nervous regions could lead to obesity and AD. Such resistance may be as a result of genetic polymorphisms or due to long-term exposure to high amounts of circulating insulin as a result of insulin resistance at the peripheral level (21). Such disorder is possibly produced by toxic lipids and ceramides that cross the blood-brain barrier through a liver-brain axis. Once in the brain spaces, the resultant effects are brain insulin resistance, oxidative stress and neuro-inflammation (22). Any injury to the body produces an inflammation principally due to the innate immune response and through the systemic circulation, the inflammatory reaction is propagated to the CNS. In chronic conditions and in obesity as well as diabetes, this type of event can be observed. Inflammation in the CNS contributes to the pathogenesis of neurodegenerative disorders principally AD, multiple sclerosis and Parkinson's disease. These disorders are prone to exacerbation as a result of increased inflammation

Table I. Novel and previous antidiabetic drugs used to improve blood glucose levels.

Drug	Effects	(Refs.)
Metformin	Principal therapy for T2D. Increases adenosine monophosphate-activated protein kinase activity	(29)
Empagliflozin	SGLT2 inhibitor with a mechanism of action that is independent of β -cell function and the insulin pathway	(30)
Sitagliptin	Improves glycemic control with a lower risk of hypoglycemia and weight gain in diabetic patients	(31)
Imeglimin	Improves β -cell function, which may contribute to its glucose-lowering effect in T2D	(32)
Luseogliflozin	Potent and competitive SGLT2 inhibitor for the management of T2D	(33)
Canagliflozin and dapagliflozin	New SGLT2 inhibitors for management of T2D	(34)
Ipragliflozin	SGLT2 inhibitor for T2D	(35)

T2D, type 2 diabetes; SGLT2, sodium glucose co-transporter-2.

within the CNS, following peripheral injury (23). Although obesity is linked to structural brain changes, little is known regarding these associations with the rate of brain atrophy. The only major decline was observed in the volume of gray matter, precuneus, cingulate and orbito-frontal gyro in globally obese people. Midlife obesity may be an important modifier of brain atrophy in individuals who are developing cognitive impairment and dementia, but in demented older adults, it has little effect on structural brain integrity (24). Metabolic disturbances such as insulin resistance, diabetes, obesity and neuropsychiatric diseases have been demonstrated in human and animal studies, which suggest the likelihood of sharing the same pathophysiological mechanisms. As a pleiotropic peptide, insulin is associated with neuroplasticity, neurotrophism and neuromodulation. Furthermore, this compound has an important role in the progression of various neuropsychiatric diseases, such as the mechanisms associated with the pathogenesis and evolution of obesity, diabetes and neurodegenerative problems such as AD (25).

The neurotrophic effect of insulin is clearly manifested at moderate concentrations. Reduction in the clearance of A β in brain regions is possibly due to the action of insulin, for the fact that the two share a common and depurative mechanism: The insulin-degrading enzyme (IDE). IDE is more selective for insulin than for A β , hence, brain hyperinsulinism may exclude A β proof from its principal clearance mechanism (26).

Insulin is the most effective pharmacological treatment for the control of hyperglycemia, and the main target tissue is the liver (27). Insulin resistance leads to hyperinsulinemia and eventually hyperglycemia. In the United States, the diabetic rate has continued to rise. It is estimated that >25 million people in the United States currently have either T1D or T2D (28).

5. Diabetes and drug treatments

Despite advances in detection and insulin therapies, the prevalence of diabetes has continued to increase. The choice of an insulin treatment, timely initiation and schedule of insulin therapy are crucial factors in reaching optimal glycemic control. This involves a proper combination of insulin

and antidiabetic agents in a way that guarantees safety and improves blood glucose levels (Table I) (29-35).

The chemical structure of metformin is open with numerous electrophilic atoms, while that of Imeglimin is a cyclic structure. The two drugs have similar moieties and consist of five nitrogen atoms. The other structures, including potent antidiabetic agents, are large and contain phenyls and pyrans moieties C-6 substituted with methyl, fluorine and chlorine atoms that suggest abundant steric effects in the receptor tissues.

Regardless of the intensive glycemic control, mortality in diabetic patients with cardiovascular diseases has not reduced. This poses a significant challenge indicating that a scheme of strict glycemic control in the management of diabetes is required. The use of sulfonylurea is significantly associated with severe hypoglycemia in patients with type 2 diabetes treated with insulin. However, the use of biguanide (45-76%) and thiazolidinediones (15-34%) is associated with the development of severe hypoglycemia (36).

Currently, there are ~9 different oral pharmaceutical classes and several insulin and noninsulin injectable medications for the treatment of T2D (37). The antidiabetic drugs have widely been used as first-line antidiabetic medicines for the treatment of T2D and for suppressing hepatic glucose production. The latter is the main mechanism by which metformin improves hyperglycemia through the suppression of gluconeogenesis and stimulation of glycolysis (38).

Insulin prevents synaptic deterioration which is the basis of severe memory loss in early AD (39). Insulin signaling impairment in the brain could promote the formation of neurofibrillary tangles with abnormally hyperphosphorylated tau protein (40), and a reduction in tyrosine hydroxylase in the brain has been found to occur in this disease (41). Similarly, the effects of metformin were found to be antagonized by the addition of insulin, which reduced A β levels, oxidative stress, mitochondrial dysfunction and eventually cell death (42).

6. Expectance

It appears that adiposity is instrumental in Parkinson's disease and AD. The development of obesity is a result of early-life events. There may an association between early determinants

of obesity, as insulin resistance is associated with the development of these neurological disorders (43). Treatments aimed at preventing β -cell loss or increasing the number of β -cells may inhibit the progression of diabetes and enhance the restoration of normal metabolism, and the targets for this are β -cell proliferation, neogenesis and survival (44). An integral knowledge of the key risk factors involved in obesity and their management is vital in the implementation of early-life strategies, intervention and prevention, with a view to avoid adverse outcomes later in life.

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