ISSUE TOPIC
Đuran I. Contribution of insulin to mood disorders. pp. 26 – 28

CONTRIBUTION OF INSULIN TO MOOD DISORDERS

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Abstract

Insulin is one of the most important hormones in the human body. Research on insulin has moved from it being an anabolic hormone controlling blood glucose levels, to a hormone that has many different effects not only on the internal organs and the musculoskeletal system but also profound effects on the central nervous system (CNS). The aim of this literature review is to serve as an aid, or a starting point, in understanding the influence of insulin on the CNS, as it will provide valuable insight into various molecular interplays and interesting pathways by which insulin could possibly modify not only mood, but the whole understanding of mood disorder patophysiology.

KEYWORDS: central nervous system, dopamine, insulin resistance, molecular psychiatry, mood disorders, serotonin

INTRODUCTION

Major depressive disorder (MDD), schizophrenia (SCZ), bipolar disorder (BD) and many other pyschiatric conditions show a connection, which is often far from simple, to metabolic syndrome (MetS).[1,2] MetS is characterized by obesity, glucose intolerance, hypertriglyceridemia, hypertension and insulin resistance.[3] Insulin, being a multifaceted hormone, is mostly in charge of blood glucose level control, but also, exerts its physiological influence across almost every system within the human body, extending its effects particularly to the central nervous system (CNS).[3-6]

INSULIN AND ITS EFFECTS ON BRAIN

As uncomplicated as it may seem, the pathways by which insulin induces its action are far from it, as there are countless molecules with which insulin interferes. Insulin crosses the blood-brain barrier (BBB) at the level of brain endothelial cells.[7] It is transported via a mechanism called transcytosis through insulin receptor (IR)-mediated transport and lipid rafts.[7] Brain regions do not take up insulin at the same rate, so there is a possibility that the uptake rate could serve as an explanation for different insulin effects on the CNS.[8] After entering the CNS and reaching IRs at specific points, insulin exerts its action. The binding of insulin to its IR starts a cascade that recruits insulin receptor substrates 1 and 2 (IRS 1 and 2). The downstream effects of IR activation include effects of phosphatidylinositol 3-kinase (PI3K), mammalian target of rapamycin (mTOR), and protein kinase B. Those products modify neurotransmitter release, synaptic plasticity, and neuronal behavior.[9,10] IRs have been found in different regions of the CNS; the dorsal raphe nucleus (DR), serotoninergic (5-HT) neurons,[11] dopamine neurons in the ventral tegmental area (VTA), neurons in the substantia nigra compacta (SNc),[12] in the supraoptic nuclei, dorsomedial nuclei of hypothalamus[13] and others.[14] In a study by Martin et al., it was shown that in mice fed a standard food diet (SFD), insulin first induces an increase in DR 5-HT neuron action potential frequency, which in turn leads to an increase in extracellular 5-HT concentration in the aforementioned neurons.[11] After the accumulation of 5-HT by the observed, but not yet understood, autoinhibitory mechanism, the rate of firing decreases. An increase in 5-HT produces anxyolitic effects in mice fed the SFD. However, in mice fed a high-fat diet (HFD), which produced MetS-like symptoms in mice, insulin application failed to induce anxyolitic effects via a 5-HT-induced mechanism.[11] MDD onset is linked to low 5-HT levels;[15] therefore, this conclusion can support the influence of MetS and insulin resistance on the onset of MDD.

METABOLIC SYNDROME AND PSYCHIATRIC DISEASES

Many psychiatric conditions, including MDD, SCZ, BD , and others, show dysregulation in numerous different molecules such as dopamine (DA) and γ-aminobutyric acid (GABA). Their levels are altered in MetS, which can influence the onset of such diseases.[16–18] DA is highly influential on mood control, reward control, and addiction control.[19,20] It is important to note that body mass index (BMI) is higher in individuals resistant to insulin and is also increased in those with MetS, modifying genes regulated by DA . This takes place in both the dorsolateral prefrontal cortex (dlPFC), which plays a crucial role in behaviour, and in the hippocampus. The effects of BMI on the dlPFC and hippocampus contribute to the symptoms and presentations of BD, SCZ, and MDD.[21] Directly, insulin increases the number of GABA A (GABAA)[22] and N-methyl-D-aspartate (NMDA)[23] receptors on neuronal surfaces.[24] NMDA receptors and their antagonists play an important role in suppressing treatment-resistant depression.[25] Proton magnetic resonance spectroscopy proved that depressive disorders show significant deficits in GABA levels in different parts of the human brain cortex.[26,27,28] GABA is also widely regarded as a molecule that plays a significant role in mood, anxiety and brain development.[29,30] This means that the intricate interplay behind IRs and insulin

resistance on these receptors could serve as an important staple regarding future scientific advances in treating frequent psychiatric disorders in people who suffer from insulin resistence. The relationship between depression and MetS is bidirectional - MetS patients often report depression, and vice versa.[31] BD and SCZ, besides MDD, are also conditions that are more prevalent in individuals with MetS and insulin resistance.[32,33] Treatment of such conditions, as well as other psychiatric conditions, often involve multiple psychiatric medications, which in turn lead to the worsening of MetS.[34]

CONCLUSION

The sheer complexity of insulin is yet to be understood. Huge progress has recently been made by massive advances in science, especially molecular biology and genetics. As discussed, insulin is a multifaceted hormone that exerts effects on almost every organ in the human body. It crosses the BBB and binds to specific IRs in different parts of brain. Downstream effects of insulin include IRS1 and 2, mTOR and others. Insulin also interplays with DA, 5-HT, GABA receptors, NMDA receptors and many other molecules and their receptors which are found in different areas of human brain. MDD, SCZ, BD , and other psychiatric conditions show a relation to MetS, a condition characterized by insulin resistance, among other clinical manifestations. Advances have been made in understanding the metabolic pathways through which insulin resistance and MetS could be linked to psychiatric conditions. As time goes by, it is becoming clearer that future discoveries in areas regarding the effect of insulin on psychiatric disease onset might play a significant role in the treatment of such conditions.

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UČINAK INZULINA NA POREMEĆAJE RASPOLOŽENJA

Sažetak

Inzulin je jedan od najvažnijih hormona ljudskog tijela. Istraživanja na temu inzulina su napredovala od toga da se radi o anaboličkom hormonu koji regulira razine glukoze u krvi, do činjenice da inzulin ima mnoštvo različitih učinaka, ne samo na unutarnje organe i koštano-mišićni sustav, nego i središnji živčani sustav (SŽS). Cilj ovog pregleda literature je bio poslužiti kao pomoć, odnosno kao početna točka u razumijevanju samog učinka inzulina na SŽS, jer će pružiti vrijedan uvid u razne molekularne interakcije, kao i zanimljive puteve kojima inzulin potencijalno utječe na promjenu, ne samo raspoloženja nego i cijelog razumijevanja patofiziologije tih poremećaja.

KLJUČNE RIJEČI: dopamin, inzulinska rezistencija, molekularna psihijatrija, poremećaji raspoloženja, serotonin, središnji živčani sustav