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THE INTRANASAL CO-ADMINISTRATION OF C-PEPTIDE AND INSULIN IMPROVES THE METABOLIC PARAMETERS AND THE ACTIVITY OF THE ADENYLYL CYCLASE SYSTEM IN THE HYPOTHALAMUS, MYOCARDIUM AND EPIDIDYMAL FAT OF RATS WITH THE TYPE 2 DIABETES MELLITUS

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The C-peptide, the product of proinsulin proteolysis, regulates the physiological and biochemical processes by increasing the bioavailability of insulin due to the formation of complexes with it or by binding to the receptors for C-peptide. In the conditions of insulin deficiency in severe forms of the type 2 diabetes mellitus (DM), the levels of C-peptide and insulin within the brain, which is their target, are reduced. This deficiency can be compensated by intranasally administered C-peptide (ICP) and insulin (II). It is assumed that the use of ICP and II in the type 2 DM will lead to normalization of activity of the adenylyl cyclase signaling system (ACSS) in the hypothalamus and periphery and, thus, provide the therapeutic effect of ICP and II. The aim of the work was to study the effect of 9-day treatment of four-month-old male rats with the neonatal model of the type 2 DM with ICP (10 μ g/rat/day) and II (20 μ g/rat/day) using their combined and separate administration on the metabolic and hormonal parameters and the activity of ACSS in the hypothalamus, myocardium and epididymal fat (EF). The treatment of diabetic rats with II and ICP+II resulted in a decrease in hyperglycemia and insulin resistance, an improvement of lipid metabolism and a decrease in the atherogenic index. In the hypothalamus, the regulation of adenylyl cyclase (AC) activity by ag-

onists of the MC_4 -melanocortin and D_2 -dopamine receptors, impaired in type 2 DM was restored. The restoration of stimulating effects of the β_1/β_2 - and β_3 -adrenoreceptor agonists on AC activity in the myocardium and the EF was showed, indicating the improvement of hormonal regulation of the cardiovascular system and lipolytic processes in the adipose tissue. The combined use of ICP+II was more effective than the II monotherapy, which demonstrates an increase of the regulatory effects of insulin in the presence of C-peptide. The treatment of diabetic rats with ICP had a weak effect. The obtained data indicates the prospects of co-administration of equimolar quantities of ICP and II to correct the metabolic and functional disorders in severe forms of the type 2 DM.

Keywords: adenylyl cyclase system, proinsulin C-peptide, insulin, intranasal administration, type 2 diabetes mellitus, insulin resistance, hypothalamus, myocardium, epididymal fat