学位論文内容の要旨
Abstract of the dissertation

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学位論文題名
The title of the doctoral dissertation

Study on the role of hypothalamic prostaglandins in the regulation of systemic glucose metabolism

(マウスの全身糖代謝調節における視床下部プロスタグランジンの役割に関する研究)

The hypothalamus, especially the ventromedial nucleus of the hypothalamus (VMH) plays a critical role in regulating glucose homeostasis by detecting blood glucose levels. The VMH has glucose-sensing neurons, which control peripheral glucose utilization and hepatic glucose production to maintain normal blood glucose. Obesity disturbs functions of glucose-sensing neurons and systemic glucose homeostasis. Deciphering the mechanism of hypothalamic glucose-sensing and how obesity impairs glucose-sensing will provide new strategies to develop a therapy for diabetes and obesity.

The brain is enriched with phospholipids containing polyunsaturated fatty acids, which regulate several physiological responses by themselves or their metabolites including prostaglandins. However, the relationship between hypothalamic prostaglandins and systemic glucose metabolism is unclear. Besides, whether diet-induced obesity affects the production of hypothalamic prostaglandins is also unknown. Therefore, this study aims to understand the role of hypothalamic prostaglandins in glucose-sensing by which regulates systemic glucose metabolism. In this study, we used imaging mass spectrometry to quantify amounts of phospholipids in the hypothalamus. Intraperitoneal glucose injection decreased amounts of hypothalamic phospholipids, especially arachidonic acid (AA)-containing phospholipids. Pharmacological inhibition of AA releasing or production of prostaglandin in the hypothalamus impaired glucose-sensing of VMH. The data strongly indicates that the production of prostaglandin from phospholipid-derived AA is important in hypothalamic glucose-sensing. Knockdown of cytosolic phospholipase A2 (cPLA2), a key enzyme for generating arachidonic acid from phospholipids, in the VMH, lowered glucose-sensing of the dorsomedial-VMH (dmVMH) and insulin

sensitivity of muscles during regular chow diet (RCD) feeding. Conversely, the down-regulation of hypothalamic glucose-sensing and systemic glucose metabolism by high-fat diet (HFD) feeding was improved by knockdown of cPLA2 in the VMH. During HFD, the knockdown mice have recovered glucose-sensing in ventrolateral-VMH (vlVMH) with an ameliorated hypothalamic inflammation and increased hepatic insulin sensitivity. Our data suggest that cPLA2-mediated hypothalamic phospholipid metabolism is critical for controlling systemic glucose metabolism during RCD, while continuous activation of the same pathway to produce prostaglandins during HFD deteriorates glucose metabolism.