HYPERCALORIC DIET MODELS IN RODENTS

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Abstract

Metabolic syndrome characterized by the occurrence of obesity, hyperlipidemia, and hypertension and glucose intolerance collectively poses serious health concern to people worldwide. Consumption ofhypercaloric dietsin rodents provides a suitable model to mimic the human metabolic diseases. There are several forms of a diet to induce obesity that have proved effective and resemble human obesity in reality closely.Thesehypercaloricdiets are mostly composed by adding carbohydrates or fats and they vary between 3.7 Kcal/g and 5.4 Kcal/g.It's of great concern that only very less researchers make sure that diets to be studied have identical nutrients differing only in relative amounts of fat and carbohydrate. This review aims to summarize the use of and factors associated with hypercaloric diet models for the induction of obesity as well as hyperlipidemia.

Keywords: *Metabolic syndrome, obesity,hypercaloric diet*

Hyperlipidemia and obesity are the major modifiable risk factors for metabolic syndrome leading to increased risk of developingcardiovascular events.Metabolic syndrome characterized by the occurrence of obesity, dyslipidemia,hypertension and glucose intolerancecollectively (Albertie*et al.*,2009) poses serious health concern to people worldwide. These metabolic diseases generally arise as an outcome of a diet abundant in calories and asedentary lifestylebesides the genetic susceptibility.Clinical therapy for hyperlipidemia and obesity requires prompt dietary changes.It becomes inevitable to establish an experimental model that resembles the disease characteristics in humans for thebetter understanding of the pathophysiology of the disease.Highfat diets have been used to model obesity, dyslipidaemiaand insulin resistance in rodents for many decades.

The dietary components that have been shown to influence serum lipids are total energy or caloric intake, total fat, saturated fat, dietary or exogenous cholesterol, alcohol and fibre intake. Foods rich in cholesterol are usually also high in calories contributes to obesity. Dietary fat exceeding 30 % of energy intake from fat often has been claimed as responsible for the increase in adiposity (Jequier, 2002). The build up of cholesterol in the artery walls can restrict blood flow, which elevates blood pressure eventually leading to hypertension.

Animal models have contributed significantly to the study of various metabolic disorders and these allow researchers to gain

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knowledge on its management and treatment in humans. The multifactorialetiology of obesity gives a number ofpossibilities for thedevelopment of experimental models obesity.Because of the polygenic character of these metabolic diseases, monogenic models such asobese Zucker rats do not reflect the human disease fairly.There are many animal models of obesity and hyperlipidemia some of which develop spontaneously or in a diet induced manner while others show a genetic predisposition to the disease. Rodent and non-human primates are good modelsfor greater understanding of the metabolic disorders. Rodents are more preferableowing to practical as well as economic aspects and also the time taken for the outcome in offspring is very short (Williams *et al*., 2014).Hypercaloric diets have been successfully used as experimental models of obesity. This review analyses various modalities in hypercaloric dietary interventions, factors influencing and challenges of human translatabilityin the hypercaloricdiet models in rodents.

Hypercaloric diet

Hypercaloric diet refers to diet that is abundant in energy and the source of energy being either from fat or carbohydrate. High fat or hyperlipidemic diet is more preferred over high carbohydrate diet for inducing obesity or related metabolic diseases.The hypercaloric diet models are valuable tools in the study of many metabolic disorders. The trend of using these animal models has tremendously increased since years. As high calorie intake in humans is considered as the major cause of metabolic syndrome including obesity and hyperlipidemiaand thus animal models used are based mainly on dietary manipulation.There are several types of hypercaloricdiets to induceobesity effectively and these arecomposed by adding carbohydrates or fats, and these vary between 3.7 Kcal/g and 5.4Kcal/g. These diets are highly palatable and induce obesity(Diemen *et al*.,2006).Obesity is the resultant of an increase in energy input and a decrease in energy output. Elevated levels of dietary fat will increase intake of energy, body fat and insulin resistance (Wataraiet *al*.,1983).

Recent trend shown by researchers is to use commercially available predefined or purified ingredient mix of high fat dietcontaining a widerange of fat compositions and types. These purified ingredient diets can be easily bemodified or exactly reproduced giving results with much less variability.

Obesity inductionis most effective when the diet is started at a youngage and continues for several weeks. Anincrease in body weight can be observed within 2 weeks while the other phenotypes of metabolic syndrome to be induced takes more than 4 weeks of high fat feeding(Buettner*et al*., 2007).Rodents are either obesity prone or obesity resistant types. Obesity prone rodents are hyperphagic,due to a central resistance to the anorexigenicaction of insulin (Ribeiro,2009) and a decreased hypothalamicexpression of anorexigenic peptides.Rats that are still lean onahigh fat diet eat the same amount of calories as standardchow fed controls (Farley *et al*.,2003) and are considered as obesity resistant.

Studies demonstrate that maternal high fat diet exposure as *in utero*either during pregnancy or lactation poses risk in offspring for developing metabolic diseases (Williams *et al*., 2014). In the fetus, a maternal high fat dietwas associated with increased hepatic expression of genes involved in glycolysis, gluconeogenesis, inflammation and oxidative stress (Hartil*et al.,* 2009). Reducedfetal growth and altered the placental structure maternal high fat diet has also been shown. (Mark *et al*., 2011).Maternal obesity was associated with an increase in offspring adiposity and increased serum leptin as well as reduced insulin tolerance (White *et al*., 2009).

Factors affecting dietary obesity

Satiety signals

The intestinal hormone cholecystokinin (CCK) and the gastrointestinal neuropeptide, bombesin are considered as the satiety signals.High fat diets results in reduced sensitivity to thesesignals leading to reduced food intake (Covasa and Ritter,1998). A similar observation was reported in obese Zucker rats which required higher doses of CCK to significantly reduce food intake compared to lean rats (Maggio *et al*.,1988). It was observed that

ratson high fat diet ate significantly lessamount of the diet than control rats(Diniz*et al*.,2004).

Hyperphagiais an important mechanism by which high fat diets develop obesity (West *et al.*, 1998).Certain studies utilized cafeteria diets that includes a mixture of commercialsupermarket foods consumed by humans (Rothwell*et al*., 1988). Rats become more obese with cafeteria diet than with high fat dietsbecause of greater hyperphagia arising from the food variety andthey also tend to select and consume a high proportion of energy from fat (Prats *et al*., 1989).

Species, strain and age

Dietary obesity has been produced bygiving a high fat diet to Sprague Dawley(SD) rats(Corbet*et al*.,1986) and male Wistar rats(Hill *et al*.,1983). Wistar and SD rats were compared to evaluate the metabolic effects of high fat diet incomparison to a standard chow, in both strains by Marques *et al*(2016). High fat diet increased weight gain, body fat mass, mesenteric adipocyte's size, adiponectin and leptin plasma levels and decreased oral glucose tolerance in both Wistar and SD rats,but were more pronounced or earlier detected in Wistar rats.Wistar rats fed with HF diet consumed higher amounts of food and higher amounts of energy throughout the study when compared to SD rats fed with the same diet. Weightgain was larger in these animals and was mainly due toan expansion of adipose tissue mass.High fat diet susceptibility also depends more on the specific strain of rodent model used like C57BL/6J mice develop obesity and insulin resistance similar to Wistar rats, while 129S6 and A/J mice do not (Buettnet*et al*., 2007).The hypercaloricdiet for inductingmetabolic syndrome differed between SD rats of different developmental stages (Cheng *et al*., 2017). The post weaning rats(3 weeks) on high fat diet is a better and less timeconsuming model for metabolic syndrome research than the adult rats (8 weeks).

Energy density,fat type and flavor

Studies have shown a positive relationship between dietary fat intake and obesity.Energy density (Rolls and Shide, 1994) contributes forweight gain obtained in several animal studies(Prentice *et al*.,1996).Saturated fat intake leads to a faster induction of metabolic syndrome than monounsaturated fatty acid(Storlien*et al*., 1991).Studies showed that diet based on lard containing SFA (saturatedfatty acid) and MUFA (monounsaturated fatty acid) as well as olive oil containing MUFA produced pronounced obesity and insulin resistance than diet based on coconut fat (Buettner, 2006).Olive oil and coconut fat have been used much less frequently in rodent high fat diets. Polyunsaturatedfatty acid(PUFA) are more potent activators of peroxisome proliferator□activated receptors (PPAR) than SFA or MUFA (Duplus*et al*., 2000), and consequently the PPAR-dependent genes of the fat oxidation cluster were strongly activated in fish oil fed high fat rats.The effect of variety in the flavor of food on rats' consumption of a meal was examined (Treit*et al.*, 1983).

High fat diet models for obesity

There are several types of diets to induceobesity that have proved effective.Obesitywas induced in rats by feeding diets containing condensed milk, saccharine(Naderali*et al*., 2001),maize oil and other fat sources.High fat diet with 70–80% of total energy derived from fat were used leading to prodigious obesity (Fenton and Carr, 1951).Most studieshave employed only one high fat formula in contrast withstandard chow and did not analyze the influence of thespecific fat component in the model.Woods *et al*(2003) prepared high fat diet with butter oil and soyabean oil with energy intake of 19.3kJ/g and induced obesity leading to increased gain in body weight and elevated carcass fat percentage.Fat source can be derived from ingredients such as butter, pork fat, beef tallow, lard,eggand various oils such as corn, coconut, cottonseed, soybean, olive,peanut, sesame, cocoa butter and fish oils.Beef tallow when used as fat source (40% of energy)increased plasma insulin and leptin concentrations withincreased plasma lipid concentrations and hepatic steatosis(Hsu *et al*.,2009).

High fat dietfeeding in mice increased systolic blood pressure and induced endothelial dysfunction (Kobayasi*et al*., 2010).The final body weight may not differ between control and high fat diet groups due to less consumption of food rich in fat and fructose as well as due to

the higher caloric intake.Rats eat for calories and are precise regulators of their body weight and also well controlled by sensory-specific satiety signals.

Peckam*et al*(1962) showed that the total fat content of the epididymal fat of the rat is a function of the number of fat cells in that tissue. The capacity for generation of these new cells is retained for at least the first 34 weeks of life. Rats fed a high fat diet, having an average weight 23% greater than that of rats fed a standard laboratory pellet diet, were capable of reverting not only to the average weight of rats fed the pellet diet but also to the same body composition, when transferred from the high-fat to the pellet diet 31 weeks after weaning . The data suggest that the greater weight gain may be related to a greater number of adipose tissue cells in the rats that had once been obese.

Feeding dams with highfat hypercaloric diet (25% fructose and 25% saturated fat) developed metabolic abnormalities persistent throughout development in pups born.Newborns delivered to high fat fed dams had higher insulin/glucose ratios, more body fat percentage, higher liver weight, liver lipid content, and higher blood glucose and triglyceride (Guo and Jen, 1993).

High carbohydrate diets models

Fructose is abundantly used in synthetic foods and beverages.It has been established that the consumption of high amounts of refinedcarbohydrates in food raises the risk of hyperlipidemia, obesity and cardiovascular diseases (Elliot *et al*.,2002).High carbohydrate diets such as highfructose and high sucrose diets are also used to induce features of the human metabolic syndrome in rodents.The dose of fructose administrated to rodents was higher(50–60 % of the diet) than that given to humans(10–15 %).High carbohydrate diets can be used alone or in combination with a high fat diet. A diet containing sucrose or fructosewhen combined with high fat induces the symptoms such as increased body weight and hyperlipidemia(Panchal *et al*., 2011,Kadnur*et al*.,2005).

Diets rich in cholesterol for Hyperlipidemia and atherosclerosis

Rodents itself havetraditionally not been ideal models of cardiovasculardisease research because they have verylow levels of total cholesterol andlow density lipoprotein cholesterol(LDL-C) but high levels of highdensity lipoprotein cholesterol (HDL-C). So, for adequate induction of hyperlipidemia in rodents requires us toinclude high concentrations of dietary cholesterolwith cholic acid(Harnafi*et al*.,2009, Ji*et al*., 2007, Hassarajani*et al*., 2007).Hypercholesterolemia was induced in rats fed with 3% cholesterol in 28 days. A slight elevation in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level was observed during the first two weeks (Mani *et al.,* 2012).Cholicacidwill promotesfat and cholesterol absorption from the intestine and its inclusion gives better outcomes.Also, diets high in monounsaturatedfats promoted atherosclerosis. Golden Syrian hamster and guinea pigs are also frequently used to induce atherosclerosis.

Normal vs high fat diet: Challenges

Only few researchers make sure that diets their studyhave identical nutrientsdiffering only in content of fat and carbohydrate especially when compared to normal diet (Warden and Fisler, 2008).They reported that two important difference between regular chow and defined diets are the phytoestrogen content fromsoy that is high in normal diets but is absent in defined diets.Dietary phytoestrogensinfluence food and water intake, anxiety related behaviors, locomotoractivity, fat deposition, blood insulin, leptin and thyroid levels,lipogenesis and lipolysis in isolated rat adipocytes (Torre-Villalvazo*et al*.,2008). Secondly, sucrose present in defined diets will be absent in normal diet. Sucrose is 50%fructose and can influence weight gain and contributeto insulin resistance and dyslipidemia (Stanhope and Havel, 2008).

Human translatability of dietary rodent models is immensely less due to the reason that human diet is much complex. Masek and fabrey induced obesity in albino rats as early as 1959 by feeding high fat diet. Followed by this, numerousstudies were taken place with various compositions. The literature survey revealed-

diverse diets with different fatty acid compositions summarized under the term high fat diet. This in turnresultedin variability in the results reported so far.

Absence ofrelationship between intake of dietary fat and body fat content in human studies may bedue to genetic heterogeneity.Difficulties in assessing dietary intakes in humans and the inaccuracy of body mass index for measuring of body fat (Garn *et al*., 1986)also contribute to the less translatability in human studies.

Neither the exact fat content nor the exact fat composition of the diets employed is standardized by researchers. Different types of high fat diets have been prepared with relative fat fractions between 20% and 60% energy as fat and the fat sourcecan be animal derived such as lard, butter oil or beef tallow, or plant derived such as corn or safflower oil. Researchers either use semi-purified hypercaloric diets or else fatis added to a standard rodent chow. This often leads to an unbalanced diet composition with regard to macro and micronutrients. Dietary compositions,species/strain, sex and age variability, inter laboratoryvariability severity and duration and lack ofresemblance to the human obesogenic pathophysiology collectively demands high care from the side of researchers while choosing appropriate models.

Conclusions

The best model to induce a disease is the one which best reproduces its pathophysiological characteristics well.Thehypercaloric diet models are valuable tools in the study of many metabolic disorders.A thorough understanding of specific hypercaloricmodel should be analyzed before examining the effects of any dietary intervention.These diets composed of identical fat typesmight yield different results due to uncontrollable differencesbetween primary fat sources and the diet preparation.An ideal animal model based on dietary changes should be reproducible with minimal variability for the better understanding of results.

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