INSIGHTS INTO OBESITY’S PATHOGENESIS AND PHARMACOLOGICAL MANAGEMENT

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Abstract

Obesity is an increasing public health problem, the fifth leading risk for global deaths according to WHO. It is associated with major comorbidities, such as type 2 diabetes mellitus, ischemic heart disease, hypertension, dyslipidemia, sleep apnea, osteoarthritis, nonalcoholic fatty liver disease and depression.

The obesity pathogenesis increasingly became clearer. It is thought to be the result of a neuroendocrine dysregulation of energy intake and energy expenditure. One of the most studied cytokines involved in obesity, leptin is secreted from adipose tissue, proportional to fat mass. It inhibits neuropeptide Y/Agouti-related peptide neurons and activates pro-opiomelanocortin (POMC)/cocaine amphetamine-related transcript neurons in the hypothalamus, resulting in an anorectic effect.

Key words: obesity, leptin, POMC.

INTRODUCTION

Obesity is an increasing public health problem, the fifth leading risk for global deaths according to WHO. It is associated with major comorbidities, such as type 2 diabetes mellitus, ischemic heart disease, hypertension, dyslipidemia, sleep apnea, osteoarthritis, nonalcoholic fatty liver disease and depression.

The obesity pathogenesis increasingly became clearer. It is thought to be the result of a neuroendocrine dysregulation of energy intake and energy expenditure. One of the most studied cytokines involved in obesity, leptin is secreted from adipose tissue, proportional to fat mass. It inhibits neuropeptide Y/Agouti-related peptide neurons and activates pro-opiomelanocortin (POMC)/cocaine amphetamine-related transcript neurons in the hypothalamus, resulting in an anorectic effect. Its effects are best described in children with congenital leptin deficiency, resulting in extreme early onset obesity. Recently, it was described in a 2 years old boy with mutant biologically inactive leptin from a mutation in leptin gene, with consecutive hyperphagia and food seeking behavior (1). Besides food behaviour induced by fat mass signaling, leptin has also a role in energy expenditure by promoting browning of white adipocyte through POMC neurons, in parallel with insulin (2). It is already known that “beige” adipocytes exist in white adipose tissue and stimulating white adipose tissue browning could represent a way to increase energy expenditure and fight against obesity. Deletion of the phosphatases PTP1B and TCPTP enhanced insulin and leptin signaling in POMC neurons and prevented diet-induced obesity (3).

Epigenetic factors are also important. In a recent study of Drosophila melanogaster, Ost et al. (3) found that features of obesity can be transmitted from the father to male offspring. F1 male offspring of the fathers fed with a high-sugar diet had increased triglyceride reserves and increased weight. Common genes and the perinatal environment induced this transmission of phenotype, a concept named “development programming” associated with an increased risk of cardiovascular diseases and diabetes mellitus later in life (4).

However, in the last two years, new drugs for obesity became available. Endocrine Society recently released a new Clinical Practice Guideline on the pharmacological management of obesity (5). Although lifestyle changes continue to maintain a central role in reducing body weight, drugs could amplify adherence to behavior changes and could ameliorate comorbidities. Orlistat is the only drug approved in Europe for weight loss management. It acts through decreasing 25-30% of intestinal lipid absorption by inhibiting pancreatic and gastric lipase.

The other medications available act primarily in the arcuate nucleus to stimulate the POMC neurons, which promote satiety. Phentermine and diethylpropion are norepinephrine releasing agents. They could be used

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as short-term medication, as cardiovascular effects and the central nervous system overstimulation restricts their long term use; they should not be used in patients with uncontrolled high blood pressure or heart disease.

Lorcaserin is a serotonin agent stimulating the serotonin type 2c receptor. Topiramate acts through GABA receptor modulation, is a neurostabilizer and antiseizure medication, but also enhances appetite suppression by unknown mechanisms. Its effects are additive with phentermine and this combination could be used for the long term management of obesity. Another combination that could be used is with naltrexone, that potentiates the stimulation of POMC neurons induced by bupropion, a dopamine and norepinephrine reuptake inhibitor.

Since some diabetes medications are associated with weight gain, patients with diabetes mellitus and obesity should use medication that promotes weight loss. Therapy should include one or more of three currently available drug classes: metformin, the GLP-1 agonists (exenatide, liraglutide), and the new class of SGLT-2 inhibitors. Clinical trials have shown significant weight loss in patients receiving GLP-1 agonists (6). GLP-1 agonists also affect POMC neurons and cause satiety. SGLT-2 inhibitors promote weight loss by preventing the reabsorption of glucose as well as of water in the renal tubules. The first-line insulin regimen patients with diabetes and obesity should be basal insulin.

Conflict of interest
The author declares that he has no conflict of interest concerning this article.

References