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Hypothalamic control of hepatic lipid metabolism via the autonomic nervous system

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Our body is well designed to store energy in times of nutrient excess, and release energy in times of food deprivation. This adaptation to the external environment is achieved by humoral factors and the autonomic nervous system. Claude Bernard, in the 19th century, showed the importance of the autonomic nervous system in the control of glucose metabolism. In the 20th century, the discovery of insulin and the development of techniques to measure hormone concentrations shifted the focus from the neural control of metabolism to the secretion of hormones, thus functionally "decapitating" the body. Just before the end of the 20th century, starting with the discovery of leptin in 1994, the control of energy metabolism went back to our heads. Since the start of 21st century, numerous studies have reported the involvement of hypothalamic pathways in the control of hepatic insulin sensitivity and glucose production. The autonomic nervous system is, therefore, acknowledged to be one of the important determinants of liver metabolism and a possible treatment target. In this chapter, we review research to date on the hypothalamic control of hepatic lipid metabolism.

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Introduction

Many studies have shown that the brain and liver are connected both anatomically and functionally. The neural connection between the brain and the liver consists of both branches of the autonomic nervous system, i.e., the sympathetic and parasympathetic nervous system. Retrograde tracing studies showed that the sympathetic and parasympathetic connections to the liver originate from different brain regions within the hypothalamus and brain stem [1–4]. The hypothalamus consists of different nuclei with distinct neuronal populations. The arcuate nucleus at the base of the hypothalamus is conceived as the hormonal and metabolic 'window of the brain', being able to receive humoral signals from the periphery, such as insulin and leptin, due to a selective permeability of the blood–brain barrier. In close proximity to the arcuate nucleus are the ventromedial hypothalamus (VMH), dorsomedial hypothalamus (DMH) and lateral hypothalamus (LH), which are known to be anatomically connected and functionally implicated in energy metabolism [4]. Located centrally in the hypothalamus, the paraventricular nucleus (PVN) is believed to integrate a variety of signals both from within and outside the hypothalamus. Moreover, the PVN is central in the outflow of information from the hypothalamus as its contains distinct populations of neuroendocrine neurons that drive hormone release from the pituitary and pre-autonomic neurons that control the activity of the sympathetic and parasympathetic branches of the autonomic nervous system [3].

Sympathetic nervous system

All sympathetic input to the liver is relayed via the sympathetic preganglionic cells in the lateral horn of the thoracic spinal cord. These cell bodies lie in the intermediolateral column (IML) and associated cell groups. In the hypothalamus, the pre-autonomic neurons in the PVN and LH send either direct projections to the preganglionic neurons in the IML or project indirectly to the IML via brainstem circuits [5–7]. In the brainstem, central autonomic regions that show direct projections to the preganglionic motorneurons in the IML are the rostroventrolateral medulla (RVLM), A5 region and the parapyramidal region (which can be separated into ventromedial medulla and raphe nucleus) [1,3,8,9]. The IML in the spinal cord is connected via splanchnic nerves to the celiac ganglion innervating the liver. Sympathetic hepatic nerves innervate the liver through nerve bundles that accompany the large vessels in the liver hilus from where they penetrate to different extents into the acinus [7,10]. Large species differences exist in the extent of sympathetic innervation of liver parenchyma [11–13]. Sympathetic hepatic nerves can modulate hepatocyte function by direct action of their neurotransmitter noradrenaline on the α and β adrenergic receptors. In addition to noradrenaline, sympathetic hepatic nerve endings may also release neuropeptides, such as NPY and galanin [7].

Parasympathetic nervous system

The efferent parasympathetic autonomic signal is conveyed via preganglionic neurons in the dorsal motor nucleus of the vagus (DMV) in the brain stem. Tracing studies, combining a sympathetic denervation of the liver with injection of a tracer, confirm that many of the above mentioned central autonomic nuclei (PVN, LH, A5, parapyrimidal area) also contribute to the control of the parasympathetic function, although from separate populations, indicating a functional specialization [3] The DMV is directly connected by the vagal nerve to ganglion cells, without involvement of the spinal cord [7]. The right posterior subdiaphragmatic vagal nerve branches into the left and right hepatic branch proper and the ganglion cells concerned are located close to the liver [10]. Postganglionic parasympathetic nerves mainly use acetylcholine as their neurotransmitter, although peptides (such as cholecystokinin) are also involved [7]. Acetylcholine acts on two types of receptors, i.e., the muscarinic and nicotinic cholinergic receptors.

Hypothalamic control of lipid metabolism

A host of studies in the past decade have reported the involvement of several hypothalamic neuropeptides in the control of hepatic insulin sensitivity and glucose production. Remarkably, each of