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Alterations in Hormonal Signaling Systems in Diabetes Melitus: Origin, Causality and Specificity

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Editorial

Diabetes Mellitus (DM) is a complex metabolic disease associated with many complications including hypertension, coronary heart diseases, atherosclerosis, retinopathy, nephropathy, reproductive and neurodegenerative disorders. A new view on the origin and pathogenesis of DM and its complications shared by many specialists nowadays has emerged from the study of changes in hormonal signaling systems in the tissues and organs of diabetic individuals. These changes occur not only in the signaling pathways regulated by insulin and IGF-1, the principal players responsible for development of DM and its central and peripheral complications, but also in the signaling systems regulated by a wide spectrum of other hormones and neurotransmitters, including leptin, biogenic amines, glutamate, purines, neuropeptides and glycoprotein pituitary hormones. It would be logical to suppose that alterations in these systems may be due to DM-induced changes in the expression, processing and functional activity of hormonal molecules, their cognate receptors and a majority of the downstream signal proteins, which finally leads to abnormalities in fundamental cellular processes, such as growth, differentiation, metabolism and apoptosis and contributes to triggering and development of pathological processes in the diabetic organs and tissues. However, there are many questions concerning the origin, causality and specificity of these alterations in DM and their role in the development of DM-induced complications, which are still unclear and controversial. The first to be solved are the folowing: (1) what is the causal relationship between the altered hormonal signaling and DM, (2) what is the role of the signaling system alterations in the compensatory mechanisms triggered by DM-induced metabolic and functional abnormalities, (3) what is the temporal and functional dynamics of these changes and in which conditions they are irreversible, (4) what is the interaction between the altered signaling cascades in DM and what is its mechanism, and how the changes in some individual cascades extend to the entire signaling network, (5) to which extent alterations in the signaling cascades are specific to the tissues and the cell types, as well as to certain hormones and signal cascades. There is no common view concerning these questions.

It is generally accepted that a severe hyperglycemia and insulin deficiency in type 1 DM (T1DM), mild hyperglycemia and insulin resistance typical of type 2 DM (T2DM) and recurrent hypoglycemia as a result of inadequate insulin therapy are the major factors inducing the compensatory changes in hormonal signaling systems. These changes at the initial stage are reversible and can be completely restored with adequate therapy, usually by insulin treatment. With a prolonged action of the above pathogenetic factors the changes in hormonal systems are irreversible and fail to be restored with insulin therapy. This eventually leads to severe functional disturbances in CNS and peripheral tissues characteristic of the late decompensated DM. In favor of reversible compensatory changes in hormonal signaling speak the following data. In the heart of rats with Streptozotocin (STZ) model of T1DM the content and activity of β_1- Adrenergic Receptors (AR) were markedly decreased due to a significant increase of the level of noradrenaline that has high affinity for β_1-AR, the number of β_2-AR and their responsiveness to hormonal stumulation did not change significantly, whereas mRNA and protein levels of β_3-AR showed a two-fold increase, which was a compensation of the imapired β_1-AR signaling [1]. As a result, the ratio of β_1-, β_2-, and β_3-AR in the heart of diabetic rats was 40:36:23 and markedly differed from control (62:30:8). Two-week insulin therapy increased β_1-AR content, decreased the number of β_3-AR and restored the ratio to control values (57:33:10). At the same time, in the prostatic membranes isolated from STZ rats the efficacy of Adenylyl Cyclase (AC) stimulating effects of forskolin and isoproterenol were decreased significantly compared with control and the insulin treatment did not restore these effects, which indicates irreversible alterations in AC system and adrenergic signaling in the diabetic prostate [2]. We showed that the sensitivity of AC to human chorionic gonadotropin, PACAP and somatostatin was decreased in the ovaries of rats with the neonatal model of T2DM, and the long-term therapy with intranasal insulin restored gonadotropin effect, but did not influence significantly AC effects of PACAP and somatostatin [3]. This is probably due to the fact that some disturbances are compensatory; these are reversible for a long time, while those due to compensatory changes in the other signaling cascades rather quickly become irreversible. To know the nature and reversibility of changes in hormonal signaling systems with DM is very important for development of optimal strategies in diagnostics and treatment of this disease.

Another question is whether in DM damages occur in the tissue or organ in a single signaling system and, if so, how they cover the other signaling pathways, i. e. as a result of cross-talk and the interaction between the functionally coupled signaling cascades or at the initial stage they occur independent of each other in multiple signaling pathways. The latter seems more likely since a few days after STZ diabetes was induced in animals the disturbances were detected in multiple signaling pathways not related functionally. In rats with short-term STZ T1DM, the AC effects of relaxin, D_2-agonist bromocriptine and somatostatin in the brain and the corresponding effects of gonadotropin, PACAP-38 and relaxin in the testes were significantly reduced [4]. Numerous alterations in the signaling cascades regulated by serotonin, dopamine, adrenerghic and cholinergic agonists, glutamate and purines were identified in the brain of rats with early STZ T1DM [5-7].

However, there are few reports on the temporal dynamics of alterations in signaling cascades, on the severity of alterations and the interaction of the altered cascades with unchanged cascades in DM. Therefore, it is not to be excluded that the changes in one signaling cascade can induce, according to the "domino" principle, changes in

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the other signaling cascades. Besides, the experimental models of DM, especially STZ T1DM, are characterized by severe metabolic disorders adversely affecting a large number of functional systems of organism and causing multiple alterations in them. This is why these models are not always reliable in reflecting adequately the situation with development of the disease in humans.

Alterations in the hormonal systems in DM are specific to the tissues and the cell types as well as for some signaling cascades, which depends on the type of human DM, its severity and duration, DM-induced complications, and also on the model of DM. In the brain of STZ rats the changes in hormonal signaling, dopamenergic and cholinergic in particular, were shown to be brain area-specific. In the cerebral cortex the expression of D_1- and D_2-dopamine receptors (DAR) and total DAR binding were increased, in the cerebellum D_1-DAR was down regulated and D_2-DAR up regulated, a total number of DAR being decreased, and in the hypothalamus and brainstem the number of D_2-DAR was significantly decreased [5,7]. In the cerebral cortex, hypothalamus and brainstem of STZ rats the number of m_1-muscarinic acetylcholine receptors was decreased, so was their expression, whereas in the cerebellum and corpus striatum the binding parameters and gene expression of the receptors were increased [6]. Adrenergic signaling in the heart, brain, skeletal muscles, uterus and reproductive tissues of rats with STZ T1DM and neonatal T2DM changed in a different manner due to the pattern and functional activity of α/β-AR in these tissues [3,8]. A similar picture was shown for PACAP-induced AC stimulation that in the brain and uterus of rats with neonatal T2DM did not change, but in the ovary and testes were significantly reduced. We showed also that the signaling cascades regulated by selective agonists of type 1 5-hydroxytryptamine receptor (5-HT_1R) were decreased significantly in the brain of rats with neonatal T2DM, whereas the cascades regulated by 5-HT_6R agonists, on the contrary, did not change, which indicates the receptor specificity of DM-induced alterations in the central serotoninergic system [3].

Earlier, it was generally accepted that the abnormalities in the signaling systems regulated by insulin and IGF-1, which are typical of both types of DM, induce metabolic disturbances and, as a result, lead to alterations in a wide range of hormonal signaling systems and their network. Quite recently, the convincing evidences were obtained in favor of the fact that alterations in the signaling cascades regulated by hormones other than peptides of the insulin family, such as leptin, melanocortin, dopamine and serotonin, can also be causal factors leading to DM. First, it concerns the brain signaling systems and allows putting forward the concept of central genesis of DM [9-11]. In accordance with this conception, the abnormalities in hormonal signaling systems of the brain will trigger the mechanism leading to insulin resistance or insulin deficiency and, as a result, to the development of DM and its central and peripheral complications. The blockade of types 3 and 4 melanocortin receptors (MC_4R) with selective antagonists, hypothalamic agouti-related peptide and antibodies against extracellular loops of these receptors induces obesity and T2DM-like state [12-14]. The attenuation of serotonin signaling in the brain induces hyperphagia and leads to the obesity and T2DM, this happens due to a decrease of 5-HT_{2C}R-mediated stimulating action of serotonin on melanocortin signaling [15,16]. Both MC_4R knockout mice and 5-HT_{2C}R knockout mice have an elevated plasma insulin level, insulin resistance, hyperphagia and obesity, all typical of T2DM [17,18]. In the years to come, the list of hormones and signaling cascades responsible for DM development will, no doubt, be extended.

Summing up, the changes in hormonal signaling systems and multiple interrelations between the altered signaling pathways underlie the understanding of etiology and pathogenesis of DM and its complications as to know them is necessary for a search and development of a new strategy in DM treatment and diagnostics. The causality between DM and the altered signaling systems regulated by hormones other than insulin and IGF-1 is not a one-way avenue, from DM to alterations of hormonal signaling and, further, to CNS and endocrine disorders, as the alterations in non-insulin/IGF-1 signaling may be a causal factor of DM. This speaks in favor of the use on a wide scale of hormonal and non-hormonal agents that control functional activity of signal and regulatory proteins, the components of hormonal systems, and influence availability, transport and sectretion of hormonal molecules not only in the treatment of DM, but also to prevent its development. The reports are available describing successful attempts to use D_2-agonist bromocriptine, 5-HT_{2C}R-agonists and selective serotonin reuptake inhibitors, fluoxetine in particular, in clinical practice. In addition to normalizing intracerebral serotonin and melanocortin signaling markedly decreased in DM, they also improve the metabolic control in diabetic individuals and increase the sensitivity of the peripheral tissues to insulin [19-21]. We showed that a long-term treatment of rats with neonatal T2DM by intranasal serotonin had a beneficial effect on the CNS functions and brain hormonal signaling [22]. Currently, the data is available showing that MC_3R and MC_4R agonists, leptin, and other hormones and neurotransmitters can be used in the treatment of DM and its complications, which opens a new era in their therapy [23-25]. The development of the new strategies that have been mentioned above in the treatment and diagnostics of DM is hampered by the lack of adequate modeling and monitoring of the abnormalities in hormonal signaling systems in DM, which involves a wide range of methods and approaches of molecular endocrinology, proteomics and peptidomics, pharmacology, and clinical and experimental medicine. The development of such strategies makes it necessary carrying out, on the one hand, the comprehensive comparative studies of the altered hormonal signaling in human and experimental DM, and on the other, a systemic analysis of the influence on it of such factors as drug therapy, the severity and duration of the disease, the frequency and severity of hypoglycemic episodes, concomitant diseases and complications.

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