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Control of Bone and Glucose Homeostasis by Neuropeptide Y System

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The hypothalamus is a portion of the brain that contains several small nuclei with a variety of functions. One of the essential functions of the hypothalamus is to link the nervous system to the endocrine system via the pituitary gland[1]. This linkage happens through the synthesis and secretion of certain neurohormones, often called hypothalamic-releasing hormones, and these, in turn, stimulate or inhibit the secretion of pituitary hormones. Through these neurohormones, the hypothalamus controls body temperature, hunger, important aspects of parenting and attachment behaviors, thirst, fatigue, sleep, and circadian cycles[2-4]. Many factors and pathways have been implicated in the regulation of appetite and energy homeostasis, but of all them, the neuropeptide Y system seems to perform the most critical function.

Neuropeptide Y is a 36-amino acid neuropeptide that acts as a neurotransmitter in the brain and autonomic nervous system of humans and is a complex system consisting of three ligand genes (neuropeptide Y, peptide YY, and pancreatic polypeptide) and at least five different receptors (Y1, Y2, Y4, Y5, and Y6)[5-7]. Whereas central neuropeptide Y is known to stimulate appetite and feeding behavior, the mostly peripherally expressed family members PYY and PP have the opposite effect and have been identified as potent satiety factors. Neuropeptide Y is expressed in the arcuate nucleus[8]. In the autonomic system, it is mainly produced by neurons of the sympathetic nervous system and causes the growth of fat tissue, also serves as a potent vasoconstrictor[9]. In the brain, it is produced in various locations including the hypothalamus and is thought to have several functions, including increasing food intake and storage of energy as fat, reducing anxiety and stress, reducing pain perception, affecting the circadian rhythm, reducing voluntary alcohol intake, lowering blood pressure and controlling epileptic seizures[10]. Negative energy balance leads to increased hypothalamic neuropeptide Y expression and the activation of appetite stimulatory pathways and other feeding-related behaviors. However, this increase in neuropeptide Y expression also causes neuroendocrine and metabolic changes which favor energy storage including decreased thermogenesis, hyperinsulinemia, insulin hyper-responsiveness in white adipose tissue, activation of the hypothalamic-pituitary-adrenal axis, and reduced activity of the hypothalamic-pituitary-thyrotrophic, -somatotropic, and –gonadotropic axes[11]. Interestingly, neuropeptide Y expression affects the whole-body homeostasis of fat and lean mass in a way that coordinates the regulation bodyweight with

bone mass, i.e., the larger body mass, the larger and stronger the bones. Recent data shows the elevation in bone formation and bone volume occurs with reduced central and peripheral Y-receptor signaling[12-14].

Neuropeptide Y receptors are a class of G-protein coupled receptors which are activated by the closely related peptide hormones neuropeptide Y, peptide YY, and pancreatic polypeptide. These receptors are involved in the control of a diverse set of behaviors, including appetite, circadian rhythm, and anxiety. Activated neuropeptide receptors release the G_i subunit from the heterotrimeric G protein complex. The G_i subunit, in turn, inhibits the production of the second messenger cAMP from ATP[15].

There are five known mammalians neuropeptide Y receptors designated Y1 through Y5. Four neuropeptide Y receptors, each encoded by a different gene have been identified in humans, all of which may represent therapeutic targets for obesity and other disorders. Mice lacking Y1 receptors solely in cells of the osteoblastic lineage show not only increased bone formation but also altered whole-body glucose metabolism[14,16]. This is due to significantly decreased pancreatic insulin content, pancreas weight, and insulin secretion in these mice, leading to elevated glucose levels and reduced glucose tolerance, but with no effect on insulin-induced glucose clearance. Furthermore, increased activity of Y1 signaling induced by adult onset over-expression of its ligand PYY in osteoblastic cells also leads to reduced glucose tolerance, elevated insulin secretion, and impaired insulin sensitivity in mice[17]. These data reveal a novel mechanism by which neuropeptide Y signaling in bone tissue is involved in the control of energy homeostasis.

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