Overfeeding, Autonomic Regulation and Metabolic Consequences

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Summary. The autonomic nervous system plays an important role in the regulation of body processes in health and disease. Overfeeding and obesity (a disproportional increase of the fat mass of the body) are often accompanied by alterations in both sympathetic and parasympathetic autonomic functions. The overfeeding-induced changes in autonomic outflow occur with typical symptoms such as adiposity and hyperinsulinemia. There might be a causal relationship between autonomic disturbances and the consequences of overfeeding and obesity. Therefore studies were designed to investigate autonomic functioning in experimentally and genetically hyperphagic rats. Special emphasis was given to the processes that are involved in the regulation of peripheral energy substrate homeostasis. The data revealed that overfeeding is accompanied by increased parasympathetic outflow. Typical indices of vagal activity (such as the cephalic insulin release during food ingestion) were increased in all our rat models for hyperphagia. Overfeeding was also accompanied by increased sympathetic tone, reflected by enhanced baseline plasma norepinephrine (NE) levels in both VMH-lesioned animals and rats rendered obese by hyperalimentation. Plasma levels of NE during exercise were, however, reduced in these two groups of animals. This diminished increase in the exercise-induced NE outflow could be normalized by prior food deprivation. It was concluded from these experiments that overfeeding is associated with increased parasympathetic and sympathetic tone. In models for hyperphagia that display a continuously elevated nutrient intake such as the VMH-lesioned and the overfed rat, this increased sympathetic tone was accompanied by a diminished NE response to exercise. This attenuated outflow of NE was directly related to the size of the fat reserves, indicating that the feedback mechanism from the periphery to the central nervous system is altered in the overfed state.

Autonomic Influences on Energy Substrate Homeostasis

The storage, mobilization and utilization of the different energy substrates is regulated by very sensitive and specific (neuro)hormonal mechanisms. Figure 1 schematically visualizes our present view on the hormonal and neuronal effects on energy substrate homeostasis.

Increased parasympathetic activity leads to the storage of energy substrates such as glucose and free fatty acids (FFA) (for reviews see 17,42,46,59). The main parasympathetic efferents involved in energy substrate homeostasis are those projecting on the liver and the endocrine pancreas. In the liver, stimulation of parasympathetic nerves leads directly to conversion of circulating glucose into glycogen (42). Stimulation of the parasympathetic neurons that enervate the pancreas leads to an increased outflow of insulin by pancreatic β-cells. In turn, insulin lowers blood

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glucose concentrations via suppression of endogenous glucose production and stimulation of glucose uptake. More specifically, it inhibits hepatic glycogenolysis and gluconeogenesis, and stimulates the storage of glucose in liver in the form of glycogen. In addition, in other insulin-sensitive tissues like resting muscle and adipose tissue, insulin stimulates the uptake, storage and utilization of glucose. Insulin is the only major physiological factor causing a decline in plasma FFA concentrations. It inhibits lipolysis and enhances the re-esterification of FFA by accelerating the transport of glucose into the fat cell.

Activation of the sympathetic branch of the autonomic nervous system leads to the outflow of neuronal norepinephrine (NE; from sympathetic nerve endings) and hormonal epinephrine (E; from the adrenal medulla). Sympathetic activation results in the mobilization of glucose and FFA from the storage tissues (35,42,59,60). The main sympathetic efferents involved in energy substrate homeostasis are travelling through the preganglionic splanchnic nerve and end directly on specific target organs such as liver and pancreas. The effects of E and NE include both direct and indirect actions mediated via α- and β-adrenoceptor mechanisms. Catecholamines directly enhance hepatic glucose production via stimulation of both glycogenolysis and gluconeogenesis in liver. Catecholamines also limit expenditure of circulating glucose via β2-adrenoceptor stimulation of muscle glycogenolysis. The α2-adrenoceptor mediated inhibition of pancreatic insulin release and α- and β-adrenergic stimulation of glucagon secretion represent the most important indirect effects of catecholamines on glucose metabolism. Lipolysis is predominantly influenced by neuronal NE (but not physiological doses of E) via activation of β3-adrenoceptors on the fat cell (18,38). This effect of NE on FFA mobilization is a typical example of a hormonal action of NE since white adipose tissue cells are not directly enervated by sympathetic neurons. Finally, E and NE may stimulate glucose and FFA mobilization indirectly via the α2-adrenergic inhibition of insulin release.

**Energy Substrate Homeostasis and Autonomic Functioning**

Activation of one of the two branches of the autonomic nervous system thus leads to alterations in peripheral energy metabolism. One may argue that this relation between autonomic activity and substrate availability must be bidirectional; in other words that changes in the availability of glucose and/or FFA will lead to the activation of one of the two branches of the autonomic nervous system. Indeed, increased availability of energy substrates activates the parasympathetic...