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A Comprehensive Insight into the Development of Animal Models for Obesity Research

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Abstract

Obesity, a multifactorial, metabolic disorder, involves complex interaction between genetic and environmental factors. With an alarming increase in the prevalence of obesity worldwide, it has become a major health care burden not just in terms of the increased risk of type 2 diabetes, cardiovascular morbidity, cholelithiasis, arthiritis and certain malignancies, but also in the economic costs to healthcare providers. The great similarity and homology between the genomes of rodents and humans make these animal models an important tool in unraveling the mechanisms involved in the etiology, prevention and treatment of obesity. This review summarizes the various approaches for the induction of obesity in the rodent models via genetic manipulation, hypercaloric diets and neuroendocrine perturbations.

Index terms— Obesity; Animal models; Rodents; Hypercaloric diet; Genome.

1 INTRODUCTION

besity is a metabolic disorder characterized by an excessive accumulation of fat in the body to a sufficient magnitude which adversely affects the health of an individual. It is a direct consequence of perpetual imbalance between energy intake and expenditure with storage of extra calories in the form of triglycerides in the adipose tissue [1][2] . It is increasing probably, as a consequence of easily available hypercaloric diet and an increasingly sedentary lifestyle. Thus it can be appropriately termed as New World Syndrome or Disease of Civilization 3 . In obesity, there is an increase in intake of high fat and high energy food and a decrease in daily energy expenditure 4 . Diet and physical reduce appetite or to inhibit fat absorption 5 . However in exercise remain as main stay in obesity management; nonetheless antiobesity drugs may be required either to gastric balloon may be placed to reduce stomach volume and or bowel length, leading to earlier satiation and reduced ability to absorb nutrients from food ??6][7] .

Animal models of obesity not only allow us to investigate the basic mechanisms by which food intake is regulated but also act as tool for investigation of mechanism of antiobesity drugs. These models also provide significant insights into the etiology of human obesity consequently aiding in the development of pharmaceuticals for treatment of obesity. The animal models used for study of obesity either have a spontaneous origin or the result of experimental manipulation of the environmental or hypothalamic center that regulate food intake and energy balance or gene expression 8 . The rodent models are advantageous also in terms of their size, ease of handling, fast reproduction rate, shorter generation time availability of accurate and reliable metabolic tests 2,5,9 . This review summarizes the various approaches for induction of obesity in the rodent models via dietary manipulations, genetic interventions or neuroendocrinological perturbations.

2 II.

3 DIET INDUCED MODELS

Diet induced obesity models are best suited and simplest obesity induction models and possibly the one that most closely resembles the reality of obesity in humans. Hypercaloric value diets varying between 3.7Kcal/g and 5.4Kcal/g have proved effective for induction of obesity 10 . The environmental conditions including temperature,

duration of light and dark period, number of animals per cage or the feeding system used for the cages are important to develop these types of models 11 . Hence, to minimize the data variability, it is important to control the environmental conditions. Another factor that has to be considered is the age of the animals at which 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. a) High Fat Diet (HFD) Induced Models O Exposure to HFD results in positive energy balance and obesity in certain rodent models that can be considered an adequate model of human obesity [13][14] . The male C57BL/6J mouse is the gold standard for a diet induce obese model. The C57BL/6J mouse develops obesity only when allowed ad libitum access to a high-fat diet whereas on a low-fat diet, C57BL/6J mice remain normal. In 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 HFD 15 . The adipocyte hypertrophy and hyperplasia are responsible for obese phenotype in the C57BL/6J mouse. The outbred Sprague-Dawley rat is markedly more sensitive to HFD-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) [16][17] . The obesity prone subset of rats becomes obese, hyperphagic, hyperleptinemic, hyperinsulinemic, hyperglycemic, and hypertriglyceridemic 17 . The obese phenotype results from hyperphagia which is caused by an increase in meal size and increased energy efficiency 18 . 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 19 .

4 b) High Fructose Fed Animal Models

Fructose has several adverse metabolic effects, including hypertriglyceridemia, hyperinsulinemia and hypertension in rodents and induces moderate obesity 20 .

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 21 . Recent findings also provide a novel hypothesis: Fructose raises uric acid, which in turn inhibits nitric oxide availability. Since insulin requires nitric oxide to stimulate glucose uptake it can be speculated that fructose-induced hyperuricemia may have a pathogenic role in promoting insulin resistance and metabolic syndrome 22 .

5 c) Cafeteria Rats

The mixture of palatable commercially available supermarket food can act as a diet to stimulate energy intake in rodents. This diet is known as cafeteria diet, It is the combination of the high fat content with a high carbohydrate content 23 . These diets can be implicated in the development of obesity, leading to significant body weight gain, fat deposition and also insulin resistance 24 . 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 25 .III. VENTEROMEDIAL HYPOTHALAMIC (VMH) NUCLEUS LESION a) Monosodium Glutamate (MSG)

The ventromedial hypothalamic and arcuate nuclei is considered to be the area which controls the food intake and energy expenditure. The administration of monosodium glutamate to newborn rats is responsible for the destruction of the ventromedial hypothalamic and arcuate nuclei which leads to development of obesity. The subcutaneous or intraperitoneal route can be used for administration of MSG [26][27] . The dose that varies by 2-4 g/kg of body weight of the rat for 5 times every other day, during the neonatal period of rat causes obesity [28][29][30][31] . Overeating is not responsible for the obesity in neonatal MSG treated rodents. MSG obesity is associated with high level of corticosteroids 28 . The increase in the level of glucocorticoids is due to the chronic exposure of the adrenal gland to high serum levels of leptin, which occurs in rats treated with MSG [32][33] .

6 b) Electrical VMH Lesion

The Electrical VMH lesion can be used to induce obesity. A bilateral destruction of hypothalamic nuclei, which leads to obesity can be caused by passing a current of 1.2 mA for 4 seconds, repeated thrice at an interval of 30-second each after adjusting the position of electrodes 34 . The stereotactic instruments can be used to cause injury with a single electrical current of 2.5 mA for 15 seconds by placing the tip of the rat nose 3.3 mm below the interaural line and positioning the tip of a stainless steel electrode 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 35 . 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 of 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. Therefore, both mechanisms are involved in the development of obesity [36][37][38][39] .

IV.

7 OVARIECTOMY

The initial leptin drops by the removal of gonads from female rats, which causes 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 [40][41] . 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 42 . It appears that leptin and estradiol do not regulate themselves directly, because administration of these in intact female rats did not show that it altered either of them, and the reciprocal is true [43][44] . 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 when 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 41,45 .

V.

8 GENETIC MODELS OF OBESITY

The genetic models of obesity are very useful and can be easily developed. The use of these models to study obesity increased in the 1990s because of cloning and identification of the product of five different genes causing obesity. Furthermore, it was discovered that by crossing quantitative trait loci (QTL) with known genes, i.e., obese phenotypes vs identified genotype, the influence of quantitative gene loci, and its penetrance in the quantity of body fat and its distribution [46][47] .

9 a) Monogenic Model Of Obesity

The diabetic (db/db), obese(ob/ob), Tubby (tub), "Agouti" yellow(Ay) and fat (fat) were first five monogenic models of obesity. Over a century ago The "Agouti" rat was described for the first time and it was the first obesity gene to be cloned and characterized at the molecular level in1992. Agouti is expressed in adipose tissue as well as in several other tissues in humans, suggesting that it could be involved in regulating the energy balance. The over expression of agouti in adipose tissue, by genetic modification in rats, results in increased body weight than the non genetically modified ones, without any change in the amount of intake. This suggest that the increase of fatty mass in these rats could be the result of changes in the energy expenditure [46][47] . The gene of the obese rat (ob/ob) was cloned at the end of 1994, followed a year later by cloning the diabetic one (db/db). In experimental studies, it was found that a circulating factor of a normal rat or a db/db rat, when administered in an ob/ob rat, normalized its weight. But when this factor of a normal rat or an ob/ob was placed in a db/db rat, there was no weight change. These results strongly suggested that both genes were from the same metabolic pathway, and that db/db could be an ob/ob receptor, which was later proved. This factor was called leptin, i.e., a hormone produced by the ob/ob gene, that was responsible for communicating with the brain concerning the level of energy stored in adipose tissue in the form of fat [46][47] .

10 b) Polygenic Models of Obesity

The body weight, adiposity and related metabolic traits shows significant variability in rodents, as with human beings 48 .The high fat diet causes obesity and insulin resistance in inbred C57Bl/6J mice, but this strain remains non obese when fed on chow diet 49 Susceptibility to diet-induced obesity in this strain is polygenic and has been associated with hyperphagia and leptin resistance. AKR/J mice are also prone to diet induced obesity, however, unlike C57Bl/6J, AKR/J do not become hyperglycemic on a high-fat diet 50 . The SWR/J strain prefers carbohydrates and remains thin on high calorie diets 51 . Similarly, A/J mice are less prone to obesity 49 . As expected, these obesity-resistant mouse strains are less susceptible to hyperglycemia 49 . Obesity prone and resistant rats have also been bred in Sprague-Dawley and Fischer 344 genetic background 52 Together, these models facilitate the study of how diet and other environmental factors affect body weight, adiposity and metabolic disorders 53 .

11 VI.

12 TRANSGENIC MODELS OF OBESITY a) Pro-Opiomelanocortin and Melanocortin Receptor Knockouts

Adrenocorticotropin (ACTH), ?, ?-and ? melanocyte stimulating hormone (MSH), and the opioid ?-endorphin are the Pro-opiomelanocortin (POMC) February derived peptides. Leptin, a soluble hormone secreted from the adipocytes, acts on the POMC neurons of the hypothalamic arcuate nucleus [54][55] . The acute anorectic effects of leptin 4 appears due to the activation of POMC neurons and its activation might also be involved in the stimulation of metabolism by leptin 56 . Five melanocortin receptors have been cloned (MC1-5R). Two of these receptors (MC3R and MC4R) are expressed in the CNS in regions involved in energy homeostasis. The development of MC3R and MC4R knockouts help us to know the roles of the neurons expressing these receptors as there is no specific melanocortin receptor agonists. Melanocortin-4 receptor knockout (MC4RKO) mice exhibit the same phenotype observed in Ay/a mice, notably obesity, hyperphagia, increased longitudinal growth and in some cases the development of type 2 diabetes [56][57] . Mice in which the Pomc1 gene has been inactivated, exhibit obesity and hyperphagia and mice lacking a functional Mc3r gene also exhibit increased adiposity [58][59] . Y (NPY) is a 36-amino acid peptide neurotransmitter found in the brain. The genetic approaches to the study of the role of NPY in energy homeostasis have included knockouts of the NPY receptor genes Npy1r [60][61] , Npy2r 62 , and Npy5r 63 . It has been shown that there are at least six receptors for . Surprisingly, for the receptors of an orexigenic all of the NPY receptor knockout mice developed so far exhibit a mild late-onset obesity. The Npy1r knockout mouse exhibited a 27% increase in mature bodyweight in females. The Npy2r knockout mouse exhibited mild late-onset obesity in response to a HFD, th greater sensitivity in the females 63 .The Npy5r knockout mouse exhibited mild obesity with increased adiposity and hyperphagia 64 .

The PPAR are members of the steroid/ thyroid/retinoid receptor superfamily that transactivate a variety of genes involved in the control of lipid metabolism65. The PPAR? isoform is primarily expressed in liver, kidney, heart and skeletal muscle. The development of a mouse line with a disruption of the gene encoding PPAR? has made it possible to determine the role of this receptor in vivo66. PPAR??/? mice develop late-onset obesity.

Estrogens are not just sex hormones, they play an important role in white adipose tissue regulation as estrogen replacement decreases white adipose tissue. ER knockouts exhibit an increase in white adipose tissue and reduced energy expenditure 67 . The ER knockout mice have helped to unravel the role of estrogen receptors in obesity 68 . Follicle stimulating hormone receptor is expressed on the granulose cells of the developing ovary 69 . Follicle stimulating hormone receptor knockouts (FORKO) retards ovarian development and causes chronic estrogen deficiency. Female FORKO develop obesity that is associated with an increased deposition of abdominal fat and that is reversed by estradiol treatment.

13 VII. ?3-ADRENORECEPTORS

All three known subtypes of ?-adrenergic receptors (?-ARs) are expressed in adipose tissue; however, the ?3-AR appears to predominate in brown fat in the rodent. Mice lacking expression of the ?3-AR (?3-KO) have normal body weight compared to WT mice, although they do exhibit modest increases in total body fat. Fed insulin and glucose levels and food intake are unchanged in the ?3-KO mice; however, the increase in insulin and metabolic rate and decrease in glucose and food intake in response to a ?3-AR agonist is eliminated. Compensatory mechanisms might operate in the ?3-KO animals to maintain normal energy homeostasis and, in fact, the expression of ?1-AR mRNA is upregulated in brown and white adipose tissue in these mice.

14 VIII.

15 CONCLUSION

As the incidence of obesity is progressing at alarming rate worldwide, there is a great need for relevant experimental models to provide a better understanding of the pathophysiology of this epidemic to facilitate its therapy and prevention. The multifactorial etiology of obesity provides substantial alternatives for induction of obesity in the experimental models. The animal models may be grouped into genetic, dietary and neuroendocrine forms depending on the origin of the obesity. Although the ultimate model for this human malady is man himself; nevertheless these models provide in valuable insight into the physiological mechanisms that control the energy homeostasis. This information further catalysis the future prospective research for identification of potential therapeutic interventions for obesity. The key factor governing the choice of the model may be either environmental or genetic, depending on the characteristics to be targeted for research.

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