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Preface

Obesity is an increasing health problem in Western societies. More than 5% of the national health expenditure in the United States is directed at medical costs associated with obesity. Comorbidities of obesity include type 2 diabetes, hypertension, dyslipidemia, cardiovascular diseases, stroke and osteoarthritis. Certain cancers are associated with obesity as well, such as prostate and colorectal cancer in men and endometrial, breast, and gallbladder cancer in women. Although dieting and exercise are important in the treatment of obesity, many people find it difficult to loose excess body weight and to maintain a healthy body weight (BMI < 25). A drug that would help with losing weight or maintaining a lower body weight would thus be very useful. Drugs such as sibutramine and orlistat, which are now on the market for the treatment of obesity, are reviewed in this special issue.

During the last decade, much progress has been made with the understanding of the mechanisms underlying regulation of body weight. Milestones in this search are the identification of genetic defects that underlie the extreme obesity in the *ob*/*ob* mouse and the viable yellow mouse (A^y), the leptin gene and the agouti gene. This research has yielded many new potential targets for drugs for the treatment of obesity. Since most obese individuals have high leptin levels, a current idea is that obese humans are resistant to the effects of leptin. Since the main target of leptin is the brain and, in particular, the hypothalamus, research has focused on the downstream effector pathways of leptin in the hypothalamus. The highest density of leptin receptors is in the arcuate nucleus, where there are at least two populations of leptin-sensitive neurons. Pro-opiomelanocortin (POMC)/cocaine- and amphetamine-related transcript (CART) producing neu-

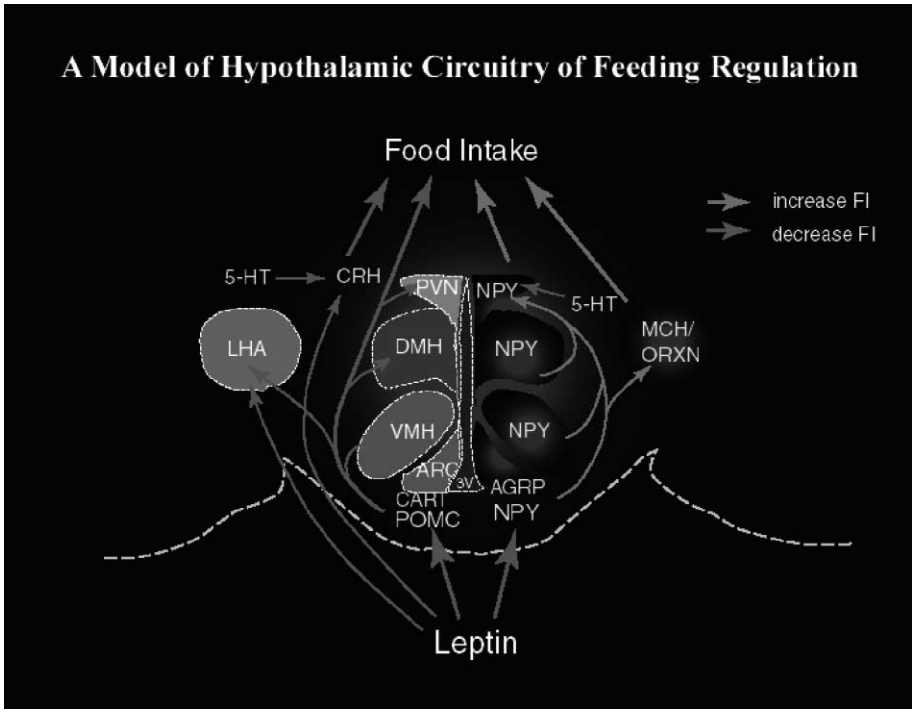

Fig. 1. Schematic representation of hypothalamic nuclei involved in the control of food intake, energy expenditure and diverse endocrine functions. Leptin can modulate leptin receptor function on hypothalamic neurons expressing cocaine-and amphetamine-regulated transcript (CART) and pro-opiomelanocortin (POMC) (red) or agouti-related peptide (AgRP) and neuropeptide Y (NPY) (green). These neurons project to the arcuate nucleus (ARC), ventral medial hypothalamus (VMH), paraventricular nucleus (PVN) and lateral hypothalamic area (LHA). Serotonin and corticotropin-releasing hormone (CRH) are among the neuronal pathways that can modulate the activity of this neuronal circuitry. (From MacNeil et al., 2002 (this issue), with permission).

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rons of the arcuate nucleus are activated by leptin. Agouti-related protein (AgRP)/neuropeptide Y producing neurons of the arcuate nucleus are inhibited by leptin. The primary leptin-responsive neurons project widely throughout the brain, including to areas associated with regulation of energy balance and food intake, such as the paraventricular nucleus, the ventromedial and dorsomedial nuclei and the lateral hypothalamus (Fig. 1). POMC is the precursor of melanocyte-stimulating hormone (MSH), the endogenous agonist of melanocortin receptors. AgRP is an inverse agonist, inhibiting melanocortin receptor activation. Thus, melanocortin receptors, whose activity is regulated by both leptin-activated and leptin-inhibited primary neurons of the arcuate nucleus, are a likely target for anti-obesity drugs. Results of genetic studies in mice and humans confirm the validity of this approach. The genetic defect in the viable yellow mouse (A^y), a gain of function of agouti protein (an endogenous inhibitor of melanocortin receptors) and the obese phenotype of the POMC − / − mouse indicate the important role of the melanocortin system in body weight regulation of mice. In human, the finding of mutations in the melanocortin MC_4 receptor gene and in the POMC gene associated with obesity also demonstrates the importance of the melanocortin system for energy balance. The importance of the melanocortin system in the treatment of obesity is reviewed in this issue. Neuropeptide Y and CART are reviewed separately.

Secondary leptin-responsive neurons in the paraventricular nucleus produce corticotropic hormone and those in the lateral hypothalamus produce orexin. These two neuropeptides are reviewed in the light of their importance for body weight regulation. New signaling pathways related to regulation of energy balance have been identified in the periphery also. Of these, ghrelin, ACRP30 and peroxisome proliferator-activated receptors are reviewed in this issue. Other neuropeptides involved in the regulation of energy balance, such as bombesin, glucagon-like peptide and galanin are reviewed separately.

This special issue thus provides an up-to-date review of most of the drug targets currently being explored for the treatment of obesity.

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