Neuropeptide Y

GERALD F. DiBONA
Departments of Internal Medicine and Physiology and Biophysics, University of Iowa College of Medicine and Veterans Administration Medical Center, Iowa City, Iowa 52242

Neuropeptide Y (NPY) was identified as a neuropeptide that is colocalized and coreleased with the neurotransmitter norepinephrine from sympathetic nerve terminals. In this regard, a large body of research on NPY focused on its role in autonomic physiology and pharmacology as a potentiator of the postsynaptic actions of norepinephrine. However, with the increased understanding of the genes and their encoded proteins involved in the central nervous system regulation of feeding behavior and food intake (9, 10, 20), there is expanding research on the role of NPY as one of the most potent orexigenic signal molecules in the brain of mammals. Thus application of NPY is a common feeding stimulus (6, 23). Because feeding behavior and food intake are important determinants of the balance between energy intake and energy expenditure in the regulation of body weight, it is not surprising to learn that NPY is also a major regulator of food intake in nonmammalian species, such as the goldfish (Carassius auratus) (22).

Uncoupling proteins (UCP) are mediators of thermogenesis that may contribute to the regulation of energy balance. For example, in differentiated adipocytes, UCP-1 is coexpressed with metallothionein, which is strongly expressed during activation of thermogenesis in brown adipose tissue (2). Injection of NPY into the paraventricular nucleus (PVN) of rats increased food intake and this was associated with a decrease in expression of UCP-1 mRNA in brown adipose tissue, whereas the expression of UCP-2 and UCP-3 mRNA in white adipose tissue and skeletal muscle, respectively, was not regulated by NPY. Thus NPY produces a specific and differential regulation of the expression of genes for the UCPs, which, as mediators of thermogenesis, may contribute to the regulation of energy balance (17). The PVN seems to be a crucial region for the control of food intake by different substances (7, 8). The increase in food intake produced by injections of NPY into the PVN is blocked by injection of the opioid antagonist naltrexone into the medial portion of the nucleus of the solitary tract (mNTS). It remains to be determined whether this functional pathway from PVN (NPY) to mNTS (opioid) is monosynaptic or multisynaptic (16).

A number of peptides control food intake under specific conditions, such as leptin (5, 12, 24). Contrasting the behavioral responses to NPY and leptin, it appears that NPY stimulates the responses used to obtain food but inhibits those used to consume food [such as gastric emptying (13)], whereas leptin has the opposite effect. In regard to the specificity of the responses, NPY-treated male rats chose to ingest a sucrose solution rather than copulate with a female, whereas lepin-treated male rats made the opposite choices. Therefore, NPY is not merely an orexigenic peptide but one that directs attention to food. Leptin may not be an anorectic peptide but one that diverts attention away from food toward alternate stimuli. Under some conditions, leptin seems to inhibit NPY mRNA expression (19). It may be speculated that the leptin-NPY neuroendocrine system serves the purpose of directing attention to food acquisition when energy stores are depleted (low leptin, high NPY) and to other activities when energy levels are high (high leptin, low NPY) (1).

Sibutramine is a centrally acting weight loss agent that inhibits neuronal reuptake of norepinephrine and serotonin. In diet-induced obese rats, food restriction was associated with decreased body weight, increased NPY mRNA in the arcuate nucleus (Arc), and increased urinary excretion of epinephrine and norepinephrine. With food restriction plus sibutramine treatment, there was a greater loss of body weight, a normalization of NPY mRNA in the Arc, and further increases in the urinary excretion of epinephrine and norepinephrine (18). Thus sibutramine decreases body weight in association with alterations in central pathways involved in energy homeostasis and the regulation of body weight.

NPY produces sustained potentiation of phenylephrine-induced (but not ATP induced) release of vasopressin (VP) from hypothalamo-neurohypophysial supraoptic neurons in vitro. This mechanism is different from the VP stimulation induced by somatostatin analogs that require an intact renin-angiotensin system (11). Because NPY is colocalized with VP in hypothalamo-neurohypophysial magnocellular neurons and potentiates VP release from the neural lobe of the pituitary, the role for NPY to contribute to the regulation of VP release is expanded (14).

There are differences in the size and metabolism of adipocytes of the elderly (15). The “anorexia of aging,” a clinical syndrome seen in elderly patients, is, how-
However, more complex and includes a spontaneous decrease in food intake and body weight. Intracerebroventricular administration of NPY to young and old weight-stable Fischer 344 rats caused similar increases in food intake. However, NPY-stimulated food intake was less in old Fischer 344 rats with declining body weight. Thus anorexia of aging is characterized by central hyporesponsiveness to NPY-induced food intake (4).

Rats that lack the CCK-A receptor [Otsuka Long-Evans Tokushima Fatty (OLETF)] are hyperphagic, obese, and diabetic. When fed ad libitum, OLETF rats have decreased NPY mRNA levels in the Arc and normal NPY mRNA levels in the dorsomedial hypothalamus (DMH) compared with control rats. However, when OLETF rats are pair fed to the control rats, the OLETF rats show a normalization of the NPY mRNA levels in the Arc and a marked increase in NPY mRNA levels in the DMH compared with control rats. These findings suggest a role for DMH NPY upregulation in the etiology of OLETF hyperphagia and obesity (3).

NPY-transgenic rats (as with NPY-knockout mice) displayed no changes in body weight or development. Despite increased concentrations of NPY in a variety of organs and tissues, plasma concentrations of NPY were not increased. Mean arterial pressure (MAP) was slightly but not significantly increased, and cardiac output (CO) was slightly but not significantly decreased; the calculated value of total vascular resistance (MAP/CO) was significantly increased (~50%). There was increased pressor responsiveness to norepinephrine and less hypotension and bradycardia in response to a standard hemorrhage protocol. This model offers a unique opportunity for the evaluation of the role of NPY signaling in cardiovascular regulation, particularly regarding its functional cooperation with norepinephrine (21).

REFERENCES