Alterations in Hormonal Signaling Systems in Diabetes Mellitus: 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 following: (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 signaling 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 β1-Adrenergic Receptors (AR) were markedly decreased due to a significant increase of the level of noradrenaline that has high affinity for β1-AR, the number of β2-AR and their responsiveness to hormonal stimulation did not change significantly, whereas mRNA and protein levels of β2-AR showed a two-fold increase, which was a compensation of the impaired β2-AR signaling [1]. As a result, the ratio of β1-, β2-, and β3-AR in the heart of diabetic rats was 40:36:23 and markedly differed from control (62:30:8). Two-week insulin therapy increased β2-AR content, decreased the number of β2-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, D3-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, adrenergic 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, dopamnergic 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 a/b-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$_R$) were decreased significantly in the brain of rats with neonatal T2DM, whereas the cascades regulated by 5-HT$_R$ agonists, on the contrary, did not change, which indicates the receptor specificity of DM-induced alterations in the central serotonergic 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. By means of diabetes on expression of beta1-, beta2-, and beta3-adrenoreceptors in rat hearts. Diabetes 50: 455-461.


References


