Hepatic Control of Energy Metabolism via the Autonomic Nervous System

Naoya Yahagi
Nutrigenomics Research Group, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

Although the human liver comprises approximately 2.8% of the body weight, it plays a central role in the control of energy metabolism. While the biochemistry of energy substrates such as glucose, fatty acids, and ketone bodies in the liver is well understood, many aspects of the overall control system for hepatic metabolism remain largely unknown. These include mechanisms underlying the ascertainment of its energy metabolism status by the liver, and the way in which this information is used to communicate and function together with adipose tissues and other organs involved in energy metabolism.

This review article summarizes hepatic control of energy metabolism via the autonomic nervous system.

Key words: Autonomic nerves, Energy metabolism, Liver, Adipose tissue, Lipolysis

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started occurring at the same time when glycogen storage was depleting. We observed that when the overexpression of glycogen synthase 2 (Gys2) was induced using adenovirus and glycogen was pre-loaded, lipolysis was suppressed, and the difference between the two groups was canceled by the HVx (Fig. 4). Conversely, when the Gys2 was knocked down by RNA interference, the decrease in liver glycogen content caused further acceleration of lipolysis during fasting.

The next question we addressed was how the decline in stored glycogen was recognized within the liver. In particular, we wondered whether the depletion of glycogen itself could be detected, or a decline in the quantity of glycogen degradation products (e.g., glucose-1-phosphate) had to be detected. To determine this, we performed RNA interference on a glycogen phosphorylase liver-type gene (Pygl); adenoviral shRNA (Pygl-i) was expressed in the liver, which targets Pygl. When glycogenolysis was suppressed by this RNA interference, the liver glycogen content was elevated and this in turn led to a decrease in lipolysis in the adipose tissue. This result demonstrates that the shortage of glycogen, but not that of the downstream metabolites, is the key to triggering the neurocircuitry. Thus, the glycogen quantity itself, and not the glycogen degradation product should be monitored.

These experimental results revealed that glycogen storage levels in the liver are monitored by some kind of mechanism. When glycogen stores are nearly depleted during starvation, the liver-brain-adipose-neural axis is activated and fat utilization is accelerated; thereby, the energy source shifts from carbohydrates to fats.

**Hepatic-origin Autonomic Nervous System Signals with Excess Glucose and Amino Acids**

In addition to their analysis of hepatic-origin autonomic nervous system signals after accumulation of excessive fatty acids, Katagiri et al. analyzed and recently reported the effects of neuronal signals on white and brown adipose tissue after excessive glucose uptake, and after excessive uptake of amino acids (AAs) by the liver.¹⁴

According to their report, when there is an excess of hepatic glucose uptake, neural modulation sup-
presses thermogenesis in brown adipose tissue (BAT) (Fig. 5). That is, when there is excessive glucokinase expression in the liver that accelerates glucose uptake, changes in glycometabolism occur in the liver. Signals elicited from these changes are communicated via vagal afferent nerves, which when received, reduce sympathetic nervous activity from the medulla oblongata to BAT; thermogenesis in BAT is suppressed, and fat accumulation is accelerated. This mechanism is considered responsible for reduced energy consumption in response to increased energy uptake. From this perspective, it can be considered as an economizing mechanism at the individual organism level.

When the same method is used to induce excess hepatic expression of SNAT2, an AA transporter, an unexpected result was a marked presentation of hypertriglyceridemia (Fig. 6). Excess AA uptake in the liver activates mTORC1/S6K, and neuronal signals
Fig. 5. Hepatic glucokinase modulates obesity predisposition by regulating BAT thermogenesis via neural signals.

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Fig. 6. Link between hepatic AA metabolism and WAT function.

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understanding their mechanisms, to using this information for therapeutic applications.

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