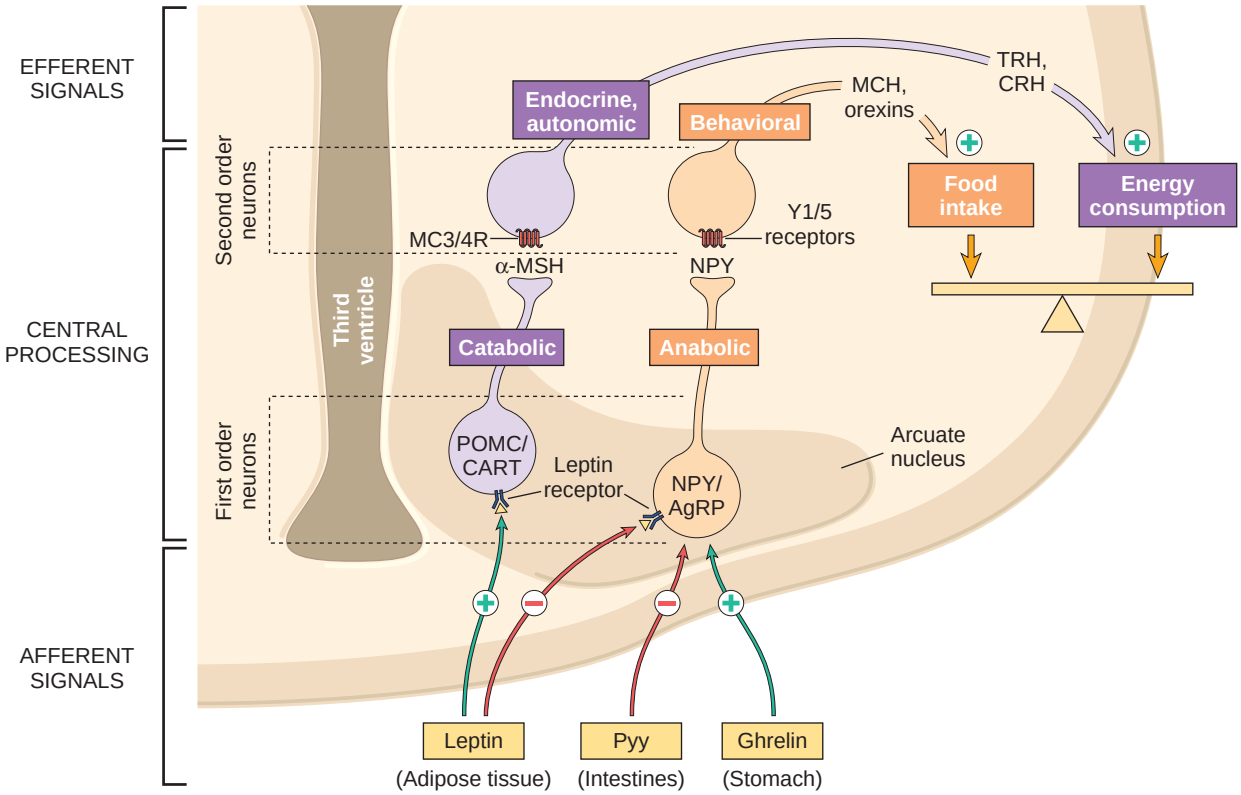

Figure 9-31 Neurohumoral circuits in the hypothalamus that regulate energy balance. Shown are POMC/CART anorexigenic neurons and NPY/AgRP orexigenic neurons in the arcuate nucleus of the hypothalamus, and their pathways. See text for details.

Adiponectin. Injections of adiponectin in mice stimulate fatty acid oxidation in muscle, causing a decrease in fat mass. This hormone is produced mainly by adipocytes. Its levels in the blood are very high, about 1000 times higher than those of other polypeptide hormones, and are lower in obese than in lean individuals. Adiponectin, which has been called a "fat-burning molecule" and the "guardian angel against obesity," directs fatty acids to muscle for their oxidation. It decreases the influx of fatty acids to the liver and the total hepatic triglyceride content, and also decreases the glucose production in the liver, causing an increase in insulin sensitivity and protecting against the metabolic syndrome (described later). Adiponectin circulates as a complex of three, six, or even more aggregates of the monomeric form, and binds to two receptors, AdipoR1 and AdipoR2. These receptors are found in many tissues, including the brain, but AdipoR1 and AdipoR2 are most highly expressed in skeletal muscle and liver, respectively. Binding of adiponectin to its receptors triggers signals that activate cAMP-dependent protein kinase (protein kinase A), which in turn phosphorylates and inactivates acetyl coenzyme A carboxylase, a key enzyme required for fatty acid synthesis.

Gut Hormones. Gut peptides act as short-term meal initiators and terminators. They include ghrelin, PYY, pancreatic polypeptide, insulin, and amylin among others. *Ghrelin* is produced in the stomach and in the arcuate nucleus of the hypothalamus. It is the only known gut hormone that increases food intake (orexigenic effect). Its injection in rodents elicits voracious feeding, even after repeated administration. Long-term injections cause weight gain, by increasing caloric intake and reducing energy utilization. Ghrelin acts by binding the growth hormone secretagogue receptor, which is abundant in the hypothalamus and the pituitary. Although the precise mechanisms of ghrelin action have not been identified, it most likely stimulates NPY/AgRP neurons to increase food intake. Ghrelin levels rise before meals and fall between 1 and 2 hours after eating. In obese individuals the postprandial suppression of ghrelin is attenuated and may contribute to overeating.

PYY is secreted from endocrine cells in the ileum and colon. Plasma levels of PYY are low during fasting and increase shortly after food intake. Intravenous administration of PYY reduces energy intake, and its levels generally increase after gastric bypass surgery. By contrast, levels of PYY generally decrease in individuals with the *Prader-Willi syndrome* (caused by loss of imprinted genes on chromosome 15q11-q13), a disorder marked by hyperphagia and obesity. These observations have led to ongoing work to produce PYYs for the treatment of obesity. *Amylin*, a peptide secreted with insulin from pancreatic β-cells that reduces food intake and weight gain, is also being evaluated for the treatment of obesity and diabetes. Both PYY and amylin act centrally by stimulating POMC/CART neurons in the hypothalamus, causing a decrease in food intake.

Actions of Adipocytes. In addition to leptin and adiponectin, adipose tissue produces cytokines such as TNF, IL-6, IL-1, and IL-18, chemokines, and steroid hormones. The

www.PTools.ir