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Review Article

OBESITY: PATHOPHYSIOLOGY AND MANAGEMENT-A PHARMACOLOGICAL PERSPECTIVE

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ABSTRACT

The rising prevalence of the pandemic of obesity urges the need for newer and effective drugs in its management. The pharmacotherapy of obesity is burdened by limitations in the number of drugs, inefficacy and side effects of existing drugs and continuous withdrawal of marketed drugs. This article gives an overview of factors involved in the regulation of energy homeostasis and the occurrence of obesity by a presumable shift in the controlling pathways. There are various putative targets which are implicated in the pathogenesis of obesity and these are the potential targets of drugs used in the treatment. A better understanding of Pathophysiology of obesity and the current status of pharmacotherapy can open up new vistas in this promising and needful area of research.

Keywords: Obesity Pathophysiology, Antiobesity Drugs, Peptides, Energy Homeostasis

INTRODUCTION

Obesity is a worldwide epidemic and is referred to as "*globesity"* by World Health Organization[1]. It is not merely a cosmetic problem but a rapidly escalating public health problem[2]. This disease state is a great threat to health and has great impact on health care expenditure[3]. In a developing country like India, obesity and malnutrition among children are two ends of spectrum, obesity being an emerging issue needs close monitoring.

Obesity is a complex multifactor disease that develops from the interactions of genetic, metabolic, social, behavioral, and cultural factors [4]. There is an increase in its prevalence in this decade and are attributed primarily to psychological and behavioral factors, rather than biological factors[5]. A series of events tip the fine balance between homeostatic mechanism of energy control and these factors resulting in obesity. The exact role and mechanisms of these events are still not fully understood.

The primary options of management of obesity are lifestyle modification and behavioral therapy. It includes promotion of healthy physical activity, eating patterns, psychosocial well-being and resolution of or improvement in medical complications[6]. But the effect is not predictable and once the homeostasis is altered it is very difficult to restore the balance.

The pharmacological approaches to the problem of obesity are still in its infancy. Many licensed drug are withdrawn due to unfavorable side effects and only very limited drugs are there in the market. Surgical interventions are more efficacious than currently available drugs, but the compliance of the patients are not satisfying. Now it has become apparent that interaction of many genes and gene polymorphisms has a role in this polygenic disorder and pharmacogenomics will have its impact in management in coming years[7]. Obesity being a disease of adipose tissue, there is a need for proper demarcation between obesity, and overweight which is due to increase in mass of bone or muscle tissue [8].A better understanding of pathophysiology of obesity and an insight into current drug treatment helps in pharmacological exploitation of new mechanism and molecular targets.

Pathophysiology of obesity

Obesity is characterized by excessive fat deposition which may be generalized, or may occur preferentially in different adipose tissue compartments [8]. The process of adipogenesis can occur throughout life but two particularly sensitive periods are the post-natal period and puberty. The biological process regulating this is called Energy Homeostasis[9, 10].This metabolic disorder is known to occur when there is an imbalance between energy intake and energy expenditure.[11]

The regulatory mechanism of energy homeostasis is primarily in the brain. The arcuate nucleus in the mediobasal hypothalamus forms the main integrating centre for feeding and regulation of body weight. The neuronal circuits here consist of two groups of neurons[12]. In one group Peptide Neuropeptide Y, Agouti related protein controlling anabolic pathway stimulating food intake, reducing energy expenditure and promote weight gain. In the other group Preproopiomelanocortin and cocaine, amphetamine related transcript which secrete alpha melanocyte stimulating hormone, controlling catabolic pathway reducing food intake and subsequently activating serotonin receptors[13, 14]. Various peripheral organs with its neuro hormonal, sensory and other cytokine signalling pathways also send inputs to this homeostatic system[15].

Adipose tissue through its peptides leptin, adiponectin, and resistin send *Adiposity signals* about the fat store to the hypothalamus [15]. Of this leptin is the primary messenger sending two signals, one to the brain satiety centre and other to the fat inside cells to break down it into a kind of fat that can be burned as energy[16].

These signals are integrated with neurosensory *satietysignals* from stomach, liver and GIT through peptide hormones released from the gut during feeding. It includes Ghrelin, which convey sensation of hunger, CCK conveying satiety signals, PYY_{3-36} conveying satiation to the hind brain. There is a central autonomic pathway connecting the relay stations of adiposity and satiety signals. In addition there are controlling pathways connecting signals from adipose tissue and GIT[17, 18].

The brain processes these integrated signals and produce its output to the Feeding centre (Lateral hypothamus)) and Satiety centre (Ventromedial hypothalamus). It results in neuroendocrine activation from the hypothalamo pituitary glands; stimulating autonomic activities and motor behaviors like eating[19, 20].

Leptin resistance

When too many fat cells build up, a protein called CRP sticks to the leptin and prevents it from delivering its message to the brain and the signaling is lost. This is called *Leptin resistance*[21, 22]. This reduces natural metabolism of fat for energy. It triggers a series of other signal problems. One is with messenger –*adiponectin* which controls the sensitivity to insulin and adequate fat production. This results in unfavorable fat formation. Another messenger which is activated is *glycerol-3-phosphate dehydrogenase* which is an enzyme which turns blood sugar into fat [23]. Presumably such shift in the regulation of these rhythmic signals which tunes the orchestra of energy balance causes the entire disharmony.

Consequences of overweight and obesity affect almost every system of body leading to various diseases like diabetes, dyslipidaemia, cardiovascular disease, hypertension, stroke, liver disease, respiratory disorders, gout, osteoarthritis, polycystic ovary syndrome, metabolic syndrome, immune dysfunction and innumerable types of cancers [24, 25,26].

Peptides implicated in obesity are shown in table1 [27]. The putative targets which are implicated in the pathogenesis of obesity are mutation of B3 receptor, leptin receptor gene, Promelanocortin (POMC) gene, alteration of brown adipose tissue gene, over expression of GLUT-4 [28] .Some of the potential targets for new anti obesity drugs include these antagonists or inhibitors, agonists, and/or stimulators and enzyme inhibitors or blockers .

Table 1: Peptides Implicated in Obesity

BRAIN ANTAGONISTS	NPY (Neuropeptide Y) MCHR-1 (Melanin-Concentrating Hormone Receptor-1,) AGRP (Agouti-Related Protein) Galanin Ghrelin Orexin Opioid receptor
BRAIN AGONISTS	Adiponectin MC4R (Melanocortin-4 Receptor) Leptin CART (Cocaine And Amphetamine-Regulated Transcript) CNF (Ciliary Neurotrophic Factor) BDNF (Brain-Derived Neurotrophic Factor) Oxytomodulin
BRAIN,GIT AND OTHER TISSUES	CCK- (Cholecystokinin-A Receptor agonists Enterostatin Agonists Ghrelin Antagonists Amylin Digestive Enzyme Inhibitors Growth Hormone GLP-1 (Glucagon Like Peptide-1) Insulin Mimetics

Therapeutic Implications

Management of Obesity

The primary step of management of obesity is lifestyle modification and behavioral therapy. Promotion of healthy eating patterns, increase physical activities, promotion of a healthier body weight and psychosocial wellbeing are among the strategies[29].

The Pharmacotherapy of obesity is still controversial. The rising prevalence of this pandemic urges the need for newer, tolerable and effective drugs in the management of obesity. Drug treatment is now primarily meant for adults with BMI >30 kg/m^2 or with BMI 27-30 kg/m^2 and associated co morbid conditions and as last resort in others who are not responding to primary care management[30]. These drugs affect appetite, metabolic rate, and/or inhibit caloric absorption, and generally fall into 3 broad classes: 1) peripherally acting, 2) centrally acting, and 3) combination (central and peripheral acting.)[31, 32].

Peripherally acting drugs mediate their effects by reducing the calorie absorption in the gastrointestinal system or by affecting metabolism of systems outside the central nervous system. Currently, the only peripherally acting anti obesity drug globally approved for long-term use is orlistat[33]. It is a lipase inhibitor that prevents the absorption of dietary fat from the intestines. Table 2 shows drugs acting on periphery[34].

Table 2: Drugs Acting On GIT

Gastric and pancreatic lipase inhibitor	Orlistat Cetilistat
Non absorbable fat substitute	Olestra
dietary fiber	Chitosan Methyl Cellulose Guar gum

Centrally acting anti obesity drugs are mainly that suppress appetite (anorectic agents) .These drugs act on the CNS by 3 mechanisms; Adrenergic drugs mainly noradrenaline and dopamine mediated, drugs which are 5-hydroxytryptamine mediated, or combined drugs which increase both NE & 5HT [35]. Satiety may be regulated through an effect on 5HT, noradrenalin or dopamine receptors in the hypothalamus. Sibutramine is the only centrally acting drug currently approved for long-term treatment of obesity in adults[35, 36]. But it was withdrawn from US market in 2010. Lorcaserin a selective serotonin receptor (5-HT2C) agonist has recently received the U.S. Food and Drug Administration (FDA) approval for chronic weight management by stimulating satiety centre[37]. Centrally acting drugs are shown in table3 [38].

Table 3: Drugs acting on the CNS

Adrenergic drugs	Amphetamine Benzamphetamine Phentaramine Buproprion Phenyl propanolamine Mazindole
Drugs that increases 5HT	Fenfluramine Dexfenfluramine Fluoxetine
Drugs which increase both NE & 5HT	Sibutramine

Central- and peripheral-acting drugs

Rimonabant is a selective endo cannabinoid (CB) 1 receptor antagonist that acts both centrally and peripherally. It inhibit food intake and regulate metabolic functions in peripheral organs, like gut, liver, adipose tissue, and skeletal muscle [39]. Rimonabant was approved initially but recently failed to gain FDA approval due to neurologic and psychiatric problems[40].

Drugs in clinical development

All currently available drugs and drugs under investigation are directed towards reducing energy intake either by suppressing appetite or limiting intestinal absorption whereas energy expenditure may be increased directly by thermo genesis and lipolysis or through the stimulation of the sympathetic nervous system[41]**.** Drugs that increase the metabolic rate are an important newer targets .B3 agonists increase the expression of uncoupling protein-1 in BAT, thereby increase thereby increase thermo genesis[42]**.** Nonselective beta blockers with B3 agonistic action, Oxprenolol, Alprenolol, Pindolol, Cyano pindolol, Nadolol are under investigation [43]. B3 agonists will be beneficial in obese patients with stressed cardiovascular system. Some of the promising novel anti obesity drug targets are thermogenic pathway regulated by peroxisome proliferators-activated receptor beta co activator1alpha, endogenous slimming peptides Leptin analogues, Neuro Peptide Y receptors, various peripheral enzymatic targets like acetyl co A carboxylase , diacylglycerol acetyl transferase, protein tyrosine phosphate -1B and various nutrient absorption inhibitors[44]. Some drug combinations like Naltrexone + Buproprion, Topiramate + Fenfluramine are also being successfully tried but long term pharmacotherapy of obesity is a matter of debate [45].

CONCLUSION

Despite great advancement in understanding of pathophysiology of the disease process the effort to curb the pandemic of obesity by drugs is not yet fruitful. Less number of effective drugs and withdrawals of marketed drugs are the limitations. There are specific genes associated with the complex networking of energy homeostasis which is regulated by neuro endocrine and autonomic control[46]. This reveals the role of pharmacogenomics in the future development of drugs in obesity. The physical, psychosocial, emotional well beings of obese patients as well as treatment of co morbid conditions are also essential components of management[47].

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