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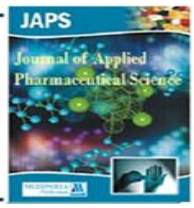

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Obesity being the major health burden needed to be chased: A systemic review

Gurudev Singh Raina

ABSTRACT

"Obesity" originates from the latin word "obesus" that means fat, plump or swollen. Obesity is multifactorial, chronic disorder with complex interaction between genetic and environmental factors. It is the major health burden in the western world, not just in terms of the increased risk of diabetes (type 2), cardiovascular morbidity, and cancer, but also in the economic costs to healthcare providers. Obesity is a medical condition in which excess body fat has accumulated to such a level that it may have an adverse affect on health. However, the genetic liability for the vast majority of the population does not reside in a single gene, thus obesity is a multigenic disorder. It can be described as "New World Syndrome" and "diseases of civilization" which is widespread, crippling and life shortening disease. Several therapeutic strategies are available for overweight and obese population: behavioral strategies, bariatric surgery for those at greatest risk and medication. The primary treatment for obesity is controlled diet and physical exercise, if these fail, anti-obesity medication is recommended to reduce appetite or inhibit fat absorption. In severe cases, surgery is performed or an intra-gastric balloon is placed to reduce stomach volume or bowel length, leading to earlier satiation and reduced ability to absorb nutrients from food. Sibutramine and orlistat are the only two drugs approved by FDA for long term use in obesity. Several FDA approved drugs for conditions other than obesity have been investigated for treatment of excess body weight. Conclusively, the obesity is one of the leading causes of morbidity and mortality.

Key words: Obesity, metabolic disorders, Diabetes.

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INTRODUCTION

The incidence of obesity is increasing due to fat-rich food intake and a sedentary lifestyle. Obesity is the major health burden in the western world, not just in terms of the increased risk of Type 2 diabetes, cardiovascular morbidity, and cancer, but also in the economic costs to healthcare providers (McIntyre, 1998). Cultural changes is the influence of genetic predisposition, which is most easily demonstrated in populations that have evolved in situations where food supply was variable, for example, the North American Pima Indians. Obesity is a pathological condition in which excess fat accumulated in the body may induce an adverse affect on health (WHO 2000; Haslam and James, 2005). "Obesity" originates from the latin word "obesus" that means fat, plump or swollen (WHO, 2000). Obesity is measured by the body mass index (BMI), a person's weight (in kilograms) divided by the square of his or her height (in metres). A person with a BMI of 30 or more is generally considered obese. A person with a BMI equal to or more than 25 is considered overweight. In obesity, there is increased intake of high fat and energy food; and an decreased energy expenditure (Labib, 2003). The hypothalamus regulates the feeding and energy expenditure through afferent signals which include leptin, insulin, ghrelin, CCK, PYY, GIP, GLP-1; and efferent signals such as sympathetic nervous system (SNS), which promotes energy

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expenditure, and parasympathetic nervous system, which promotes energy storage (Wilding, 2002). Obesity increases the risk of several physical and mental conditions. These comorbidities are reflected predominantly in metabolic syndrome (Haslam and James, 2005) and certain clinical conditions like diabetes mellitus (type 2), hypertension, hypercholesterolemia, and hypertriglyceridemia (Grundy, 2004). Obesity is associated with many disorders particularly heart disease, type 2 diabetes, breathing difficulties during sleep, certain types of cancer and osteoarthritis (WHO 2000). It increases the risk of death in current and former smokers as well as in those who have never smoked (Pischon *et al*, 2008). The primary treatment for obesity is controlled diet and physical exercise, If these fail, anti-obesity medication is recommended to reduce appetite or inhibit fat absorption. In severe cases, surgery is performed or an intra-gastric balloon is placed to reduce stomach volume or bowel length, leading to earlier satiation and reduced ability to absorb nutrients from food (NICE 2006; Imaz et al., 2008). Conclusively, the obesity is one of the leading causes of morbidity and mortality (Allison et al., 1999; Mokdad et al., 2004; Barness et al., 2007).

Pathophysiology

Many possible pathophysiological mechanisms are involved in the development and maintenance of obesity (Flier, 2007). The research in this field gained pace after the discovery of leptin in 1994. Since leptin's discovery, there are other hormonal cascades involving mediators like ghrelin, insulin, orexin, PYY 3-36, cholecystokinin, adiponectin have been elucidated to participate in regulation of appetite, food intake, storage pattern of adipose tissue, and development of insulin resistance. The adipokines produced by adipose tissue; are thought to modify many obesity-related diseases. Leptin and ghrelin (fig.1) are considered to be complementary in their influence on appetite. Ghrelin produced by the stomach modulating short-term appetitive control (i.e. to eat when the stomach is empty and to stop when the stomach is stretched).

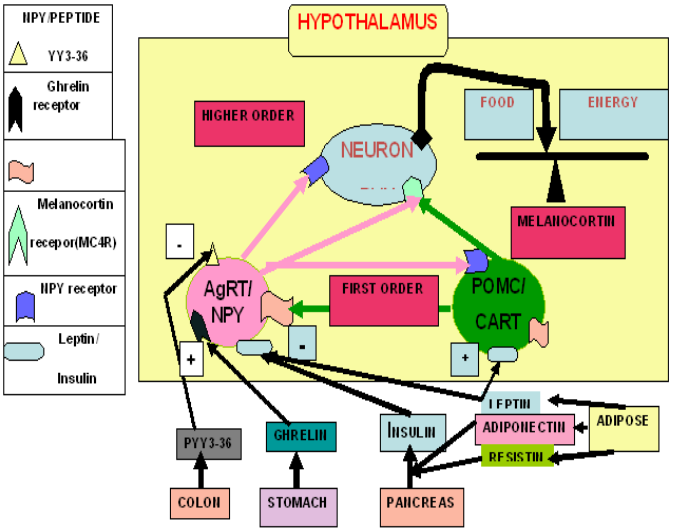

Fig 1: Role of Neuronal Mechanism in Food Intake. (Gale *et al.*, 2004).

Leptin is produced by adipose tissue to signal fat storage in body, and mediates long-term appetitive controls (i.e. to eat more when fat storages are low and less when fat storages are high). Although administration of leptin may be effective in a small subset of obese individuals who are leptin deficient, most obese individuals are thought to be leptin resistant and have been found to have high levels of leptin (Flier, 2007; Hamann and Matthaei, 1996).

Leptin and Ghrelin are produced peripherally and control appetite through their actions on the central nervous system. In particular, they and other appetite-related hormones act on the hypothalamus, a region of the brain central to the regulation of food intake and energy expenditure by modulating several circuits like melanocortin pathway being the most well understood (Flier, 2007). The circuit; has outputs to the lateral hypothalamus (LH) and ventromediahypothalamus (VMH), the brain's feeding and satiety centers, respectively (Boulpaep et al., 2003). The arcuate nucleus contains two distinct groups of neurons (Flier, 2007). The first group coexpresses neuropeptide Y (NPY) and agouti-related peptide (AgRP) and has stimulatory inputs to the LH and inhibitory inputs to the VMH. The second group coexpresses pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) and has stimulatory inputs to the VMH and inhibitory inputs to the LH. Consequently, NPY/AgRP neurons stimulate feeding and inhibit satiety, while POMC/CART neurons stimulate satiety and inhibit feeding. Both groups of arcuate nucleus neurons are regulated in part by leptin. Leptin inhibits the NPY/AgRP group while stimulating the POMC/CART group. Thus a deficiency in leptin signaling, either via leptin deficiency or leptin resistance, leads to overfeeding or may account for some genetic and acquired forms of obesity (Flier, 2007).

Experimental models of obesity

A number of rodents models of obesity have been established, due to great homology between the genomes of rodents and human beings. The most widely used models are High Fat Diet (HFD) induced obesity, Oophorectomy induced obesity, ventromedical hypothalamic nucleus lesion-induced obesity (induced chemically or surgically), genetically-induced obesity and viral-induce obesity (Butler and Cone, 2001; Buettner et al., 2007).

Diet induced models

Researchers conducting feeding studies in rodents have to take into consideration several important measures, as energy intake or expenditure are influenced by a variety of factors: The choice and the consistency of the environmental conditions including room temperature, duration of light and dark period, number of animals per cage or the feeding system used for the cages are of utmost importance. Also any experimental manipulation will influence locomotor activity and feeding behavior. Hence, control over environmental conditions is important to minimize data variability. Another factor that has to be considered is the age of the animals at which a study is conducted. It is most effective to start high fat diet feeding at a young age, but it is also important to take into consideration that

the energy balance differs in young compared to older animals. For example rats in their pubertal age rapidly gain lean mass and show completely different metabolic features compared to aged rats, which may in turn be losing lean mass and gaining fat mass. Another important variable is the duration of an obesity producing diet, that is the longer the feeding period, the greater the increment of bodyweight gain and presumably body fat.

High fat fed diet induced models

This is the simplest obesity-induction model, and possibly the one that most closely resembles the reality of obesity in humans. Diet-induced obesity (DIO) has a late onset and is developed after feeding mice with high-fat diet (HF diet). The use of high-fat diets to induce obesity, IR and hyperglycemia is well documented (Gajda et al., 2007). Prolonged Exposure to HFD results in positive energy balance and obesity in certain rodents' models that can be considered an adequate model of human obesity (Gaiva et al., 2001; Lin et al., 2000).

The high fat fed mouse (DIO mouse)

The gold standard for a diet induced obese (DIO) model is the male C57BL/6J mouse. The C57BL/6J mouse develops an obese phenotype only when allowed ad libitum access to a high-fat diet, whereas on a low-fat diet, C57BL/6J mice remain normal. In marked comparison to C57BL/6J, other strains such as the A/J mouse or the C57BL/KsJ are relatively resistant to these effects when fed a high fat diet (Surwit et al., 1995). The obesity in the C57BL/6J mouse results from both adipocyte hypertrophy and hyperplasia. The fat gained in the C57BL/6J mouse is deposited selectively in the mesentery. C57BL/6J mice exhibit an increased weight gain per ingested energy unit (feed efficiency rate) and, the ability of ingested energy to be metabolized (metabolic efficiency) is lower in high-fat diet fed C57BL/6J mice compared with control mice (Parekh et al., 1998). The weight gain observed in C57BL/6J mice may thus not fully be explained by increased energy intake but is also caused by a reduced metabolic rate (Winzell et al., 2004).

The high fat fed rat (DIO rat)

The most popular and best-studied DIO rat model is the outbred Sprague-Dawley rat. It is markedly more sensitive to high fat diet-induced obesity than other common rat strains. However, when outbred Sprague-Dawley rats are placed on a high-energy diet, only a subset of them overeat and develop diet induced obesity (DIO) whereas others remain lean (diet resistant, DR) (Sclafani et al., 1976; Chang et al., 1990). The obesity prone subset of rats become obese, hyperphagic, hyperleptinemic, hyperinsulinemic, hyperglycemic, and hypertriglyceridemic (Chang et al., 1990). The DIO rat displays a central resistance to circulating leptin indicating that reduced central leptin signaling may be involved in the etiology of hyperphagia in the obesity proneness. DIO rats exhibit a positive energy balance and a significantly higher respiratory quotient than DR rats, indicating a lower usage of fat as energy substrate. The physiological aspects of this model replicate many of the features observed with the human obesity syndrome: a polygenic mode of inheritance, a persistence of the phenotype once it is established, and dysregulated glucose homeostasis (Levin et al., 1997).

High fructose fed animal models

Fructose is more lipogenic than glucose or starches and induces moderate obesity and several adverse metabolic effects, including hypertriglyceridemia, hyperinsulinemia and hypertension in rodents (Zavaroni et al., 1980). The abnormalities and the disease progression in fructose fed rats resemble the human condition of metabolic syndrome, and are important risk factors for coronary heart disease. As to the metabolic mechanisms underlying the effects of dietary fructose the general notion is that hepatic intermediary metabolism is more affected by ingestion of fructose than of glucose. Fructose bypasses the phosphofructokinase regulatory step and enters the pathway of glycolysis or gluconeogenesis at the triose phosphate level, resulting in increased hepatic triglyceride production (Park et al., 1992).

Cafeteria rats

The so-called 'cafeteria diet' involves feeding experimental animals a mixture of palatable commercially available supermarket foods to stimulate energy intake (Rothwell et al., 1988). What is most characteristic for such diets is the combination of the high fat content with a high carbohydrate content. Such diets have pronounced implications in the development of obesity, leading to significant body weight gain, fat deposition and also insulin resistance (Prats et al., 1989). It has been suggested that rats become more obese with cafeteria diets than with pure high fat diets, indicating a greater hyperphagia arising from the food variety, texture and palatability (Kretschmer et al., 2005).

Ventromedial hypothalamic nucleus (VMH) lesion

Monosodium Glutamate (MSG)

The administration of monosodium glutamate to newborn rats causes the destruction of the ventromedial hypothalamic and arcuate nuclei, leading the rats to develop obesity due to the lack of control between absorption and energy expenditure. The real mechanism by which this hypothalamic injury leads to obesity is not known, but it is not because of increased food intake. In a single dose during the neonatal period, although it did not develop obesity, MSG caused a drop in the hypothalamic dopamine (Caudle & Lorden, 1986) . The involvement of enzyme activity of the small bowel in the induction of obesity after the use of MSG and the influence of the adrenal gland have been researched (Miskowiak et al., 1993; Guimaraes et al., 2002; Martins et al., 2004). MSG has shown a number of changes related to the lack of control of the hypothalamo-pituitary axis with a dose dependent curve including hypophagia, obesity, hypoactivity, reduction of ovarian weight, late puberty and high serum levels of corticosteroids (Lorden et al., 1986; Moreno et al., 2005). There is evidence that chronic exposure of the adrenal gland to high serum

levels of leptin, which occurs in rats treated with MSG, is involved in the loss of the inhibitory regulatory effect that leptin exerts on the adrenal gland. Therefore, it is responsible, at least in part, for the increase of glucocorticoids found in these adult rats (Tokuyama et al., 1989; Perello et al., 2003). MSG can be administered subcutaneously or intraperitoneally (Bunyan et al., 1976; Shivshankar et al., 2005) at doses that vary by 2-4 mg/g of body weight of the rat during the neonatal period and for periods ranging by 4-10 doses causing obesity (Dolnikoff et al., 2001; Mello et al., 2001; Carvalho et al., 2002; Souza et al., 2003). Since MSG is a substance found in several foods consumed daily, it has been targeted by studies on its effects when taken orally. In a recent publication, compared 4 groups of rats, one fed standard chow, another standard chow added to 100g of MSG/kg of weight, a fiber-rich diet and another with a fiber rich diet added to 100g of MSG/kg of weight (Diniz et al., 2005). In this study, MSG increased food intake, induced metabolic disorders associated with oxidative stress (prevented in the group with a fiber-rich diet), even in the absence of obesity, and also presented a rise in the glucose, trial glycerol, insulin (with increased peripheral resistance)25 and leptin26 levels.

Electrical VMH Lesion

The VMH lesion was described by Saito et al (1985) and now, with a few changes, it can be used to induce obesity. A 1.2 mA current lasting 4 seconds, repeated 3 times at 30-second intervals after positioning the electrodes, can cause bilateral destruction of the hypothalamic nuclei, leading to obesity. The tip of the guinea pig's nose is positioned 5mm above the inter aural line in a stereotactic instrument, and the electrode tip is placed 0.6 mm lateral to the bregma and 9 mm below the cranium (Shimizu et al., 2003). The injury can also be caused with a single electrical current of 2.5 mA for 15 seconds using stereotactic instruments placing the tip of the rat nose 3.3 mm below the interaural line and positioning the tip of a stainless steelelectrode 2.6 mm behind the bregma, 0.5-0.6 mm lateral to the midline and below the base of the brain and raised 0.5mm (Dube et al., 1999). Paradoxically, concerning what was found in the hypothalamic lesiong by MSG, this electrical ablation causes obesity by hyperphagia. The real mechanism involved in this process is not known. Initially the irritative theory was believed, in which the deposition of iron ions caused by the introduction of electrodes in the hypothalamus would destroy the hypothalamic nuclei over the long term. Other authors suggested that the injury was caused only by the electric current, the ablative theory. Studies were performed comparing electric injury with radio frequency (without iondeposition) using the conventional technique and the results obtained were a lower index of obesity using radio frequency. Therefore, the most widely accepted theory is ablative/irritative , i.e. both mechanisms are involved in the development of obesity (King, 1985; King, 1986; King; 1989; King, 1991). More recent studies have shown involvement of the participation of leptin, insulin and neuropeptide Y, and their interrelations in the hypothalamus, causing weight gain after this type of lesion (Scallet et al., 1986; Dube et al., 1999). It is known that the electric lesion of the hypothalamus causes an increased level of leptin, reduction of the total neuropeptide Y, maintaining the fluctuations of the circadian rhythm and there appears to be a loss of the feedback mechanism between insulin and leptin (Dube et al., 1999).

Oophorectomy

The obesity induction model in rats through oophorectomy, on the contrary of the previous ones, results from the observation of women who, after menopause, present a number of metabolic changes, including weight gain. This model is used in order to achieve a better understanding of these modifications in women after the end of their fertile age and also to study interventions that could alter the impact of hormone reduction in a woman. The removal of gonads from female rats causes a drop in the initial leptin levels, which is correlated with a period of hyperphagia and marked weight gain. Seven weeks after ovariectomy, the leptin levels rise again reaching much higher levels that the preoperative ones. It is not known whether this increase is due to resistance to leptin, and could involve hypothalamic receptors, or to the increased production due to weight gain itself, since the studies are conflicting (Chu et al., 1999; Meli et al., 2004). More recent studies have tried to find changes in the expression of genes related to energy expenditure in ovariectomized rats to account for weight gain. It appears that leptin and estradiol do not regulate themselves directly, because administering the former and the latter in intact female rats did not show that it altered either of them, and the reciprocalwas true(Pelleymounter et al., 1999; Shimomura et al., 2002). Therefore, it is believed that there is a factor responsible for alerting the hypothalamus to the fact that estrogen production has ceased. A few studies speculate on the participation of neuropeptide Y. It appears to serve as a signal to the hypothalamus that the estrogen levels have dropped, since it would be raised after ovariectomy and would remain at the same levels if hormone replacement occurred in the female rats(Shimizu et al., 1996; Ainslie et al., 2001).

GENETICALLY OBESE ANIMAL MODELS

The genetic models of obesity began to be used increasingly in the 1990s because of cloning and identification of the product of five different genes causing obesity. There are over 50 different types of genetic models of obesity in rodents.

SPONTANEOUSLY OBESE RATS

Zucker-Fatty Rat

The Zucker-fatty rat is a classic model of hyperinsulinemic obesity. (Augstein and Salzsieder, 2009). Obesity is due to a simple autosomal recessive (fa) gene and develops at an early age. The fat rat has a mutation in chromosome 8 and its phenotype is late obesity with infertility and hyperinsulinemia, and was identified in 1973. Obese Zucker rats manifest mild glucose intolerance, hyperinsulinemia, and peripheral insulin resistance similar to human NIDDM. The rat obesity gene fatty (fa) has

homology with the mouse gene diabetes (db). A normalizing effect of an inhibitor of thromboxane synthase on the hyperinsulinemic state of obese Zucker rats and diet-induced obese rats has been reported (Triscari and Sullivan, 1987). The anti-obesity effect of an imidazoline derivative in genetically obese (fa/fa) Zucker rats has also been reported (Savontaus et al., 1997).

WDF/TA-FA rat

The WDF/Ta-fa rat, commonly referred to as the Wistar fatty rat, is a genetically obese, hyperglycaemic rat established by the transfer of the fatty (fa) gene from the Zucker rat to the Wistar Kyoto rat. (Kava et al., 1989; Velasquez et al., 1990). The Wistar fatty rat exhibits obesity, hyperinsulinemia, glucose intolerance, hyperlipidemia, and hyperphagia similar to Zucker rats being, however, more glucose intolerant and insulin resistant than Zucker rats. Pioglitazone increases insulin sensitivity by activation of insulin receptor kinase in Wistar fatty rats (fa/fa) (Kobayashi et al., 1992).

Otsuka Long-Evans Tokiushima fatty rat (OLETF RAT)

This strain of rats developed from a spontaneously diabetic rat of Long-Evans rats colony. The characteristic features of OLETF rats such as late onset of hyperglycemia (after 18 weeks of age), a chronic course of disease, mild obesity, inheritance by males, hyperplastic foci of pancreatic islets, and renal complications (nodular lesions). Administration of diazoxide (0.2% in diet), an inhibitor of insulin secretion, to OLETF rats from the age of 4 to 12 weeks completely prevented the development of obesity and insulin resistance (Aizawa et al. 1995). This mice model is an excellent model of NIDDM because features of this disease closely resemble human NIDDM (Kanemoto et al., 1998).

Obese SHR rat

The strain of obese SHR rats was developed by mating a spontaneous hypertensive female rat of the Kyoto-Wistar strain with a normotensive Sprague Dawley male (Koletsky, 1973). After several generations of selective inbreeding, these obese SHR exhibited obesity, hypertension, and hyperlipidemia. In addition, some rats developed hyperglycemia and glucosuria associated with giant hyperplasia of pancreatic islets.

JCR: LA-CORPULENT rat

This substrain was developed from obese SHR rats, such as the JCR: LA-corpulent rat which exhibits a syndrome characterized by obesity, hypertriglyceridemia and hyperinsulinemia with impaired glucose tolerance and is susceptible to vascular arteriosclerotic lesions (Russell et al. 1986a; 1986b; 1994). An overexpression of the obese gene in the JCR: LA-corpulent rat take place (Vydelingum et al., 1995).

In conclusion Diet-induced obesity model is the simplest obesity-induction model, and possibly the one that most closely resembles the reality of obesity in humans. The use of high-fat diet (HFD) to induce obesity, IR and hyperglycemia is well documented. The first description of a HFD to induce obesity by a nutritional intervention was in 1959 (Masek and Fabry, 1959).

HFD diet significantly promotes the development of obesity (Kim et al., 2005; Saiki et al., 2007; de-Wit et al., 2008; Kizelsztein et al., 2009). Rats fed with a lard-based HFD showed distinctive visceral adiposity, hyperglycemia, dyslipidemia, hyperinsulinemia, and hepatic steatosis, which are typically associated with human obesity (Pang et al., 2008). Thus, in the present study, high fat diet (HFD) for 10 weeks was used to produced obesity and dyslipidaemia in Wistar rats.

Treatment for obesity

Sibutramine and Orlistat are the only two drugs which are approved by US: FDA for long term use in obesity *(*Mayer *et al*., 2009). Orlistat acts to prevent dietary fat absorption and Sibutramine seems to affect both food intake and energy expenditure. Another drug Rimonabant (Acomplia) which is not FDA approved is a recently developed anti-obesity medication. It decreases the appetite by blocking central cannabinoid (CB1) receptor (Akbas et al., 2009). It may also act peripherally by increasing thermogenesis and, therefore, increasing energy expenditure (Akbas et al., 2009). This drug causes mild weight loss, but prevents or reverses the metabolic effects of obesity, such as insulin resistance and hyperlipidemia. Due to safety concerns (primarily pyschiatric in nature) the drug has not been received approval in the United States or Canada, either as an anti-obesity treatment or as a smoking-cessation drug.

Exenatide (Byetta), a long-acting analogue of the hormone GLP-1 secreted from intestines in response to presence of food, is also used as antiobesity drug . Among other effects, GLP-1 delays gastric emptying and promotes a feeling of satiety. Some obese people are deficient in GLP-1, and dieting may reduce GLP-1 (De Luis et al., 2007). Some, patients find substantial loss of weight when taking Byetta. Drawbacks of Byetta include that it must be injected twice daily, and that it causes severe nausea in some patients, especially when therapy is initiated.

Pramlintide (Symlin) is a synthetic analogue of the hormone Amylin, which in normal people is secreted by the pancreas in response to eating. Amylin delays gastric emptying and promotes a feeling of satiety. Many diabetics are deficient in Amylin. Currently, Symlin is only approved to be used along with insulin in Type 1 and Type 2 diabetics. However, Symlin is currently being tested in non-diabetics as well.

Metformin a biguanide used in people with Diabetes mellitus (type 2), can reduce weight (George and Frank, 1999).

Angiotensin II can influence the activity of certain genes and cellular and biochemical pathways that may contribute to the pathogenesis of the metabolic syndrome. However, as a class, angiotensin II receptor blockers (ARBs) have been proven to be mild to moderate effective in ameliorating the disturbances in carbohydrate and lipid metabolism characterizing the metabolic syndrome. Among Renin-Angiotensin System inhibitors, Telmisartan has been shown to activate peroxisome proliferator–activated receptor–γ (PPARγ) and increase the expression of PPARγ target genes (Benson et al., 2004; Schupp et al., 2004). A recent clinical trial showed that telmisartan reduces visceral fat accumulation in patients with metabolic syndrome.

Emerging strategy is to use combination therapy to achieve greater weight loss compared to monotherapy. Combination Therapies in Phase III Clinical Trials Include-

Bupropion & Naltrexone
Bupropion & Zonisamide
Topiramate & Phentermine

Buproprion is used in the treatment of depression and as a smoking cessation aid. It tends to cause weight loss in depressed patients (Harto-Truax et al., 1983; Croft et al., 1999). Naltrexone is an opioid receptor antagonist used primarily in the management of alcohol dependence and opioid dependence. Clinical trials are ongoing regarding the use of naltrexone in combination with another drug, buproprion, as a weight loss therapy.

Zonisamide is approved in the United States and United Kingdom, for adjunctive treatment of partial seizures in adults and in Japan for both adjunctive and monotherapy for partial seizures (simple, complex, secondarily generalized), generalized (tonic, tonic-clonic and atypical absence) and combined seizures. It has also been studied for obesity (Gadde et al., 2003) with significant positive effects on body weight and there are three ongoing clinical trials for this indication.

Topiramate a marketed anti-epileptic drug, reduces body weight in humans (Penovich et al., 1994; Gordon & Price, 1999), seems explicable in terms of its interaction with AMPA, but not GABA, receptors.

Phentermine, a contraction of "phenyl-tertiary-butylamine", is an appetite suppressant of the amphetamine and phenethylamine class. It is approved as an appetite suppressant to reduce weight in obese patients as a short-term therapy and combined with exercise, diet, and behavioral modification. It is typically prescribed for individuals who are at increased medical risk because of their weight and works by helping to release certain chemicals in the brain that control appetite. The combination therapies of these drugs are under phase III clinical trials. Therefore the study was designed to evaluate the beneficial effects of combined Metformin and Telmisartan in experimental obesity using High Fat Diet model in wistar rats.

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