Regulation of insulin receptor phosphorylation in the brains of prenatally stressed rats: New insight into the benefits of antidepressant drug treatment

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Abstract

A growing body of evidence supports the involvement of disturbances in the brain insulin pathway in the pathogenesis of depression. On the other hand, data concerning the impact of antidepressant drug therapy on brain insulin signaling remain scarce and insufficient. We determined the influence of chronic treatment with antidepressant drugs (imipramine, fluoxetine and tianeptine) on the insulin signaling pathway of the brain of adult prenatally stressed rats. 3-month-old prenatally stressed and control rats were treated for 21 days with imipramine, fluoxetine or tianeptine (10 mg/kg/day i.p.). The impact of chronic antidepressant administration was examined in forced swim test. In the frontal cortex and hippocampus, the mRNA and protein expression of insulin, insulin receptor, insulin receptor substrates (IRS-1, IRS-2) and adaptor proteins (Shc1, Grb2) on the insulin signaling pathway of the brain of adult prenatally stressed rats. 3-month-old prenatally stressed and control rats were treated for 21 days with imipramine, fluoxetine or tianeptine (10 mg/kg/day i.p.). The impact of chronic antidepressant administration was examined in forced swim test. In the frontal cortex and hippocampus, the mRNA and protein expression of insulin, insulin receptor, insulin receptor substrates (IRS-1, IRS-2) and adaptor proteins (Shc1, Grb2) before and after drugs administration were measured. Rats exposed prenatally to stressful stimuli displayed depressive-like disturbances, which were attenuated by antidepressant drug administration. We did not reveal the impact of prenatal stress or antidepressant treatment on insulin and the insulin receptor expression in the examined structures. We revealed that diminished insulin receptor phosphorylation evoked by the prenatal stress procedure was attenuated by drugs treatment. We demonstrated that the favorable effect of antidepressants on insulin receptor phosphorylation in the frontal cortex was mainly related with the normalization of serine312 and tyrosine IRS-1 phosphorylation, while in

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1. Introduction

Despite many years of study, depression is still a disease with poorly recognized etiology. Recent data indicate that metabolic disturbances may be important in the pathogenesis of depression, and simultaneously, they clearly indicate a link between depression and some metabolic illness, including diabetes (Lang and Borgwardt, 2013). In fact, depression enhances the risk for diabetes, and patients with diabetes are twice as likely to experience depression as the general population (Hryhorczuk et al., 2013). Interestingly, experimental data showed that diabetic mice and rats presented more pronounced depressive-like behavior when submitted to the forced swimming test (Wayhs et al., 2013), while in an animal model of depression, metabolic disturbances similar to those reported in diabetes have been observed.

Among the common mechanisms causing similar changes in brain structures in the course of diabetes and depression, the inflammatory activation, oxidative stress as well as disturbances in the hypothalamus-pituitary axis have been proposed (de Moraes et al., 2014; Moloney et al., 2010; Wayhs et al., 2014). Glucocorticoids are essential for the maintenance of homeostasis and stress adaptation and play a crucial role in the regulation of metabolic processes, mainly glucose and insulin action. Therefore, excess of these hormones may lead to insulin resistance, disturbances in glucose metabolism, brain neurotransmitter synthesis and function, which causes brain disorders (Kuo et al., 2015; Magomedova and Cummins, 2016).

Insulin is a hormone secreted not only from pancreatic β cells in the periphery but also in some parts of the central nervous system, such as in the olfactory bulbs, the frontal cortex, the hypothalamus and the hippocampus (Duarte et al., 2012; Gerozissis, 2008; Ghasemi et al., 2013a, 2013b). Furthermore, insulin has the ability to cross the blood brain barrier via a saturable transporter, and thus the brain is a target of circulating insulin (Dorn et al., 1983). Generally, central insulin effects could be supplementary to the peripheral action of this hormone and are expressed as contributions in food intake regulation, body weight, energy homeostasis and glucose production or by gonadotropin synthesis in the pituitary. A growing body of evidence indicates that insulin is important not only for metabolic processes but also as a growth factor in the neuronal growth and differentiation, synapse density, synaptic transmission and plasticity and cognitive function (Ghasemi et al., 2013a, 2013b).

The biological function of insulin is mainly implemented by insulin receptors (IRs), which are widely expressed throughout the brain and are present in neurons and glia cells (Havrankova et al., 1981). The highest level of IRs was demonstrated in the olfactory bulbs, the cerebral cortex, the hippocampus, the cerebellum and the hypothalamus (Detka et al., 2015). IRs are transmembrane heterotetramers consisting of two extracellular α subunits that contain an insulin-binding site and two intracellular β subunits that exhibit tyrosine kinase activity. The binding of the ligand to the receptor results in conformational changes in the α subunits and autophosphorylation of the intracellular part of the IR. Subsequently, this leads to the phosphorylation of insulin receptor substrate docking proteins (IRS) mainly IRS-1 and IRS-2 (Basta-Kaim et al., 2014b; Boura-Halfon and Zick, 2009; Shaw, 2011). Apart from IRS in the regulation of insulin receptor function, Src homology-2 (SH2) domain-containing signaling molecules are involved, which in turn activate the catalytic subunit of phosphatidylinositol 3-kinase (PI3K), the growth factor receptor-bound protein 2 (Grb-2) (Duarte et al., 2012) or other intracellular signaling cascades, such as mitogen-activated protein kinase (MAPK) (Lucy and May, 2016).

The mentioned above, the ability of insulin to regulate neuronal signaling and to improve cognition leads to the hypothesis that it can act as a mediator of the onset and treatment of depression. Recent data have demonstrated that chronic fluoxetine administration stimulates neuronal progenitor cell proliferation and differentiation in the hippocampi of streptozotocin-induced diabetic mice (Beauquis et al., 2009). Moreover, short-term selective serotonin-reuptake inhibitor treatment attenuated glucose homeostasis in non-diabetic depressed subjects and improved glycemic control in depressed patients suffering from type 2 diabetes (Detka et al., 2015). However, thus far, there is no data concerning the impact of antidepressant drugs on regulation of the insulin signaling pathway in the frontal cortex and the hippocampus, which are the structures mainly involved in the pathogenesis of depression.

Therefore, the present study was designed to explore the mRNA and protein expressions of insulin and insulin receptors (IRs) and the concentrations of total and phosphorylated (active) intracellular IR subunits in an animal model of depression. Moreover, we focused on the insulin receptor substrates (IRS-1 and IRS-2) and insulin adaptor proteins (Shc, Grb2) in adult rats that were prenatally stressed. In a subsequent set of experiments, the impact of the chronic administration of antidepressant drugs belonging to various chemical groups (imipramine, fluoxetine and tianeptine) on prenatal stress-evoked changes in the brain insulin network was determined.

In the present study, we applied a widely accepted animal model of depression based on a prenatal stress procedure (Maccari and Morley-Fletcher, 2007; Szymańska et al., 2009), the face, predictive and construct validities of which have been characterized in previous studies (Budziszewska et al., 2010; Glombik et al., 2016; Szymańska et al., 2009). This model is based on the observation that early adverse life experiences can affect brain development and may be involved
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