Review Article

A Review of Preclinical Drug Development Models Utilised in Antiobesity Research

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ABSTRACT

Obesity, a metabolic disorder, multifactorial in origin, involves composite interaction between genetic, environment and physiologic factor. Obesity is reaching an epidemic portion in developed countries which increased the risk of various diseases and economic cost to health care provider for this it needs prevalence in obesity at an appalling speed. Animal models similarity and homology of genomes of humans and rodents is becoming an important tool in untangling the mechanisms involved in the etiology, prevention and treatment of obesity. This obesity review summarizes and analyse the various approaches to induce obesity in rodents via hypercaloric, chemical, surgical, genetic manipulation, transgenic models and neuroendocrine disruption.

Keywords: Animal Models, Genetic Manipulation, Obesity, Rodents.

INTRODUCTION

Obesity is one of the most life threatening lifestyle disorder and is reaching epidemic proportions in developed countries. Obesity is a common nutrition disorders presently considered as a major risk factor even more serious than diabetes because of its association with serious health disorders like coronary heart diseases, hypertension, diabetes, pulmonary dysfunction, osteoarthritis and certain type of cancer.[1, 2] Obesity is defined as an increase in total fat mass and it occur when unilocular adipocytes show hyperplasia or hypertrophy following macrophage infiltration of fat tissue. Obesity is likely multifactorial in origin with genetic, environment and physiologic factor contributing to various degrees in different individuals. Several therapeutics strategies for obesity are: medication, behavioural strategies and barrier surgery.[3]

Animal models similarity and homology of genomes of humans and rodents is becoming an important tool in untangling the mechanisms involved in the etiology, prevention and treatment of obesity. Animal models have provided a fundamental contribution to the historical development of understanding the basic parameters that regulate the body metabolism. This review paper of obesity summarises and analyse the various approaches to induce obesity in rodents via hyper caloric, chemical, Surgical, genetic manipulation, transgenic models and neuroendocrine disruption.[5]

Diet Induced Obesity Models

High Fat Diet Induced Obesity

Rat models, Sprague-dawley and wistar rats are popular strains to study obesity as they readily gain weight on high fat diets. In particular, Sprague- dawley rats have been studied for their ability to show a variable response

to a high fat diet (32 or 45 kcal% fat). Male wistar rats are housed in individual wire-bottom suspended cages in rooms maintained at 22–23°C with 12 h light-dark cycles. At the age of 3 months (body weight about 150-160 g) the animals are divided in 2 groups: group I is fed normal Purina rodent chow , group II a special diet containing Purina Rodent Chow, corn oil and condensed milk, resulting in a composition of 14.7% protein, 44.2% carbohydrate, 15.8% lipid, 2.5% fibre, 1.2% vitamin mixture, and 19% water. Body weight and food intakes are measured, and diet replaced, every 3 to 4 days. Obesity induced between 2 to 3 months from the start of the high fat diet. Three months from the start of the experiment, the rats are sacrificed by decapitation for determination of adipose tissue cell size and number, carcass composition and plasma lipids, and hormone and glucose levels.[4,6]
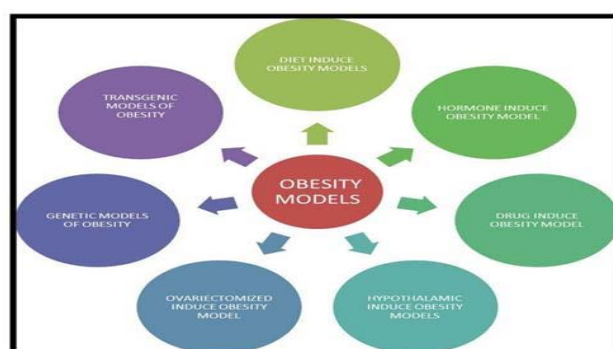

Figure 1: Diagrammatic representation of differently utilized models in obesity research.

Cafeteria Diet Induce Obesity

Cafeteria diet induced obesity is a well-established animal model for obesity which stimulates the imbalance

between energy intake and expenditure in humans. Chocolate, coconut and butter cookies are part of the cafeteria diet since these are commonly consumed food items in the modern lifestyle and represent a diet rich in sugar, fat and carbohydrates.[4,7] Young female rats (low weight range) were selected as they have been shown to be more prone to weight gain. Increase in body weight by cafeteria diet started in 2nd week. Female Wistar rats (80 to 120 g) were housed single per cage under standard laboratory conditions at a room temperature at 22 + 2°C with 12h light/dark cycle. The animals provided with pellet chow and Water and libitum. The Cafeteria diet foods included cookies; cereals, cheese, processed meats, crackers, etc. were provided in excess. Snack items were weighed before and after consumption, corrected for drying, and varied daily according to the fat, protein, and carbohydrate. The significant increase in body weight, lee's index, lipid profile, serum leptin and insulin levels demonstrate successful development of obesity in 10 weeks.[8,9]
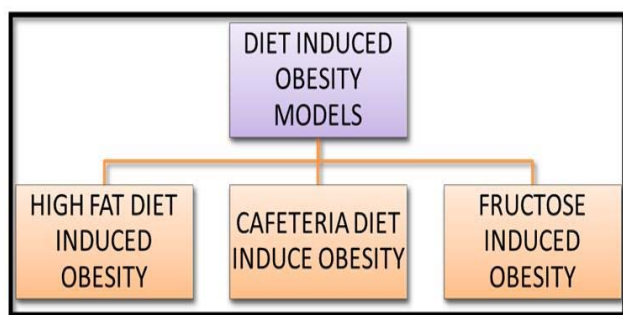

Figure 2: Diagrammatic representation of multiple diet induced obesity models.

Fructose Induced Obesity

Increased consumption of fructose is detrimental in terms of body weight and adiposity. Adult, male wistar rats were housed in individual wire cages in rooms maintained at 22-23°C with 12 hr. light dark cycle. Two groups of rats were fed diets high in fructose (10% fructose, 35% of calories, 35% starch). Diets were matched in terms of protein, vitamin, fibre and minerals. At the end of the three weeks period, animals were kept for overnight fasting and the blood samples were collected from the tail vein in the centrifuge tubes. The blood samples were allowed to clot for 30min at room temperature and then centrifuged at 5000rpm for 15min. Serum samples thus obtained were stored at -20°C until biochemical estimations were carried out. Obesity induced between 2 to 3 months from the start of the experiment.[10-12]

Hormone Induced Obesity

Progesterone induced obesity

Progesterone vial contents were dissolved in arachis oil and a dose of 10 mg/kg was administered subcutaneously in the dorsal neck region to mice for 28 days, control group received the vehicle. All drugs were given at a dose of 0.4 mL/100g body weight. The test drugs were injected

30 min before progesterone administration. Female albino mice (20-25g) were housed in wire cages in a standard controlled animal care facility at 22-25°C, 45% humidity with 12hr light dark cycle. The animals were maintained at under standard nutritional and environmental conditions throughout the experiment. All the experiments were carried out at ambient temperature. Body weights of mice (g) were recorded every week for 28 days. On day 29 of the experiment, that is, after the last test drug administration, the mice were anesthetized under light ether anaesthesia and blood for serum preparation was collected by retro orbital puncture to check biochemical parameters.[13, 14]

Drug Induce Obesity

Antipsychotic Drug (SULPIRIDE) Induced Obesity

Pharmacological effects of neuroleptics may mediate the excessive weight gain: a neurogenic effect which involves a direct stimulation of appetite through the blockade of dopaminergic and serotonergic receptors in the lateral hypothalamus and an endocrine effect related to the drug-induced hyperprolactinaemia.[15] Adult female rats of the Wistar strain weighing 200-250 g were individually housed under a 12/12 hr. light/dark cycle. A high fat diet (66.6% powdered chow pellets, 33.3 corn oil %) and water were available ad libitum. Body weight and food intake were daily assessed. After one week of adaptation to the housing and diet conditions, the animals were matched by weight and divided into two groups. One group received a single daily dose of sulpiride (20 mg/kg/intraperitoneally) and the other group received an injection of vehicle (0.1N HC1, with pH 7 adjusted with 0.1N NaOH). The significant increase in body weight, lee's index, lipid profile, serum leptin and insulin levels demonstrated successful development of obesity.[16, 17]
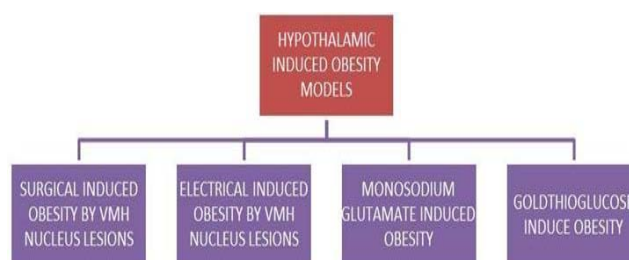
Hypothalamic Induced Obesity Models

Figure 3: Diagrammatic representation of different hypothalamic induced obesity models.

Surgical Induced Obesity by Ventromedial Hypothalamic (VMH) NucleusLesions

Bilateral wire knife cuts were sterotaxically positioned in the hypothalamus with the incision bar positioned at –3.0 mm, parasagittal wire knife cuts are placed between the medial and lateral hypothalamus using a retractable wire knife. The cuts were made 1.0 mm lateral to the midline and extended from 8.5 to 5.5 mm anterior to the ear bars and from the base of the brain dorsally 3.0 mm. Female Spraguedawley rats (190gm), received high fat diet for 5-9

days initial period of adjustment. Rats were divided in two groups. First group of Female rats fasted overnight, anesthetized with 35mg/kg pentobarbital sodium and additionally 1 mg atropine methyl nitrate intraperitoneally. Second group of rats serve as control. Some rats that are fasted overnight are killed at the time of surgery to provide data on initial body composition. Histological verification of placement of knife cuts and lesions was made in brains fixed in 10% buffered formaldehyde solution and embedded in paraffin. Serial sections through the hypothalamic area of the brain are examined histologically.[18, 19]

Electrical Induced Obesity by Hypothalamic (VMH) Nucleus Lesions

The irritative theory suggests that the hypothalamic nuclei gets destroyed due to the deposition of iron ions in the hypothalamus with the introduction of electrodes, the ablative theory is in the view that the cause of injury is electric current only. Studies were performed comparing electric injury with radiofrequency (without ion deposition) using the conventional technique and the results obtained were a lower index of obesity using radio frequency.[20] Therefore, both mechanisms are involved in the development of obesity. Female Sprague dawley rats (190gm), received high fat diet for 5-9 days initial period of adjustment. Rats were divided in two groups. First group of Female rats fasted overnight, anesthetized with 35mg/kg pentobarbital sodium and additionally 1 mg atropine methyl nitrate intraperitoneally. Electrolytic lesions are sterotaxically positioned in the hypothalamus. To produce electrolytic lesions in the ventromedial hypothalamus, the incision bar was positioned at +5.0 mm and a stainless steel electrode, insulated except for 0.5 mm at the tip, was lowered 0.6 mm lateral to the midline and 5.8 mm anterior to the ear bars. With the tip of the electrode 0.7 mm above the base of the brain, lesions were made by passing 2.0 mA of anodal current for 20 s to a rectal electrode Second group of rats served as control. Some rats that fasted overnight were killed at the time of surgery to provide data on initial body composition. Histological verification of placement of knife cuts and lesions was made in brains fixed in 10% buffered formaldehyde solution and embedded in paraffin. Serial sections through the hypothalamic area of the brain are examined histologically.[21]

Monosodium Glutamate Induced Obesity

The neonatal administration of monosodium glutamate (MSG) to rodents destroys 80-90 % of the arcuate nuclei neurons and damages other central structures, resulting in several neuroendocrine and metabolic abnormalities. As adults, these animals develop an obesity syndrome characterized by excess fat deposition and reduced lean body mass, which occurs, in the absence of hyperphagia, as a function of reduced metabolic rate.[22] Male Wistar pups are housed in individual wire cages in rooms maintained at 22-23°C with 12 hour light-dark cycle. Pups were divided in two groups. First group of Male Wistar

pups, was given subcutaneous injection of 4.0 g/kg monosodium glutamate and second group receive hyperosmotic saline (1.25 g/kg, controls) every 2nd day, for the first ten days of life. The pups were weaned at 21 days of age and had free access to rat commercial chow and water during the whole experimental period. The significant increase in body weight, lee's index, lipid profile, serum leptin and insulin levels demonstrated successful development of obesity.[23, 24]

Gold thioglucose Induce Obesity

An interperitonial injection of gold thioglucose (GTG) produces a lesion in the ventromedial hypothalamus whose localization is reproducible and which recapitulates the severe obese phenotype characteristic of lesions of the hypothalamic ventromedial nucleus produced by other means (e.g. an electrical current, an excitotoxin, or a tumour).[25] Therefore, GTG has been used as a powerful tool to assess mechanisms of hypothalamic obesity. Swiss albino Male and female mice of either sex, 4 weeks old, were individually housed in wire-bottomed cages, room temperature was maintained at 23 °C±1°C, and 12 hr. light-dark cycle were controlled . Mice were fed a commercial stock diet ad libitum for 1 week. Swiss albino mice, weighing 17 to 20gm, were injected intraperitoneally with 12.5 mg of gold thioglucose in 0.25 ml saline. After injection of GTG or saline, the mice were housed individually, and daily food intake was measured. Mice that died or showed toxic effects and mice in which GTG failed to produce an observable lesion (correlated with development of obesity) were excluded from the study. Mice were weighed at regular intervals and were killed 2 weeks after GTG (or saline) injection.[26, 27]

Ovariectomized Induced Obesity Model

Level of leptin decrease after the removal of gonads from rat (female), which lead to marked weight gain and hyperphagia. Ovariectomy increases body weight gain for 3 weeks, accompanied by an increase of daily food intake. Ovariectomy significantly reduced serum corticosterone levels.[28] After ovariectomy, the level of leptin rise again in seven weeks reaching much higher levels than the preoperative ones. Female Sprague dawley rats 78 days old weigh around 210 g were housed single per cage under standard laboratory conditions at a room temperature at 22 + 1°C with 12h light/dark cycle. The animals were provided with normal pellet chow and Water ad libitum. Rats were anesthetized with an i.p injection of ketamine hydrochloride and xylazine at dose of 50mg/kg body weight and 10 mg/kg body weight, respectively. Bilateral Ovariectomy is performed in female Sprague dawley rats. All rats are sacrificed at 14 weeks post ovariectomy. The success of the ovariectomy procedure was confirmed at the end of the study by measuring uterine weights and by determining plasma estradiol concentration using a double antibody radio immunoassay. The significant increase in body weight, lee's index, lipid profile, serum leptin and insulin levels demonstrate successful development of obesity.[29, 30]

Genetic Model of Obesity

Generally two primary genetic models are used to study obesity, the monogenic and polygenic. Most popular species are the rat and mouse.

MONOGENIC MODEL OF OBESITY	Polygenic Model of Obesity
• Lethal Yellow Mutant Mouse • *The tubby gene mutation (tub)* • *carboxypeptidase E (Cpe) gene mutation* • *leptin (Lep) gene mutation (ob)* • *leptin receptor (Lepr) gene mutation (db)*	• C57BL/6N and the C57BL/6J Mouse • M16 Mouse • Kuo Kondo (KK) Mouse • WBN/KOB RAT • OLETF RAT • OBESE SHR RAT • Jcr:La-Corpulent Rat • New Zealand Obese (NZO) Mouse • Tsumura Suzuki Obese Diabetes (TSOD) Mouse

Figure 4: Representation of different genetic model of obesity

Monogenic Model of Obesity

Obese rodents are the most studied experimental models for human genetic obesity. Six genetically and phenotypically distinct single-gene obesity mutations have been identified in mice, diabetes (db), obese (ob), fat (Fat), agouti (A" and Ay), adipose (Ad), and tubby (tub). The physiology of obesity has been intensively studied in two autosomal recessive mutations in the rat, fatty (fa) and corpulent (cp). The most well-characterized monogenic rat models have either the *fa* or *cp* mutation for obesity. The mutations are on various backgrounds– the Zucker and Wistar are several of the most common. *Fa* and *cp* are autosomal recessive mutations that cause hyperphagia, early-onset obesity and other phenotypes.

Lethal Yellow Mutant Mouse (A^y): Mice with adipose tissue-specific agouti overexpression exhibit an overgrowth of adipose tissue without alteration of food intake, suggesting that increased fat in this model is due to changes in energy metabolism . The adipose tissue agouti overexpression model could be relevant to human obesity because agouti gene expression is found in human adipose tissue and is increased in the adipose tissue of type 2 diabetic subjects.[31]

The tubby gene mutation (tub): The mice homozygous for *tub* mutation develop late-onset obesity without diabetes. Affected mice also develop slow-onset deafness and retinal degeneration. This phenotype is due to a point mutation that results in an error in the transcript splicing and the loss of the carboxyl terminus of the protein product. The *tubby* belongs to a tubby-like gene family whose function is not fully understood.[32]

The carboxypeptidase E (Cpe) gene mutation (fat): Mice with homozygous *fat* mutation develop late-onset marked obesity, infertility, and striking hyperproinsulinemia. However, hyperglycemia occurs only transiently in males.[33]

The leptin (Lep) gene mutation (ob): The *Lep* gene is one of the most extensively studied obesity genes. Homozygous *Lep* gene mutation, *ob/ob*, causes early-

onset morbid obesity with diabetes in mice. In addition, affected mice exhibit hyperphagia, hypothermia, hypercorticosteronemia, decreased linear growth, and infertility.[34]

The leptin receptor (Lepr) gene mutation (db). The *db/db* mice have the same phenotype as *ob/ob* mice, but they are resistant to leptin. The mutation resides in the leptinreceptor.[35]

Polygenic Model of Obesity

Polygenic obesity models better reflect the human obese phenotype. Obesity in these models isn't caused by one mutation, but rather from errors at multiple sites within the genome.[36] Such animals are fed a high-fat diet (as high as 60% fat (kcal)), which causes diet-induced obesity (DIO). According to the literature, standard Sprague-Dawley and Long-Evans rats are the two most common outbred animal stock used for Diet Induced Obesity studies. With mice, the most commonly used polygenic obesity model is the C57BL/6 inbred mouse. The two primary substrains used in obesity research are the C57BL/6N and the C57BL/6J. Selecting the N versus the J model depends on study focus. The J model has the Nicotinamide nuclear transhydrogenase (Nnt) spontaneous gene deletion, which is linked to glucose tolerance and lower secretion of insulin. The N model has differences in its genome that should be taken into consideration when doing studies with various therapeutic focuses. Various other polygenic model of obesity is M16 Mouse, Kuo Kondo (KK) Mouse, WBN/KOB RAT, OLETF RAT, OBESE SHR RAT, Jcr:La-Corpulent Rat, New Zealand Obese (NZO) Mouse, Tsumura Suzuki Obese Diabetes (TSOD) Mouse.[37, 38]

Transgenic Model of Obesity

TRANSGENIC MODEL OF OBESITY

- Overexpression of *Glut*-4 Gene in Adipose Tissue
- Genetic Ablation of Brown Adipose Tissue
- Inactivation of Growth Hormone Transgene
- Knockout of Neuropeptide Y-Y1 Receptor Gene
- Knockout of B3-Adrenergic Receptor Gene
- Knockout of *Mc4-R* Gene
- Knockout of ICAM-1 Gene or Integrin Amβ2 (Mac-1) Gene
- Knockout of Bombesin Receptor Subtype-3 Gene
- Knockout of PPARα gene
- Knockout of 5-HT$_{2c}$ Serotonin Receptor Gene

Figure 5: List of various transgenic models with increased body fat / obesity

Overexpression of *Glut*-4 Gene in Adipose Tissue

To elucidate the role of nutrient partitioning in the development of obesity, expressing insulin-responsive glucose transporter (GLUT4) in transgenic mice under the control of the fat-specific aP2 fatty acid-binding protein

promoter/enhancer, two lines of transgenic mice were generated, which overexpressed GLUT4 6-9-fold in white fat and 3-5-fold in brown fat with no overexpression in other tissues. This is the first animal model in which increased fat mass results solely from adipocyte hyperplasia and it will be a valuable model for understanding the mechanisms responsible for fat cell replication and/or differentiation in vivo.[39]

Genetic Ablation of Brown Adipose Tissue

Brown adipose tissue, because of its capacity for uncoupled mitochondrial respiration, has been implicated as an important site of facultative energy expenditure. This has led to speculation that this tissue normally functions to prevent obesity. Attempts to ablate or denervate brown adipose tissue surgically have been uninformative because it exists in diffuse depots and has substantial capacity for regeneration and hypertrophy. Study supports a critical role for brown adipose tissue in the nutritional homeostasis of mice.[40]

Inactivation of Growth Hormone Transgene

In the studies a possibility is generated that highly elevated production of GH in activated oMT1a-oGH transgenic mice leads to (1) enhanced promotion of preadipocyte differentiation, leading to increased numbers of adipocytes that, upon cessation of oGH production, are available for lipid deposition resulting in obesity, or (2) alterations in production of or responsiveness to insulin, leading to increased fat deposition upon removal of the chronic anti-lipogenic actions of GH. The oMT1a-oGH transgenic mouse line provides a new genetic model with by which growth hormone affects obesity.[41]

Knockout of Neuropeptide Y-Y1 Receptor Gene

In the studies it is seen that the mild obesity found in Y1-R-/- mice (especially females) was caused by the impaired control of insulin secretion and/or low energy expenditure, including the lowered expression of UCP2 in WAT. Y1-R-deficient mice I will be useful for studying the mechanism of mild obesity and abnormal insulin metabolism in noninsulin-dependent diabetes mellitus.[42]

Knockout of B3-Adrenergic Receptor Gene

Beta 3-Adrenergic receptors (beta 3-ARs) are expressed predominantly in white and brown adipose tissue, and beta 3-selective agonists are potential anti-obesity drugs. However, the role of beta 3-ARs in normal physiology is unknown.[43]

Knockout of *Mc4-R* Gene

The melanocortin-4 receptor (MC4-R) is a G protein-coupled, seven-trans membrane receptor expressed in the brain. Inactivation of this receptor by gene targeting results in mice that develop a maturity onset obesity syndrome associated with hyperphagia, hyperinsulinemia, and hyperglycaemia. This syndrome recapitulates several

of the characteristic features of the agouti obesity syndrome.[44]

Knockout of ICAM-1 Gene or Integrin Amβ2 (Mac-1) Gene

Intercellular adhesion molecule-1 (ICAM-1) is a well-characterized receptor with five immunoglobulin's (Ig). In contrast, the expression of Mac-1 is restricted to monocytes/macrophages, granulocytes, natural killer cells, and a subpopulation of T cells and it binds to domain 3 of ICAM-1. Mice deficient in ICAM-1 (ICAM-1 –/–) have both inflammatory and immune defects. These include a decreased emigration of neutrophils in chemically induced peritonitis, reduced contact hypersensitivity, and diminished ability of spleen cells to act as stimulators in mixed lymphocyte responses, and resistance to septic shock. Similarly, Mac-1-deficient (Mac-1 –/–) mice exhibit defects in several neutrophil functions including adhesion to the endothelium, phagocytosis, and neutrophil apoptosis. In experiment with ICAM-1 –/– mice and subsequently with Mac-1 –/– mice, notice an unexpected new phenotype of these mice, i.e., obesity. Data identified a novel function of leukocyte adhesion receptors, namely, regulation of body weight and adipose tissue mass.[45]

Knockout of Bombesin Receptor Subtype-3 Gene

Mammalian bombesin-like peptides are widely distributed in the central nervous system as well as in the gastrointestinal tract, where they modulate smooth-muscle contraction, exocrine and endocrine processes, metabolism and behaviour .BRS-3-deficient mice is an attempt to determine the in vivo function of the receptor. Mice lacking functional BRS-3 developed a mild obesity, associated with hypertension and impairment of glucose metabolism. They also exhibited reduced metabolic rate, increased feeding efficiency and subsequent hyperphagia. BRS-3-deficient mice provide a useful new model for the investigation of human obesity and associated diseases.[46]

Knockout of PPARα gene

The alpha-isoform of the peroxisome proliferator-activated receptor (PPARα) is a nuclear transcription factor activated by structurally diverse chemicals referred to as peroxisome proliferators. PPARα modulates target genes encoding lipid metabolism enzymes, lipid transporters, or apolipoproteins, suggesting a role in lipid homeostasis. The studies demonstrate, in rodents, the involvement of PPARα nuclear receptor in lipid homeostasis, with a sexually dimorphic control of circulating lipids, fat storage, and obesity. Characterization of this pathological link may help to delineate new molecular targets for therapeutic intervention and could lead to new insights into the etiology and heritability of mammalian obesity.[47]

Knockout of 5-HT$_{2c}$ Serotonin Receptor Gene

Serotonin (5-hydroxytryptamine, 5-HT) is a monoaminergic neurotransmitter that is believed to

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modulate numerous sensory, motor and behavioural processes in the mammalian nervous system. These diverse responses were elicited through the activation of a large family of receptor subtypes. The complexity of this signalling system and the paucity of selective drugs have made it difficult to define specific roles for 5-HT receptor subtypes, or to determine how serotonergic drugs modulate mood and behaviour. For this, mutant mice is generated lacking functional 5-HT2C receptors (previously termed 5-HT1C), prominent G-protein-coupled receptors that are widely expressed throughout the brain and spinal cord and which have been proposed to mediate numerous central nervous system (CNS) actions of serotonin. 5-HT2C receptor-deficient mice are overweight as a result of abnormal control of feeding behaviour, establishing a role for this receptor in the serotonergic control of appetite.[48,49]

CONCLUSION

As the obesity is a global health problem, resulting from an energy imbalance caused by an increased ratio of caloric intake and expenditure, now effect over 500 million individual worldwide. Obesity is abnormal or excessive fat accumulation that presents risk to health. The body mass index (BMI) of a person is 25-30 kg/m^2 indicates overweight and above 30 kg/m^2 represents obesity. Lifestyle and behavioural interventions aimed at reducing calorie intake or increase expenditure have limited long term effectiveness. Implementing and maintaining the lifestyle changes associated with weight loss but challenging for many patient. Surgical treatment for obesity, although highly effective are unavailable or unsuitable for majority of an individual with excess adiposity. Accordingly few effective treatment options are available to most individual with obesity. Although a number of pharmacological approaches for treatment of obesity have been investigated but only few are safe. Currently approved long term and short term antiobesity drugs, continuously has been monitored for efficacy and safety concern. Furthermore, evaluation of antiobesity drugs in children and elderly populations require long term postmarketing surveillance to fully elucidate its effects and mechanism. However, much emphasis now a days has been placed on reduced food intake /or body weight that made the pharmacological management of obesity at an exciting crossroads. Polytherapeutic strategies as well as new therapy targets led to identification and characterisation of specific obese subpopulations that allow for the tailor-made development and appropriate use of personalised medicines for successful development and discovery of patent and safe drugs for the treatment and prevention of obesity. Therefore the choice of the model depends upon the characteristics of the research.[50]

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