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Review Article

Animal Model for Obesity-An Overview

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ABSTRACT

Obesity is a major health problem and one of the leading causes of death globally. The needs of obesity care increased in last two decades. Obesity also increases the risk of diabetes, cardiovascular disorder, stroke and colon cancer. Obesity can be managed by physiological and pharmacological approach, but physiological approach getting failed by patient noncompliance. Pharmacological approach has its own advantages and disadvantages, moreover the needs of drug targets increasing to discover novel antiobesity agents. The developed a new target must be evaluated preclinically and clinically to determine its therapeutic efficacy. Objective of this review is to summarize the most commonly used animal models of obesity research. The model includes ventromedial hypothalamic nucleus (VMH) lesion, diet-induced (hypercaloric diets) obesity, chemical agent induced obesity, drug induced obesity, genetic models and surgical models.

Key words: Animal model, Biological evaluations, Obesity, Rodents.

SUMMARY

- Obesity is a worldwide health issue and one of the leading causes of death. Management of obesity by pharmacological approach is crucial as the needs of drug targets increasing to discover antiobesity agents. This review summarizes various type of common pre-clinical animal models used for obesity research.

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INTRODUCTION

Obesity is a major health problem and one of the leading causes (preventable) of death worldwide. In 2014, globally 39% of adult aged 18 years and above were overweight and 13% were obese. In a current era morbidity and mortality associated with obesity is increasing gradually and its causes preventable deaths.[1,2] The children and adolescents obesity is main concern and the current number of 7-10% of these is doubled by 2025. Obesity/ poor diet and physical inactivity is one of the main causes of death in developed and developing countries and most important is these deaths are preventable by changing lifestyle. In 2002 poor diet and physical inactivity caused 400000 (16.6%) death in USA.[3] The economic cost of management of obesity is to be approximately $40 billion in 1986 and it was increased to approximately $210 billion in 2008 in USA.[4,5] Obesity also increases the risk of diabetes, cardiovascular disorder, stroke and colon cancer.[5]

The needs of obesity care increased in last two decades. Obesity can be managed by physiological and pharmacological approach, but physiological approach (diet and behavioural therapy) getting failed by patient noncompliance. Pharmacological approach/ drug therapy has its own advantages and disadvantages, moreover the needs of drug target increasing to discover novel antiobesity agents. The developed a new targets must be evaluated preclinically (*in vitro*, *in vivo* chemical and biological evaluations) and clinically to determine its therapeutic efficacy. Part of it, the new target will be tested on animals, and this review is to summarize the available animal obesity models used to screen antiobesity activity of any agents.

TYPES OF OBESITY

Obesity is simple measured by calculating body mass index (BMI), if BMI between 30 and 34.9, between 35 and 39.0, more than 40 is called as class I, class II and morbidity obesity.[6]

Obesity has six different types' *viz*., type-1, type-2, child-type, adult-type, abdominal and limb obesity. Type -1obesity which is the most common type, caused by excessive eating habits, sedentary lifestyle and lack of physical activities. Types-2 obesity accounts less than 1% and it's caused by disease such as Cushing syndrome, hypothyroidism, polycystic ovarian disease and insulinoma. Child and adult type of obesities are due to enragement of fat cells in the body. Abdominal and limb obesities mainly occur in men and women respectively. Abdominal obesity is aggravating factor for disease such as ischemic heart disease, diabetes and hyperlipidemia.[7]

SCREENING METHODS FOR OBESITY

In general, hypothalamic obesity, diet-induced obesity and genetic models were used to screen obesity and its physiological effects.

Ventromedial hypothalamic nucleus (VMH) lesion

Monosodium Glutamate (MSG)

Electrical VMH Lesion

- Diet-induced (hypercaloric diets) obesity
- Chemical agents induced obesity
- Drug induced obesity
- Genetic models
- Monogenic
- Polygenic models
- surgical model

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Ventromedial hypothalamic nucleus (VMH) lesion

VMH can be achieved by bilateral destruction of the hypothalamic nuclei using monosodium glutamate (MSG) and electrical current.[8] Subcutaneous injection of MSG to newborn mice/ rat at the dose of 2 – 4 g/kg/day for alternative days of 10 days of life or 5 consecutive days will cause obesity by exhibiting vagal hyperactivity and sympatho-adrenal hypoactivity which resulting hyperinsulinemia and an increase of white fat.[9] MSG can be administered (4-10 doses) subcutaneously or intraperitoneally to the neonatal rats to get obesity. In animals MSG increases the regular food intake and causes metabolic disorder which increases the glucose, triglyceride, insulin and leptin levels.[8]

In electrical VMH model, normal adult rodents are used for the experiments. This model required anaesthesia and surgical skills. The rodents will be anaesthetized and bilateral VMH lesions will be produced by electrical destruction using stereotaxic instrument.[10]

Diet-induced (hypercaloric diets) obesity

A diet-induced model of obesity is the most commonly used for screening antiobesity activity than other models. Commonly used diet composition to induce obesity was summarized in Table 1. Most of the formula has rich amount of cholesterol/ fat to induce than carbohydrate and protein which helps to increase the body weight of the animal and also increases the lipid levels. Diet induced obesity/hypercholesterolemia/hypertriglycemia is used to screen antiobesity/antihyperlipidemic activity of any investigational compounds.[11-22]

Chemical agents induced obesity

Gold thioglucose and monosodium glutamate are used to induce obesity in rodents. In adult mice, single intraperitoneal injection of gold thioglucose (0.8 mg/gm or 30 – 40 mg/kg) is given and monitored for next two weeks to conform the induction of obesity.[23,24] Administration of gold thioglucose to mice through parenteral route produces a necrosis response in the ventromedial portion of the hypothalamus. Neural elements contiguous with capillaries in the ventromedial hypothalamus are affected primarily by gold thioglucose. The glucose moiety present in gold thioglucose is crucial for production of the lesion. The lesion which is produced by necrosis causes hyperphagia and consequent obesity. This indicates the presence of special glucoreceptor cells in the ventromedial hypothalamus that are involved in the regulation of food intake.[25]

In monosodium glutamate induced obesity model, newborn male Wistar rats or male Charles River mice are injected with 2 g/kg monosodium-L-glutamate for five consecutive days and they are weaned at 4 weeks of age. Rats are monitored for next six months its pathological changes.[24,26] Monosodium glutamate has shown a number of pathological changes related to the lack of control of the hypothalamo-pituitary axis with a dose-dependent curve including hypoactivity, obesity, hypophagia, delay in puberty, reduction of ovarian weight, and elevation serum levels of corticosteroids. The schedule of administration of monosodium glutamate to newborn rats has shown the destruction of the ventromedial hypothalamic and arcuate nuclei. Damage of the ventromedial hypothalamic leads the rats to develop obesity due to the lack of control between absorption of nutrient and energy expenditure. The mechanism by which the monosodium glutamate leads to hypothalamic injury is not known.[8]

Drug induced obesity

In pathological condition, the therapeutic agent is used to cure the illness, but few of the therapeutic agent causes obesity as adverse effect. Those substances may be used to induce obesity to the animals and this drug induced models are mostly uncommon except antipsychotics.

Weight gain is a common side effect to many widely used drugs especially antidepressant medications and antipsychotic medications. Body weight gain in many treated patients and has a serious impact on medication compliance, causes some metabolic disease. The mechanisms behind the weight gain are poorly understood. Many of these drugs interfere with central appetite-regulating neurotransmitters and may also produce anticholinergic and sedative effects, ultimately contributing to changes in energy expenditure.

There are some possible mechanism that induce obesity in patient who treated with antidepressant or antipsychotic drugs: decreased serotoninergic and dopaminergic activity, impaired mitochondrial beta-oxidation of fatty acids and other changes in substrate oxidation, reduced sympathetic nervous system activity, decreased energy expenditure, sedation, anticholinergic side effects causing dry mouth and increased intake of caloric beverages and altered activity of hypothalamic leptin and neuropeptide Y. Commonly used therapeutic agents/ drugs to induce obesity were summarized in Table 2.[27,28]

Genetic models

Monogenic or once transgenic and polygenic rodent models are available for obesity. One transgenic model led to identify most of current known monogenic forms of obesity in humans. A mutation in single gene of the leptinergic–melanocortinergic pathway, *MC4R*, *LEP*, *LEPR*, *PC1* and *POMC* is an example of monogenic model. In rodents, phenotypically *MC4R* mutation shows hyperinsulinemia, elevated growth rate and increased bone density and which is helpful to create a model mimics human beings. In polygenic model, multiple genes are stimulated simultaneously to get disease models. Diffract coding regions of *MC4R* (mutation at amino acid position 103 and 251), *FTO* and *INSIG2* are used to cause obesity in rodents.[29]

The transgenic animals such as corticotrophin releasing factor (CRF)-overexpressing animals, animals with enhanced GLUT4 glucose transporters, mice with overexpression of melanin concentrating hormone (MCH), beta-3 adrenergic/ serotonin 5-HT-2c/ Neuropeptide-y (NPY) 1/ NPY2 / bombesin 3/ neuronal insulin receptor knockout mice and 11beta-hydroxysteroid dehydrogenase type 1 (11beta HSD-1) overexpression mice are used to screen the antiobesity activity.[29]

Surgical model

Preclinical studies in women population suggest that abrupt hormone deprivation caused by oophorectomy (surgical removal of the ovaries). The reduction of hormone level such as estrogen level leads to obesity and its metabolic sequelae. Oophorectomy model is used to understand modifications in women after the end of their fertile age. The surgical removals of ovaries reduce the initial leptin levels and increase the same after seven weeks. This resistance to leptin may increase the weight gain of the rats.[8] Animal studies have consistently demonstrated a relationship between bilateral oophorectomy and insulin resistance, adiposity, and total and LDL-cholesterol level.[30]

Evaluation of anti-obesity activity

The main factor of obesity is food consumption and the larger intake of food may influence the weight gain. The assessment of regular food and water intake with changes in body weight, body mass index may give preliminary date. Determination of total body fat such as total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides level, fatty-acid synthase (FAS), weight of adipose tissue and expression of metabolic enzyme levels can be used to determine the metabolic changes in the body. In addition, evaluation of locomotor activity, beta-3 receptor, and regulating peptide hormones such as leptin may give the supporting data to the anti-obesity activity study.

Table 1: Meta-analysis of diet composition used to induce obesity

Diet composition	Duration	Reference
• 32% kcal fat • 51% kcal carbohydrate • 17% kcal protein	12 weeks	Carroll *et al*., 2006.[11]
• Cholesterol (0.2% total cholesterol) • Total fat (21% by weight; 42% kcal from fat) • High in saturated fatty acids (>60% of total fatty acids) • High sucrose (34% by weight) (Composition of Harlan Teklad TD.88137 is casein [195 g/kg], DL-methionine [3 g/kg], sucrose [341.46 g/kg], corn starch [150.0 g/kg], andydrousmilkfat [210.0 g/kg], cholesterol [1.5 g/kg], cellulose [50 mg/kg], mineral mix [35 g/kg], calcium carbonate [4 g/kg], vitamin mix [10 g/kg] andethoxyquin [0.04 g/kg])	22 weeks	Puig *et al*., 2012.[12]
HFD (45% Kcal from soy bean fat)	28th week	Shao *et al*., 2012.[13]
• Protein (26.2 gm%) • Carbohydrate 26.3 gm%) • Fat (34.9 gm%). (Composition of Research Diets, Inc., D12492 is casein [200 gm], L-cystine [3 gm], maltodextrin [125 gm], sucrose [68.8 gm], cellulose [50 gm], soybean oil [25 gm], lard [245 gm], mineral mix [10 gm], dicalcium phosphate [13 gm], calcium carbonate [5.5 gm], potassium citrate [16.5 gm], vitamin mix [10 gm], choline bitartrate [2 gm] and, FD&C Blue Dye #1 [0.05 g] and total weight is 773.85 gm].)	12 weeks/ 23 weeks/ 8 weeks/ 16 weeks.	Canto *et al*., 2012; Matsubara *et al*., 2012; Kim *et al*., 2012; Singer *et al*., 2015.[14-17]
AIN-93M diet contains 200 g of casein and 70 g of soybean oil/kg diet. (Composition of AIN-93M, Dyets Bethlehem, PA is cornstarch [465.692 g/kg], casein [140 g/kg], dextrinizedcornstarch [155 g/kg], sucrose [100 g/kg], soybean oil [40 g/kg], fiber [50 g/kg], mineral mix [35 mg/kg], vitamin mix [10 mg/kg], L-cystine [1.8 mg/kg], choline bitartrate [2.5 g/kg], tert-butylhydroquinone [8 g/kg].)	10 weeks	Woods *et al*., 1997; Reeves, 1997.[18,19]
•Protein (24 gm%) •Carbohydrate (41 gm%) •Fat 24 (gm%) Composition of Research Diets, Inc., D12451 is casein [200 gm], L-cystine [3 gm], Corn Starch [72.8gm], maltodextrin [100gm], sucrose [172.8 gm], cellulose [50 gm], soybean oil [25 gm], lard [177.5 gm], mineral mix [10 gm], dicalcium phosphate [13 gm], calcium carbonate [5.5 gm], potassium citrate [16.5 gm], vitamin mix [10 gm], choline bitartrate [2 gm] and, FD&C Red Dye #40 [0.05 g] and total weight is 858.15gm]	8/10 weeks	de La Serre *et al*., 2012.[20]
Composition of high fat diet is 23 % whole wheat, 23 % yellow corn, 11 % barley, 17 % milk powder, 1 % bone meal, 1 % calcium chloride, 1 % sodium chloride 11 % coconut oil, 11 % butter and one multivitamin capsule.	4-8 weeks	Parasuraman *et al*., 2010 and 2013.[21,22]

Table 2: Drug induced obesity

Class of Drugs	Examples
Antipsychotics (Atypical antipsychotics)	Clozapine, Quetiapine, Olanzapine
Antidepressants	Tricyclic antidepressants
Antimanics	Lithium
Anticonvulsants	Valproate, carbamazepine, gabapentin
Antimigraine and antihistaminergic drugs	Cyproheptadine, flunarizine, pizotifen
Antidiabetic agents	Sulfonylurea agents, glitazones, insulin
Glucocorticoids	Prednisone, dexamethasone
Beta-adrenergic receptor blocker	Propranolol, atenolol,
Sex hormones	Estrogen, megestrol acetate, tamoxifen
Other	Some antineoplastic agents

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