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The Contribution of Changes in Adenylyl Cyclase Signaling System of the Brain and Myocardium to Etiology and Pathogenesis of Diabetes Mellitus

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Abstract

The functional changes in hormone-sensitive adenylyl cyclase (AC) signaling system of the central nervous system (CNS) and periphery play a crucial role in etiology and pathogenesis of diabetes mellitus (DM). The identification of these changes in AC signaling system and the abnormalities in AC signaling network are necessary for creation of the new strategies to treat and prevent diabetic pathology. In this chapter, our data and the results of other authors on the changes in hormone-sensitive adenylyl cyclase signaling system (ACSS) in the diabetic brain and heart and on their contribution to etiology and pathogenesis of DM and its complications, diabetic cardiomyopathy in particular, are presented and analyzed, and the promising approaches to treat DM and its complications, which are based on the restoration of AC signaling cascades and their functional interaction, are discussed.

Keywords: diabetes mellitus, adenylyl cyclase system, brain, myocardium, bromocriptine

1. Introduction

Diabetes mellitus (DM) is a major global health problem affecting more than 350 million people worldwide. It is one of the most severe metabolic disorders in humans characterized by hyperglycemia due to insulin deficiency or insulin resistance of target tissues. Insulin-dependent, type 1, and non-insulin-dependent, type 2, DM (DM1 and DM2) induce a large number of diseases in the nervous, cardiovascular, endocrine, and other systems, and these complications of DM are found in more than one-quarter of diabetic patients [1–4]. It is generally accepted that the changes in hormonal signaling systems in the CNS and periphery play a crucial role

in etiology and pathogenesis of DM and its complications. For a long time, the main attention was focused on the signaling systems regulated by insulin, insulin-like growth factor-1, and leptin, whose functional activity is largely impaired in DM1 and DM2 [5–8]. Meanwhile, in recent years, numerous data in favor of the close relationship between the changes in G protein-coupled signaling systems and the pathogenesis of DM were obtained. These systems are regulated by a broad spectrum of hormonal agents, such as amino acids and their derivatives, peptide and glycoprotein hormones, and nucleotides, which bind specifically to G protein-coupled receptors (GPCRs) seven times penetrating the plasma membrane.

The central role among these systems belongs to adenylyl cyclase signaling system (ACSS), which is represented in all types of cells and tissues and is responsible for hormonal regulation of fundamental cellular processes. The ACSS has the following main components: (1) G protein-coupled receptor (GPCR) recognizing and specifically interacting with hormonal stimuli, (2) $\alpha\beta\gamma$ -heterotrimeric G protein of the stimulatory (G_s) and inhibitory (G_i) types, (3) the enzyme adenylyl cyclase (AC) catalyzing the formation of cyclic AMP (cAMP), and (4) cAMP-activated protein kinase (PKA) and cAMP-activated guanine nucleotide exchange factors (Epac1 and Epac2) that control the cAMP-dependent intracellular cascades and transcription factors. As the pathological changes in ACSS lead to dysfunctions in most organs and tissues, they are one of the causes of severe complications of DM such as diabetic cardiomyopathy, nephropathy, encephalopathy, and metabolic and endocrine disorders.

This chapter describes our data and the results of other authors on the changes and abnormalities in hormone-sensitive ACSS in the diabetic brain and heart and their contribution into etiology and pathogenesis of DM and its complications, diabetic cardiomyopathy in particular, and on the approaches to treat DM, which are based on the restoration of AC-signaling cascades and their functional interaction.

2. The ACSS in the diabetic brain

It is shown that in DM, the functional activity of cAMP-dependent signaling pathways regulated by dopamine (DA), serotonin, and melanocortin peptides in the brain and especially in its hypothalamic area is changed significantly. This triggers neurodegenerative processes in the CNS and affects the central regulation of energy homeostasis, inducing peripheral insulin resistance and abnormalities in the lipid and carbohydrate metabolism (**Figure 1**).

The brain DA controls locomotor activity, cognition, feeding behavior, and via central mechanisms regulates functions of the endocrine and cardiovascular systems. The DA stimulates AC activity via G_s protein-coupled dopamine receptor of the type 1 (DA_1R) and inhibits hormone-stimulated AC activity via G_i protein-coupled DA_2R . In the hypothalamus and brainstem of rats with the streptozotocin (STZ) model of DM1, the concentration of DA and the number of DA_2R decreased significantly [9]. The hypothalamus and brainstem are involved in the control of glucose homeostasis and feeding behavior. In patients and experimental animals with DM2 and metabolic syndrome, the activity of brain D_2 -dopaminergic system also reduced, as illustrated by a decrease of dopamine level and DA_2R expression [9, 10].

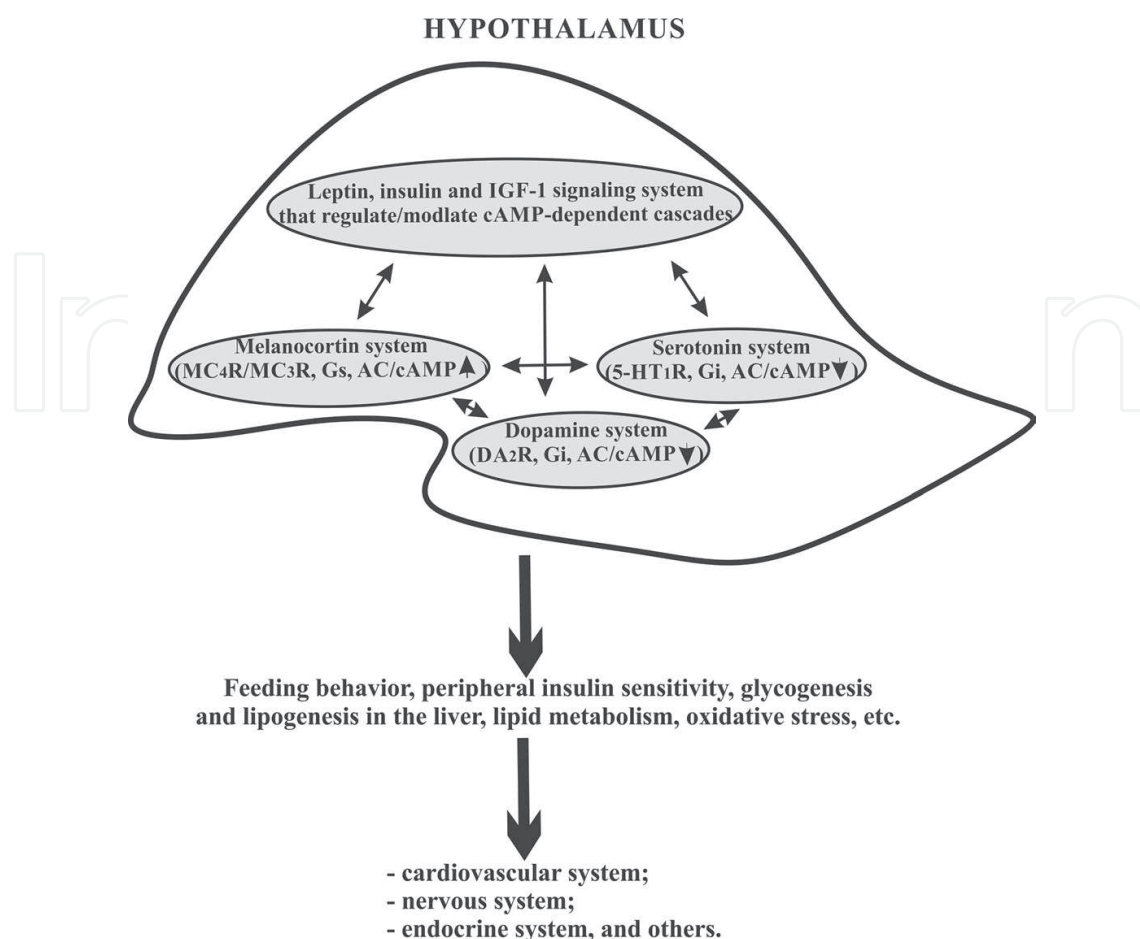


Figure 1. The interaction between hypothalamic signaling systems and their influence on the peripheral energy homeostasis and the functioning of organs and tissues.

We showed that in the brain and in the hypothalamus of rats with acute and moderate STZ-induced DM1 and with neonatal and high fat diet (HFD)/STZ models of DM2, the inhibitory effect of DA₂R-agonists on forskolin-stimulated AC activity and on the expression of the *Drd2* gene encoding DA₂R was reduced significantly, especially in DM1 [11–14]. Meanwhile, the functional activity of DA₁R pathway in the CNS of diabetic rats was changed to a small extent.

The restoration of brain D₂-dopaminergic system in experimental and human DM2 can be achieved using the alkaloid bromocriptine (BC), a selective DA₂R-agonist that activates DA₂R and decreases intracellular cAMP level in neurons. In DM2, the BC inhibits the activity of hypothalamic neurons controlling glucose production and lipid synthesis in the liver, activates dopaminergic neurons regulating insulin sensitivity, and via central mechanisms improves functions of the cardiovascular system, preventing the development of severe forms of diabetic cardiomyopathy [10, 15, 16]. The effect of BC therapy on glucose homeostasis in DM2 is comparable to that of metformin, widely used antidiabetic drug, and, as demonstrated in clinical trials and in animal models, the co-administration of BC with metformin, glipizide, and pioglitazone enhances their glucose-lowering effect and reduces effective doses of these drugs, thereby preventing their adverse effects [17, 18]. The glucose-lowering effect of glipizide when co-administered with BC is also increased in rats with the alloxan model of DM1 [19].

We demonstrated that 2-month BC treatment of rats with HFD-induced DM2 resulted in the improved glucose homeostasis and insulin sensitivity [20, 21]. The BC partially restored sensitivity of brain ACSS to agonists of 5-hydroxytryptamine receptors of the subtype 1B (5-HT_{1B}R) and somatostatin receptors, which indicates a functional relationship between DA₂R signaling and the somatostatin and serotonin systems in the CNS [21]. The treatment of diabetic rats with BC also led to normalization of adrenergic signaling in the myocardium and to restoration of AC sensitivity to gonadotropin in testes, indicating a broad therapeutic potential of BC in DM2 [20].

Brain serotonin, acting on different types of 5-HTRs, regulates feeding behavior, motor activity, pain, depression, and learning. This neurotransmitter is also involved in the control of the cardiovascular, endocrine, and reproductive systems and in the regulation of production of insulin and other hormones by pancreatic islets [22]. It was shown that in patients with DM1 and DM2 and in animals with experimental models of DM1, the brain level of serotonin and its precursor tryptophan and the ratio of free-total tryptophan were significantly decreased. The decreased serotonin level and the changes in serotonin metabolism due to decrease in activity of tryptophan-5-hydroxylase-2, the rate-limiting enzyme in serotonin biosynthesis, led to impairment of serotonin signaling pathways in the brain and to alteration of the number and affinity of 5-HTRs, which weakens serotonin-mediated regulation of lipid and carbohydrate metabolism and insulin sensitivity [23, 24].

Based on serotonin deficiency in the diabetic brain, it can be assumed that increasing the serotonin level in CNS is an appropriate approach to normalize feeding behavior and improve glucose homeostasis and insulin sensitivity impaired in diabetic pathology. This suggestion is confirmed by the results obtained in treating diabetic patients with fluoxetine and other selective serotonin reuptake inhibitors. These inhibitors induced weight loss, reduced the plasma levels of glucose and glycated hemoglobin, and improved insulin sensitivity [25, 26].

We showed that long-term treatment of rats with neonatal and HFD/STZ DM2 using intranasally administered serotonin (IS) restored hormonal sensitivity of ACSS in the brain and in the periphery and improved metabolic parameters and cognitive functions [12, 13, 27]. The 8-week treatment of female rats with neonatal DM2 with IS (20 µg/rat daily) restored AC-mediated regulatory effects of monoamines and relaxin in the brain, β-adrenergic agonists in the myocardium, and gonadotropins in ovaries [12, 28]. Along with it, using the Morris water test, we found that IS treatment improved DM-induced impairment of learning and spatial memory [12]. The 2-month IS treatment of male rats with HFD/low-dose STZ model of DM2 decreased the body weight, improved the glucose tolerance and insulin-induced glucose utilization, and also reduced the level of triglycerides and LDL-cholesterol, and the LDL/HDL-cholesterol ratio, which indicates the normalization of lipid metabolism. Besides, IS treatment restored hormonal sensitivity of ACSS in the hypothalamus and normalized the ratio of β₁-, β₂-, and β₃-adrenergic receptors (β-ARs) in the myocardium of diabetic rats. Based on these findings, we can conclude that increasing the brain serotonin level may be an effective way to treat DM2 and its complications that are induced by abnormalities in the brain and peripheral AC signaling [13].

The hypothalamic melanocortin system plays a very important role in regulation of feeding behavior, insulin sensitivity, and lipid metabolism [29]. The sensor components of this system are G_s protein-coupled melanocortin receptors of the types 3 and 4 (MC₃R and MC₄R). They are activated by α-melanocyte-stimulating hormone (α-MSH) and other peptides of

the melanocortin family generated from pro-opiomelanocortin (POMC) that is produced by POMC-expressing neurons of the arcuate nucleus of hypothalamus. The binding of MC₃R and MC₄R with agonists leads to activation of AC and cAMP-dependent signaling cascades. Along with melanocortin peptides, the agouti-related peptide (AgRP) with MC₄R antagonistic activity is produced in the arcuate nucleus, and it inhibits regulatory effects of α -MSH and triggers G protein-independent arrestin signaling [30].

The inhibition of MC₄R-signaling cascades led to hyperphagia, metabolic disorders, insulin resistance, and eventually to DM2 [31]. Mice lacking MC₄R and agouti mice with increased AgRP expression had the reduced insulin sensitivity, and treatment of healthy mice by MC₄R antagonists and high-dose AgRP enhanced appetite and induced insulin resistance [32, 33]. Some patients with DM2 and metabolic syndrome were characterized by mutations in the *Mc4r* gene and by impaired MC₄R signaling [34]. The α -MSH and other MC₄R agonists, on the contrary, had an antidiabetic effect when administered to rodents with obesity and insulin resistance. They reduced food intake and normalized the glucose and insulin level and energy metabolism [31, 32].

We showed that in the hypothalamus of rats with neonatal and HFD/low-dose STZ DM2, the activity of MC₄R-signaling pathway decreased significantly. This was illustrated by decrease of the *Mc4r* gene expression and the stimulating effects of α -MSH and selective MC₄R-agonist THIQ on AC activity and GTP-binding capacity of G_s proteins. The long-term treatment of diabetic animals with BC and intranasally administered insulin and serotonin significantly restored MC₄R signaling, and this coincided with the improvement of insulin sensitivity and the carbohydrate and lipid metabolism [13].

One of the approaches to restore hypothalamic melanocortin system in DM2 is the use of selective MC₄R-agonists, as demonstrated in the experiments with obese and diabetic animals. But currently, there are no available highly selective MC₄R-agonists, while melanotan-II, the most widely used non-selective MCR agonist, leads to a large number of adverse effects [35]. Currently, new agonists of MC₄R are being developed intensively, but they have not been used in clinic yet. The most effective among them are α -MSH analogs modified by fatty acid radicals at the N-terminus, highly selective MC₄R agonist BIM-22493 [36, 37]. The BIM-22493 easily penetrates across blood-brain barrier, activates hypothalamic MC₄R-signaling pathways, and, as a result, decreases food intake, body weight and fat mass, and improves glucose tolerance. It should be noted that even a long-term treatment of experimental animals with BIM-22493 had no adverse effects on the cardiovascular system and blood pressure [37]. The effectiveness of MC₄R agonists can be significantly enhanced when they are combined with agonist of glucagon-like peptide-1 receptor, which is widely used to treat DM2. Co-administration of BIM-22493 and liraglutide, a stable agonist of glucagon-like peptide-1 receptor, into diabetic mice prevented insulin resistance and improved energy expenditure much more effectively as compared to monotherapy [38].

3. The ACSS in the diabetic heart

The DM1 and DM2 are closely associated with severe cardiovascular diseases, such as acute myocardial infarction, congestive heart failure, and atherosclerosis [39, 40]. The pathological

changes in contractile function of the heart in DM are largely due to impairment of the adrenergic, cholinergic, and purinergic pathways of AC regulation in cardiomyocytes [28, 39, 41–44]. The adrenergic signaling has a very important role in the functioning of the cardiovascular system, and it changes to the greatest extent in DM. In rats with the STZ model of DM1, the expression of genes encoding β -ARs and the activity of the receptors are altered and the pathological changes are enhanced with increasing duration and severity of DM [41]. In the cardiac muscle, there are three pharmacologically distinct subtypes of β -ARs. The G_s protein-coupled β_1 -AR stimulates AC activity, β_2 -AR interacts with the G_s and G_i proteins, and is able to both stimulate and inhibit AC activity, while β_3 -AR interacts preferably with G_i protein, inhibiting AC.

In diabetic rats with 6–14 week DM1, the expression of gene encoding β_1 -AR was significantly reduced, while the expression of β_2 -AR gene, on the contrary, was increased. The number of functionally active β -ARs on the surface of cardiomyocytes was reduced for both β_1 - and β_2 -ARs, which is caused by increasing the rate of β_2 -AR degradation and the deterioration of post-translational processing of receptor [41, 45]. Meanwhile, the mRNA level for β_3 -AR and the number of these receptors on the surface of cardiomyocytes in rats with 14-weeks DM1 increased 2 or more times in comparison with control animals. The specificity of changes for β -AR subtypes in diabetic heart resulted in alteration of the $\beta_1/\beta_2/\beta_3$ ratio. In the myocardium of diabetic rats, the ratio was 40:36:23, while in the myocardium of healthy rats, the ratio was 62:30:8 [45]. The treatment of diabetic rats with insulin led to normalization of the $\beta_1/\beta_2/\beta_3$ ratio (57:33:10). The specific changes in β -AR activity including two or threefold increase in the number of β_3 -AR were identified in the cardiac muscle of patients with DM2 and metabolic syndrome, as well as in patients with acute heart failure [46]. The study of genotype of patients with DM2 and metabolic syndrome allowed detecting the mutation in a codon 64 of β_3 -AR gene, which led to a significant increase of activity of mutant receptor [47]. We also showed significant changes in the $\beta_1/\beta_2/\beta_3$ ratio in the myocardium of rats with different models of diabetic pathology, and the ratio was restored when the animals were treated with intranasal insulin and, in the case of DM2, with D_2 -agonist BC and metformin [13, 20, 28, 44]. The increase of β_3 -AR activity prevents AC hyperactivation caused by the increased catecholamine levels characteristic for diabetic cardiomyopathy. The increase of β_3 -AR activity can also be a compensatory mechanism contributing to the preservation of functional activity of endothelial NO-synthase and soluble guanylyl cyclase that regulate vascular contractility [46]. However, with prolonged duration of DM, the increase of β_3 -AR signaling in the myocardium leads to imbalance of adrenergic regulation and induces the negative inotropic effect of β -AR agonists and bradycardia [41].

The apoptotic processes in the cardiac muscle contribute significantly to etiology and pathogenesis of diabetic cardiomyopathy, and they largely depend on the β_1 -AR signaling. A decrease in β_1 -AR activity in the cardiac muscle in DM1 leads to inhibition of apoptotic processes in cardiomyocytes and prevents myocardial dysfunction and acute heart failure. It should be noted that in healthy animals, β_1 -AR agonists induce apoptosis in rat cardiomyocytes, while β_1 -AR antagonists suppress it [48].

We studied ACSS activity in the myocardium of rats with acute DM1 induced by high-dose STZ and found the decrease of the basal level of GTP-binding and the AC stimulating effect of

guanine nucleotides, which indicates a weakening of G_s protein function in cardiomyocytes of diabetic animals [49]. Meanwhile, the stimulation of AC by forskolin that directly interacts with catalytic site of the enzyme did not change, indicating the preservation of AC catalytic activity. The AC stimulating effect of β -agonists was decreased, but to a small extent, while the corresponding effect of relaxin, a peptide hormone that plays an important role in regulation of the cardiovascular system, was decreased by 48%. The study of ACSS in the heart of rats with 7-month DM1 induced by multiple injections of low-dose STZ shows the decrease of both basal and forskolin/guanine nucleotides-stimulated AC activity, demonstrating the reduced activity of both AC and G_s protein [50]. A significant decrease in the norepinephrine and isoproterenol effects on AC activity, more pronounced than in acute DM1, was also observed. The changes of ACSS activity significantly depended on the age of rats when DM1 was initiated [44, 50]. Our results indicate that changes in adrenergic signaling cascades in the heart are highly dependent on the experimental model of DM1.

Unlike DM1, in DM2, the number of β -ARs in the myocardium is not substantially different from control, but the sensitivity of β -ARs to agonists and their effects on AC are decreased significantly [11, 13, 51–53]. The changes in β -AR signaling strongly vary in rats with different models of DM2 depending on duration and severity of the disease [11, 44, 49, 53, 54]. In the myocardium of rats with 8-month neonatal model of DM2, the effect of isoproterenol on AC activity was increased, although to a small extent. When the duration of DM2 was 18 months, this effect was reduced as compared with the control group. The stimulating effect of relaxin on AC was reduced in DM2 with different durations, and in 18-months DM2, it did not exceed 46% of that in control [42]. The decrease of effect of guanine nucleotides on AC was shown, indicating a weakening of G_s protein function, and one of the causes for this is hyperhomocysteinemia, typical for severe DM2 [54].

It was shown that the treatment of diabetic rats with thyroid hormone levothyroxine was effective for restoration of the number and functional activity of β -ARs [55, 56]. This indicates a close relationship between hypothyroid state, typical for human DM1 and DM2, and impaired myocardial function in DM. In this regard, there are serious grounds to believe that one of the approaches to prevent diabetic cardiomyopathy is restoration of hypothalamic–pituitary–thyroid axis and compensation of thyroid hormones deficiency. The treatment of DM2 rats with D_2 -agonist BC and intranasally administered insulin and serotonin, restoring hypothalamic ACSS, also improves the function of the cardiovascular system and sensitivity of myocardial AC to hormonal regulators [20, 28].

4. Concluding remarks

Summing up, the changes in hormone-regulated ACSS in the brain and heart and abnormalities of interaction between them are the most important factors leading to the development of DM and its complications. Consequently, the identification of disturbances in these cascades and the development of approaches to their correction should be regarded as the most promising strategy to treat and prevent diabetic pathology. The causal link between DM and the pathological changes in AC signaling is not a one-way avenue, from DM to these changes in the

organs and tissues and, further, to diabetic encephalopathy, cardiomyopathy, and other complications of DM. The opposite situation can also be realized when impaired AC signaling triggers the processes leading to DM. The dysfunctions in the brain ACSS sensitive to melanocortin peptides and monoamines can induce DM2 and metabolic syndrome, while dysregulation of cAMP signaling in the pancreatic islets weakens insulin-producing function of β -cells and provokes the development of DM1. This speaks in favor of the use of a wide scale of hormonal and non-hormonal agents that control AC activity and influence the availability, transport, and secretion of hormonal molecules in the treatment and prevention of DM. The development of new approaches for the treatment of DM, which are based on the monitoring and correction of the ACSS activity in the brain, myocardium, and the other organs and tissues, requires a detailed study of the changes in the ACSS in different forms of experimental and human DM, as well as the effects on the ACSS of a number of the factors, such as the duration and severity of DM, the DM treatment with insulin, metformin, and other drugs, the frequency of hypoglycemic episodes, and the DM-induced complications. Nowadays, in our Laboratory of Molecular Endocrinology and Neurochemistry, Sechenov Institute of Evolutionary Physiology and Biochemistry, we use a lot of models of DM and various approaches of molecular endocrinology, pharmacology, and experimental medicine in order to understand etiology and pathogenesis of DM and its complications and to propose the new strategies to treat them.

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