REVIEWS

Paraventriculovagal Regulation of Carbohydrate Homeostasis as a Perspective Biological Model for Investigation of Neuroimmunoendocrine Interactions

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The existence of a new hypothalamic regulatory pathway of pancreatic insulin secretion is described and experimentally proved. This paraventriculovagal pathway connects though neural conductors (in particular, the vagus nerves) hypothalamic paraventricular neurons with pancreatic islets allowing for the parahypophyseal bypass regulation of insulin secretion. This pathway stimulating insulin secretion interacts with another (transhypophyseal) hypothalamic regulatory pathway that inhibits insulin secretion and involves hormones of the pituitary-adrenal gland system (ACTH-glucocorticoids). Thus, regulation of insulin secretion is effected through the interaction between the transhypophyseal (inhibitory) and parahypophyseal (stimulatory) regulatory pathways. Both these pathways are triggered by peptides of the immune system (interleukin-1) via a feedback mechanism. Hence, the mechanisms of hypothalamic regulation of the carbohydrate homeostasis provide an example of the interaction between three regulating systems — the nervous, endocrine, and immune systems. The interaction between these systems attracts now considerable attention. Accumulated evidence provides the grounds to consider neuroimmunoendocrinology as a new field of scientific knowledge. The described regulatory system can be used as a convenient biological model for neuroimmunoendocrinological studies.

Key Words: *neuroimmunoendocrinology; carbohydrate homeostasis*

In our studies of the regulation of endocrine functions we followed the current concepts that endocrine functions in the organism are regulated by the hypothalamic centers. Regulatory stimuli from these centers are directed to the anterior pituitary cells which are able to stimulate or inhibit hormone secretion in the target peripheral endocrine glands. Hence, the pituitary acts as a conductor controlling the hormone homeostasis via the feedback mechanism: the information on excessive or insufficient hormone production in the peripheral endocrine gland is delivered to the brain hypothalamic centers, where the humoral signal is transformed into nerve pulses (transduction) normalizing the disturbed hormone homeostasis (up- or down-regulation) [2].

However, hypothalamic regulation of the endocrine pancreas does not correspond to this paradigm. There is no specific pituitary tropic hormone for pancreatic insulin-secreting cells and therefore the usual regulatory scheme hypothalamus—pituitary—target organ has no physiological significance.

Nevertheless, ample experimental and clinical data suggest that endocrine function of the pancreas depends on the hypothalamus. The most attractive hypo-

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thesis explaining this phenomenon assumes the possibility of hypothalamic regulation of insulin secretion through a bypass parahypophyseal neural pathway connecting hypothalamic neurons with pancreatic islets [3]. It was also assumed that the role of peripheral conductors in this pathway is played by the vagus nerves.

Autonomic innervation of pancreatic islets and its role in the regulation of endocrine function are well established [1,34]. Stimulation of the vagus nerves [21,22,26,35] as well as injection of acetylcholine or muscarinic receptor agonists increase blood concentration of radiolabeled insulin, while muscarinic antagonists and vagus nerve transection [18,22,23,28] produce an opposite effect. These data suggest the existence of a hypothalamovagal regulatory pathway of pancreatic endocrine function; however, by the time we have inquired into this problem, no hypothalamic centers of this putative regulatory pathway were identified.

We used a traditional approach for identification of the hypothalamic centers: inhibition of the pancreatic endocrine function (experimental diabetes mellitus) and identification of hypothalamic nuclei (karyometry) sensitive to this dysfunction. The reactive nuclei were considered as possible sources of descending axons presumably terminating on neurons of the dorsal nucleus of the vagus nerve (DNV) in the medulla oblongata, i.e., on the neurons that give rise to efferent vagal fibers. To verify this hypothesis, we electrolytically destroyed these nuclei (using stereotactic coordinates) and examined the presynaptic nerve endings in DNV. The first signs of axon degeneration were revealed under light microscope using the Fink—Heimer silver impregnation method when the area adjacent to the paraventricular hypothalamic nuclei (PVN) was stereotactically destroyed [12]. Further electron microscopic studies demonstrated degeneration of the presynaptic nerve endings on DNV neurons after destruction of the hypothalamic PVN [15,16]. It should be noted that after unilateral destruction of the hypothalamic PVN, degenerative nerve endings were seen in the both ipsi- and contralateral DNV, which indicates partial decussation of the descending hypothalamic axons.

Long-term investigations confirmed the existence of a neural pathway between hypothalamic neurons and pancreatic islets. This is a monosynaptic pathway. It originates from the hypothalamic PVN neurons and after a partial decussation in the lower part of the brain stem synaptically ends on the DVN neurons. We called it the paraventriculovagal pathway.

In parallel, similar data were obtained using other approaches: for instance, anterograde axonal transport of a radiolabeled tracer injected to the putative hypothalamic source of these axons or retrograde transport of radish horse peroxidase injected to the putative site of axon endings [8].

After the paraventriculovagal pathway was reliably identified, its participation in the regulation of carbohydrate homeostasis was experimentally proved [11]. In these experiments two regulatory levels were defined: the hypothalamic level presented by PVN and the medullar level. Bearing in mind the sensitivity of DVN cholinergic neurons to glycemia caused by experimental diabetes mellitus, we primarily associated the medullar regulatory level with DVN [13,14]. However, DVN is only the area of efferent terminals in the medullar vagal center, while the afferent part of the vagal center — the nucleus of the solitary tract remained unexplored. It should be noted that neurons in the nucleus of the solitary tract were also sensitive to diabetic glycemia and form synapses on PVN neurons in the hypothalamus [9,25,29,31]. Therefore in further experiments the medullary regulatory level was considered as a complex consisting of DVN and the nuclei of the solitary tract and termed the dorsal vagus complex.

The accumulated evidence prompted us to reconsider our views on the hypothalamic regulatory level presented by PVN. By that time, new data on the functional morphology of PVN appeared. It was shown that PVN are a combination of cell populations, i.e., subnuclei differing in their neural contacts and neuropeptide and neurotransmitter repertoire. According to the current concepts [6], rat hypothalamic PVN consist of 10 subnuclei. Four of these subnuclei are presented by large neurosecretory neurons, 3 subnuclei are populated with medium-sized and 3 with small neurons. Evidently, when evaluating the role of PVN in the regulation of carbohydrate homeostasis, the reaction of each PVN subnucleus to experimental disturbances in the studied endocrine functions should be taken into account.

Our experiments revealed 5 subnuclei (3 of them consisted of medium-sized and 2 of small neurons) sensitive to various experimental shifts in the plasma glucose and insulin concentrations [11]. Interestingly, these PVN subnuclei give rise to the descendent paraventriculovagal pathway. It should be noted that these experimental endocrine interventions induced changes in neurons of the medial subnucleus (a medium cell nucleus) secreting corticotropin-releasing factor (CRF) which stimulates secretion of the diabetogenic pituitary hormone ACTH. Selye considered CRF as a stress-releasing factor [33]. According to current views, CRF plays an important role in the pathogenesis of diabetes mellitus. An evident biological peculiarity of the paraventriculovagal regulatory pathway of the carbohydrate homeostasis is its stress-dependence.

In this context it should be emphasized that emotional stress, an attribute of modern human life, often causes glycemia, while clinical examination often re-

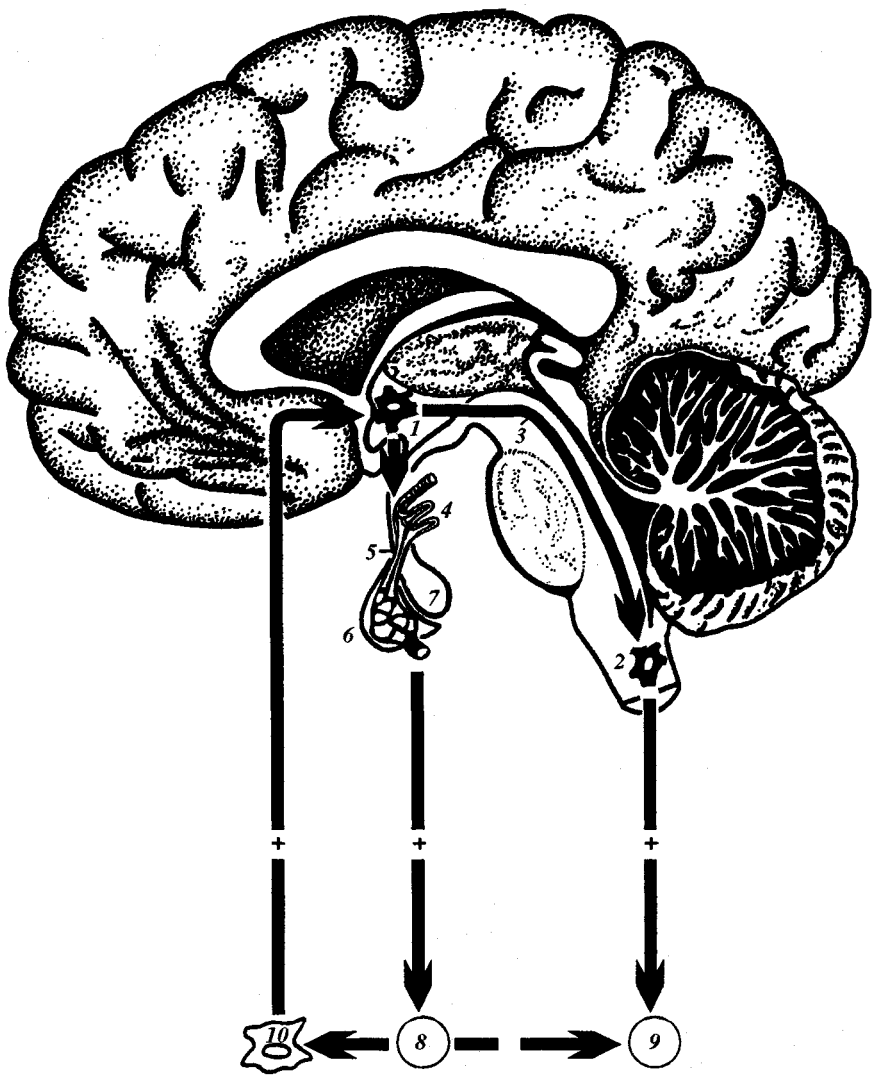

Fig. 1. Interaction between the neuroendocrine and immune systems in the hypothalamic regulation of insulin secretion. *1*) paraventriculovagal hypothalamic nucleus; *2*) dorsal nucleus of the vagus nerve in the medulla oblongata; *3*) paraventriculovagal system; *4*) afferent vessels of the portal system; *5*) portal system of the pituitary; *6*) efferent vessels of the portal system; *7*) posterior pituitary; *8*) adrenal cortex; *9*) pancreatic β-cells; *10*) macrophage.

veals symptoms of transient or established diabetes mellitus. Diabetes mellitus is now considered as an autoimmune disease, characterized by immune aggression against some β-cell components, which are recognized by the immune system as nonself structures.

The theory of molecular mimicry [17] proposes the following explanation of this autoimmune attack against pancreatic β-cell. Immune response is normally induced by nonself antigens such as viral and bacterial components. Some membrane structures of pancreatic β-cell chemically or conformationally similar to these components will be recognized by the immune system as nonself antigens and, consequently, induce immune response against β-cell. Islet 64K protein antigen identified later as glutamate decarboxylase is a candidate for such a structure. Antibodies to glutamate decarboxylase or its fragments can be detected in the blood before the clinical manifestations of diabetes mellitus appeared. The described mechanism probably underlies the development of diabetes mellitus as a complication of viral infections or as a consequence of severe stress when the role of alien antigens is played by heat shock proteins. When T cells from mice immunized with these proteins were transplanted to healthy recipients, the latter developed insulitis, a pathognomic marker of insulin-dependent diabetes mellitus [17].

It is now evident that the stress-mediating mechanisms are primarily realized via the paraventriculovagal regulatory system. Moreover, this systems attracts much attention as a convenient biological model in studies considering the interaction between the main regulatory systems in the organism [10].

The above mentioned secretion of a stress-releasing factor in the cell population within PVN giving rise to the paraventriculovagal regulatory pathway is triggered by interleukin-1, an immune peptide produced by activated macrophages [19,30]. Enhanced production of CRF stimulates secretion of ACTH and glucocorticoids in the pituitary and adrenal glands, respectively. The elevated blood concentration of these hormones inhibits production of interleukin-1 in macrophages and suppresses excessive immune reactions [24,27,32]. Thus, a feedback mechanism consisting of hypothalamic neuropeptides (CRF), hormones of the pituitary-adrenal gland system (ACTH and glucocorticoids), and peptides of the immune system (interleukin-1) coordinates the function of the paraventriculovagal regulatory system (Fig. 1). Scheme presented on Fig. 1 shows that insulin secretion is under double control. On the one hand, interleukin-1-stimulated neurons in PVN activate insulin secretion via the paraventriculovagal pathway (parahypophyseal regulation), while on the other hand, enhanced secretion of CRF via the transhypophyseal pathway activates the ACTH-glucocorticoid system, which inhibits insulin secretion in the pancreas. In other words, the interaction between the para- and transhypophyseal regulatory pathways enables double (stimulation and inhibition) control mechanisms, which are characteristic of the most important homeostatic functions [7].

In conclusion, when studying the neural or endocrine regulatory mechanisms of homeostatic functions, the mechanisms underlying the interaction between these regulatory systems, in particular, the nervous, endocrine, and immune systems should be taken into account [4,5,20]. Comprehensive data on the close integration of these systems provide a basis for a new area of scientific knowledge, neuroimmunoendocrinology, which is now becoming a priority direction in modern biology and medicine.

Progress in new scientific fields requires the development of adequate biological models. In light of this, the paraventriculovagal regulatory system of the carbohydrate homeostasis provide a perspective model for investigation of the interaction between the above-mentioned regulatory systems.

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