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Review article

# Binge eating in pre-clinical models

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ABSTRACT

Obesity is a globally widespread disease. Approximately 35% of world population has the problem of inappropriate body weight due to sedentary lifestyle, excessive food consumption and the lack of physical activity. In the course of many years, several pharmacological anti-obesity drugs have been discovered. Most of them, however, possess severe side effects. Recent findings suggest that disturbed functioning of the reward system can be involved in the development of obesity. The data coming from clinical and animal studies provide new evidence that links excessive food consumption with compulsive behavior that can lead to binge eating disease occurrence. In this review we discuss most commonly used animal models of binge eating such as restriction/refeeding, limited access and stress schedule model, and related to them neurobiological findings as well. We also present new, anti-obesity drugs, which are characterized by central mechanism of action.


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## Introduction

According to WHO, overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health [1]. There is globally increasing prevalence of obesity alongside with serious and life-threatening health conditions, which necessitate considerable financing. In the US only the medical costs of obesity treatment were evaluated at the level of $190 billion in 2012 which constitutes around 20% of total healthcare costs [2]. It has been estimated that nowadays approximately 35% of global population deal with a problem of excessive body fat, being either overweight or obese [3]. Adverse effects of highly processed food consumption and sedentary lifestyle seem to be properly reflected by 35.7% obesity rate among US adults, which is the highest in the Anglosphere [4].

There are many anthropometric and non-anthropometric methods to estimate occurrence of obesity. One of the most popular anthropometric parameter that is used for assessing impaired weight is body mass index (BMI). It is measured as the person's body mass divided by the square of their height. Overweight individuals possess BMI greater than 25 kg/m$^2$, whereas obese people have BMI above 30 kg/m$^2$. However, this parameter does not provide information about the type of obesity and the amount of adipose tissue. Moreover, it is problematic to find adequate BMI cut-off for children, because they present wide variation of BMI according to race, age and sex. Nevertheless,

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BMI is a ratio of clinical importance. The numerous clinical trials such as Nurses' Health study (116,000 patients) have revealed strong correlation between women's BMI and their mortality. BMI index also corresponds with the substantial risk of suffering from chronic diseases such as type 2 diabetes mellitus, hypertension and cholelithiasis – the disorder particularly common for individuals who possess BMI greater than 30 kg/m$^2$ [5,6]. Additionally, the individuals with BMI over 25 kg/m$^2$ are under greater risk of developing colorectal and breast cancers [7].

Another indicator of obesity, expressed in centimeters, is waist circumference (WC) which is defined as the circumference of midpoint in between lower border of ribs and upper border of the pelvis. It requires determined gender specific cut-off for men ($\geq$94 cm) and for women ($\geq$88 cm), although, it may over- or underestimate obesity among short and tall patients. It should be emphasized that values of more than 102 cm for men and 88 cm for women should involve medical treatment because they incur a high risk of metabolic complications. WC differentiates android type of obesity from gynoid one, thus it provides information about upper fat distribution. This fact has high clinical utility because it has been proved that the amount of visceral adipose tissue positively correlates with cardiovascular disease [8,9].

The waist-hip ratio (WHR) is another indicator of fat distribution pattern. It is obtained by dividing WC and hip circumference (HC); the latter parameter being measured around the pelvis at the point of maximum protrusion of the buttocks [10]. It is established that the WHR should not exceed 0.9 for men and 0.85 for women. However, WHR is not an appropriate measurement for patients who have lost weight, because weight reduction influences values of both waist and hip circumference and their ratios as well [10,11]. It is also important to mention another indicator of obesity – waist-to-height ratio (WtHR), which is defined as patients' WC divided by their height. The correct WtHR value is considered to be less than 0.5 [12].

One of the non-anthropometric methods is the skinfold thickness. It is based on the assessment of skinfold thickness (in centimeters) by using special calipers, which are usually distributed on body surface at multiple sites. As the above-mentioned indicators, this method also does not provide information about the amount of abdominal fat constitute. The only way to estimate the amount of visceral fat is using the bioimpedance. This method determines the electrical impedance of lean and fat mass [5].

The above methods are the most popular diagnostic techniques used in order to assess body weight and obesity. However, there is a strong disproportion visible in clinical usage of these parameters in different race population. Nonetheless, the longitudinal clinical trials such as Framingham Heart study have proved that overweight and obesity decrease the longevity. Some recent clinical studies have revealed that the risk of death increases respectively by 1% for each extra pound between the age of 30–42 and by 2% between the age of 50–62 [5].

## Surgical and pharmacological interventions to treat obesity

A huge effort is being made in order to minimize the negative effects of obesity and decrease its overall prevalence throughout the world. One of the main means of anti-obesity campaign, next to aiming at creating and keeping healthy habits as well as increasing physical activity, appears to be a well-guided medical therapy which would normalize effects of dysfunctional weight maintenance mechanisms.

Surgical procedures, such as bariatric surgery, remain one of the most effective methods of disposing excess weight in patients suffering from severe obesity (usually with BMI $>$ 40) [13]. Long-term studies on bariatric surgery seem to show its ability to decrease overall mortality in about 23% but the general outcome remains equivocal [14]. Recently, due to the development of laparoscopic techniques those surgeries have become less invasive and more convenient. Nevertheless, likewise any other surgery, they can still cause substantial complications, such as gastric dumping syndrome or diverse infections. Another disadvantage would be the high cost of the surgery [15].

There are various bariatric surgery procedures and the choice of the most suitable one depends on many factors, such as patient's age, anatomical built, BMI or the presence of other metabolic diseases. We can distinguish 3 main surgical procedures:

1) predominantly restrictive procedures which tend to decrease oral intake by producing satiety – the result of limiting gastric volume;
2) predominantly malabsorptive procedures that create a condition of malabsorption as well as reduce stomach size;
3) mixed procedures, which apply to the above-mentioned techniques, such as gastric bypass surgery that used to be the most common operation in the US until 2005 [16].

As a result of the surgery, patient's hunger decreases, possibly in relation to changes in hormone levels (for example ghrelin). It is also worth noting that with lack of change regarding eating habits and physical activity, bariatric surgery may not be enough to help patients in attaining their desired appearance.

Another method of curing obesity, probably the most popular, is pharmacotherapy. Throughout the years, several drugs have been widely used in obesity treatment (see Table 1). Unfortunately, extensive research and substantial funds spent on development of new medications were largely limited by their numerous notorious side effects and restricted effectiveness [17]. Orlistat (sold as Xenical or sold over-the-counter under the trade name Alli) is the most often prescribed anti-obesity drug. Its mechanism of action relies largely on preventing fat absorption from one's diet and therefore reducing overall caloric intake. Orlistat is recommended to patients with BMI $>$ 28 who are willing to comply with low-fat diet that requires them to supplement fat-soluble vitamins. The drug acts peripherally by inhibiting gastric and pancreatic lipases, thus blocking the hydrolysis of triglycerides into absorbable free fatty acids. Consequently, undigested fats are eliminated from the diet through the feces [17,18]. At commonly prescribed doses (120 mg/3 times a day), the drug can decrease fat absorption up to 30% [16]. It has a minor influence on weight loss (on average 2–3 kg per year compared to control group), but it demonstrates preventive effects to diseases, such as type 2 diabetes. On the other hand, orlistat users often experience various adverse effects, with steatorrhea (oily stools) being the most common [17]. Orlistat can lead to impairment of liver and can impair kidneys functioning, most likely as a result of the excessive oxalate absorption and its deposition into these organs [20]. As evidenced by the XENDOS study, there is a reduction in detrimental gastrointestinal effects such as fecal incontinence, oily spotting and flatus with discharge from 91% in the first to 36% in the fourth year of orlistat use. However, a slight weight loss and the presence of side effects seem to make the drug rather unhelpful [21,22].

Other commonly used anti-obesity drugs rely mainly on monoamine reuptake inhibition, thus enhancing dopaminergic, noradrenergic and, most significantly, serotoninergic (5-HT-ergic) transmission in the brain [23]. It is shown that consumption of food rich in carbohydrates ameliorates mood and suppresses appetite due to the increase of 5-HT in brain levels [24]. For that reason the original research in the field of anti-obesity drugs was aimed at increasing 5-HT concentrations within the central nervous system (CNS), which resulted in the invention of various types of anorexic drugs.