Review Article

Rodent Models for Metabolic Syndrome Research

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Rodents are widely used to mimic human diseases to improve understanding of the causes and progression of disease symptoms and to test potential therapeutic interventions. Chronic diseases such as obesity, diabetes and hypertension, together known as the metabolic syndrome, are causing increasing morbidity and mortality. To control these diseases, research in rodent models that closely mimic the changes in humans is essential. This review will examine the adequacy of the many rodent models of metabolic syndrome to mimic the causes and progression of the disease in humans. The primary criterion will be whether a rodent model initiates all of the signs, especially obesity, diabetes, hypertension and dysfunction of the heart, blood vessels, liver and kidney, primarily by diet since these are the diet-induced signs in humans with metabolic syndrome. We conclude that the model that comes closest to fulfilling this criterion is the high carbohydrate, high fat-fed male rodent.

1. Introduction

Hypertension, diabetes and obesity are common but not independent in humans and the combination is referred to as metabolic syndrome [1, 2]. While the definition of the syndrome may help understanding causes and prognosis, there are continuing arguments on the clinical usefulness of defining the syndrome in humans. Human metabolic syndrome is accepted as a consequence of dietary imbalance rather than a genetically programmed disease. This syndrome includes central obesity, insulin resistance, elevated blood pressure, impaired glucose tolerance and dyslipidaemia [1, 2]; these are accepted risk factors that increase the incidence of cardiovascular disease and type 2 diabetes [3–5]. Metabolic syndrome is also associated with an increased risk of nonalcoholic fatty liver disease and kidney dysfunction [6, 7]. Similarly, there is solid evidence for correlations between metabolic syndrome and functional changes in the lungs, dementia and cancers of the breast, pancreas and bladder (Figure 1) [8–12]. Lifestyle and diet modulate metabolic syndrome [4, 13] and this induces pathophysiological changes throughout the body. Hence it is important to study the progression and treatment strategies for metabolic syndrome.

The number of adults with metabolic syndrome is substantial and the prevalence is increasing throughout the world [14]. The gender ratio was similar in the USA [15], Singapore and Australia showed increased rates in females [16, 17], while Japan showed increased rates in males [18]. In 2002, the prevalence of metabolic syndrome in the USA was 24% and 23.4% in males and females, respectively [19]. In 2005 and 2006, this prevalence had increased to 34% in both males and females [15, 20]. In the Australian population, 18.8% of males and 25.4% of females fulfilled the requirements for diagnosis with metabolic syndrome in 2000 [17]. In a Japanese study, 45% of males and 38% of females were diagnosed with metabolic syndrome [18]. Similar prevalence rates of metabolic syndrome have been reported in the Indian subcontinent [21].

The widespread occurrence of metabolic syndrome in humans means that there is an urgent need to study relevant causes and progression of the signs. These studies require viable animal models that adequately mimic all the aspects of the human disease, developing all major signs of metabolic syndrome, especially obesity, diabetes, dyslipidaemia, hypertension and possibly fatty liver disease and kidney dysfunction. Rodents have been used for many years as models of human disease, especially hypertension,
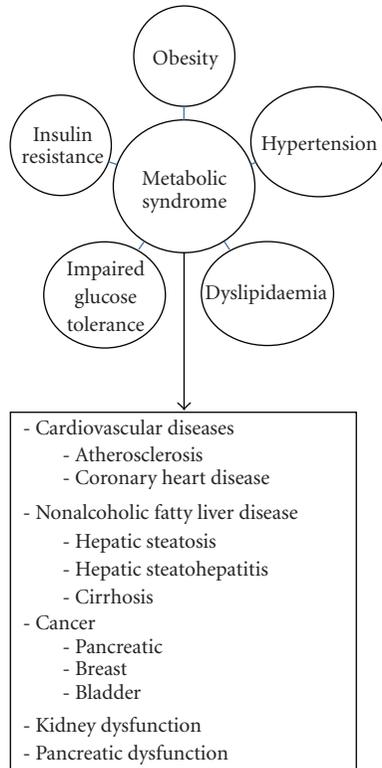
FIGURE 1: Metabolic syndrome and associated complications.

diabetes and obesity [22–25]. This review will examine whether the existing rodent models for components of metabolic syndrome mimic the range of changes in humans and are therefore suitable to evaluate potential treatments for human metabolic syndrome.

2. Genetic Models of Obesity and Type 2 Diabetes

Genetic models of obesity and diabetes include *db/db* mice, *ob/ob* mice, Zucker diabetic fatty rats and Otsuka Long-Evans Tokushima Fatty rats, while Goto-Kakizaki rats are diabetic but nonobese. These models are useful in evaluating specific molecular mechanisms that may be involved in development of obesity in rodents, but the metabolic syndrome in humans is not a monogenetic disorder. Therefore, the relevant questions are whether these genetic changes mimic those observed in humans and whether these models show the range of signs that characterise the metabolic syndrome. As an example, several of these models have mutations in the leptin gene or receptor (Figure 2), yet similar mutations are a very rare recessive genetic disorder in humans with only 4 mutations in 15 people reported up until 2009 [26]. Further, although cholecystokinin is important as a satiation signal [27], there are only a few reports of CCK-1 receptor mutations, as found in the Otsuka Long-Evans Tokushima fatty rats, inducing obesity in humans [28, 29].

3. *ob/ob* (C57BL/6J-*ob/ob*) Mice

This was one of the first genetic models used for the study of diabetes [30]. These mice inherited a monogenetic autosomal recessive mutation in the leptin gene on chromosome 6 [31, 32] and developed obesity, hyperinsulinaemia and hyperglycaemia after 4 weeks of age [33]. They showed an increased body weight compared to their lean littermates at all ages [33, 34]. The presence of impaired glucose tolerance was found after 12 weeks of age [35]. These mice developed left ventricular hypertrophy with decreased cardiac function at 24 weeks of age [36], cardiac fibrosis after 20 weeks of age [37] and hepatic steatosis and inflammation at 12 weeks of age [38, 39]. Unlike humans with metabolic syndrome, these mice showed reduced blood pressure [34] and did not develop dyslipidaemia even after the age of 36 weeks [35].

4. *db/db* (C57BL/KsJ-*db/db*) Mice

These mice have inherited an autosomal recessive mutation in the leptin receptor gene present on chromosome 4 [40] leading to higher body weights than their lean littermates after 6 weeks of age [41]. Fasting blood glucose concentrations were higher after 8 weeks of age and these mice showed increased plasma concentrations of triglycerides, total cholesterol and nonesterified fatty acids along with reduced HDL/LDL cholesterol ratio after 13 weeks of age [42]. Hyperinsulinaemia and impaired glucose tolerance were observed after 12 weeks of age [41, 43]. In the heart, both infiltration with inflammatory cells and fibrosis were present after 12 weeks of age, although blood pressure was unchanged [41]. These mice showed vascular endothelial dysfunction at 12 weeks of age [41] and developed hepatic steatosis after 20 weeks of age [44]. *db/db* mice failed to show hepatic inflammation and fibrosis [45].

5. Zucker Diabetic Fatty Rats (*fa/fa*)

Diabetic Zucker fatty rats (ZDF), a model of early onset obesity, have a mutation in the leptin receptor gene [46]. ZDF rats became hyperglycaemic after 13–15 weeks of age [47] with hyperinsulinaemia and hypertriglyceridaemia after 12–14 weeks of age along with diastolic and systolic dysfunction [48]. Serum cholesterol concentrations were slightly increased in ZDF rats compared to lean Zucker rats at 10 weeks of age whereas the serum concentration of cholesterol was ~2.5 times higher compared to lean Zucker rats at 20 weeks of age [49]. These rats also developed endothelial dysfunction after 12 weeks of age [50]. ZDF rats showed only moderate increases in systolic blood pressure by 15 weeks of age [51]. Albuminuria was present at the age of 31 weeks [52] with thickening of basal membrane and glomerular fibrosis after 47 weeks [52]. Increased hepatic triglyceride deposition was observed after 20 weeks of age in ZDF rats [53]. ZDF rats also showed increased serum markers of inflammation such as TNF-α and IL-1β after 26 weeks of age [54].
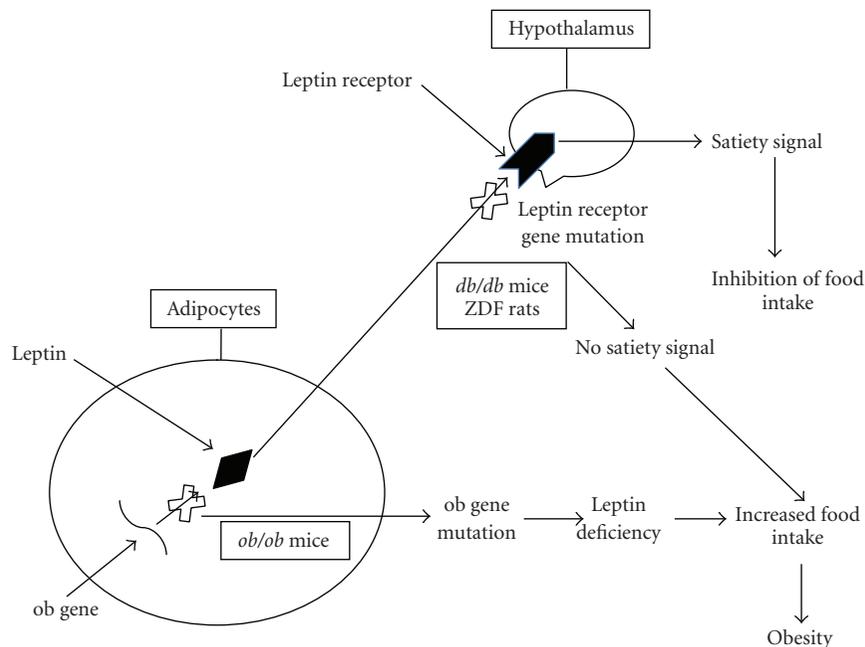
FIGURE 2: Mechanism of the actions of leptin including the effects of leptin deficiency or leptin receptor deficiency.

6. Otsuka Long-Evans Tokushima Fatty Rats

Otsuka Long-Evans Tokushima Fatty (OLETF) rats have been used as a rat model of human diabetes and obesity [55]. Pancreatic acini cells in OLETF rats were insensitive to the actions of cholecystokinin (CCK), which controls food intake [56], due to the absence of CCK-1 receptors [57]. Male and female OLETF rats were similar in body weight to lean Long-Evans Tokushima rats at the time of weaning but they became 30–40% heavier than age-matched lean Long-Evans Tokushima Otsuka rats after 20 weeks [58]. Due to the lack of CCK-1 receptors, the average meal size and overall food intake were higher in OLETF rats [57]. OLETF rats presented with high blood glucose concentrations after 18 weeks of age but they showed impaired glucose tolerance starting at 24 weeks of age [58]. Plasma triglyceride concentrations in OLETF rats started increasing from 8 weeks of age but cholesterol concentrations were only slightly higher even after 40 weeks of age [58]. After week 40 of age, OLETF rats showed diffuse glomerulosclerosis [58]. Hearts from OLETF rats showed cardiac hypertrophy with left ventricular systolic and diastolic dysfunction [59]. OLETF rats showed higher blood pressure compared to lean Long-Evans Tokushima Otsuka rats after 14 weeks of age [60]. After 34 weeks of age, OLETF rats showed 5 times higher triglyceride deposition in liver compared to the lean Long-Evans Tokushima Otsuka rats [61].

7. Goto-Kakizaki Rats

Goto-Kakizaki (GK) rats are nonobese and spontaneously diabetic [62]. The occurrence of diabetes in these rats is an interaction of several events including presence of suscep-

tibility loci for some diabetic traits, gestational impairment inducing decreased β-cell neogenesis and proliferation and loss of β-cell differentiation [63]. These inbred rats were hyperglycaemic after 4 weeks of age with impaired glucose tolerance but they were lighter than the age-matched Wistar rats [64]. These rats developed cardiac hypertrophy and decreased systolic function at 20 weeks of age [65]. There was no change in blood pressure even after 14 months of age [66]. Plasma and liver lipid concentrations were higher in Goto-Kakizaki rats after 8 weeks of age compared to age-matched Wistar rats [67]. Goto-Kakizaki rats had higher urinary excretion of albumin and decreased creatinine clearance after 14 months of age along with increases in glomerular volume, basement membrane thickness and kidney weight [66].

These genetic models consistently develop obesity and non-insulin-dependent diabetes, but metabolic syndrome is a much broader constellation of pathophysiological changes, especially including hypertension. Thus, these rodent models, although used in obesity research, replicate neither the causes nor the changes that occur in human metabolic syndrome (summarised in Table 1).

8. Genetically Engineered Diabetic Mice

In recent years, genetically engineered mice models, either transgenic or knockout, have been developed to study the normal and abnormal effects of a particular protein or a set of proteins. Different proteins, signalling molecules and hormones, important in development of diabetes and obesity, can be removed by changes in the genome of the mice. Some of the important proteins that have been deleted from the mice for obesity and diabetes research include

Table 1: Different rodent models with the signs of metabolic syndrome.

Rodent model	Age (weeks)	Signs of metabolic syndrome shown by rodents							References
		Obesity	Hypertension	Dyslipidaemia	Cardiovascular dysfunction	Impaired glucose tolerance	Fatty liver	Kidney dysfunction	
ob/ob mice	4	✓	×	×	×	×	×	U	[33–39]
	12	✓	×	×	×	✓	✓	U	
	24	✓	×	×	✓	✓	✓	U	
db/db mice	6	✓	×	×	×	×	×	U	[41–44]
	12-13	✓	×	✓	✓	✓	×	U	
	20	✓	×	✓	✓	✓	✓	U	
ZDF rat	12–15	✓	✓	✓	✓	×	×	×	[47–53]
	20	✓	✓	✓	✓	×	✓	×	
	31–47	✓	✓	✓	✓	×	✓	✓	
OLETF rats	8	×	×	✓	×	×	×	×	[58–61]
	14	×	✓	✓	×	×	×	×	
	20	✓	✓	✓	×	×	×	×	
	24	✓	✓	✓	×	✓	×	×	
	34	✓	✓	✓	×	✓	✓	×	
	40	✓	✓	✓	×	✓	✓	✓	
	60–66	✓	✓	✓	✓	✓	✓	✓	
Goto-Kakizaki rats	4	×	×	×	×	✓	×	×	[64–67]
	8	×	×	✓	×	✓	✓	×	
	20	×	×	✓	✓	✓	✓	×	
	60	×	×	✓	✓	✓	✓	✓	

This table represents the signs of metabolic syndrome at different ages. The symbols ✓ and × indicate the presence and absence of these signs of metabolic syndrome at that age, respectively, whereas U indicates unavailability of the data. The table indicates that age is an important parameter since some of the signs are developed in very young rodents whereas others take much longer to develop.

insulin receptor, GLUT4, IRS-1 and IRS-2. Insulin receptor-null mice do not survive for more than 72 hours as they develop severe ketoacidosis [68] with hyperglycaemia and hyperinsulinaemia [69]. Thus they cannot be used in long-term studies as adults. Further, the insulin receptor knockout mice are unlikely to mimic human conditions as this receptor loss is very rare in humans [68, 70]. Other models lacking GLUT4, IRS-1 and IRS-2 may give useful information about the roles of each protein [71–75], but they do not mimic the cause of human metabolic syndrome.

9. Chemically Induced Rodent Models of Diabetes

Alloxan and streptozotocin are structural analogues of glucose that enter pancreatic beta cells via the GLUT2 transporter [86]. Single injections of alloxan or streptozotocin induce selective necrosis of pancreatic β cells in rats, mice and rabbits [86–91] as a model of type 1 diabetes. Chemically induced diabetic rodents show fatty liver and inflammation [92] along with decreased ventricular contractility and function [93]. In contrast to patients with metabolic syndrome, alloxan- and streptozotocin-induced diabetic rats are hypoinsulinaemic [94], do not gain weight

and are usually hypotensive. Thus, chemically induced type 1 diabetic rodents do not show the diverse characteristics of the metabolic syndrome and therefore they are not a suitable model for this syndrome in humans.

Type 2 diabetes may be induced by low-dose streptozotocin given neonatally, for example, at a dose of 70 mg/kg on day 5 of life, producing moderate hyperglycaemia in adult rats with decreased HDL-cholesterol concentrations but no other lipid abnormalities or oxidative enzyme changes [95]. Insulin resistance and an approximate doubling of plasma C-reactive peptide and TNF-α were produced in 14-week-old rats treated on day 2 of life with streptozotocin (90 mg/kg) [96]. However, these changes following neonatal streptozotocin are insufficient to define the signs of the metabolic syndrome. A better option may be treatment with low-dose streptozotocin in a nutritional model of type 2 diabetes induced by an increased energy diet. In 8-week-old rats, the combination of streptozotocin (25 mg/kg) and a high-fructose, high-fat diet for 6 weeks increased plasma glucose, insulin and triglyceride concentrations, decreased left ventricular contractile function and reduced myocardial metabolic efficiency [97]. A similar protocol with a high-energy diet for 5 weeks followed by streptozotocin administration (40 mg/kg) produced metabolic abnormalities with insulin resistance that could be decreased by administration

TABLE 2: Effects of some treatment strategies on rodent models of metabolic syndrome.

Rodent model	Interventions	Reversal or prevention of signs of metabolic syndrome and associated complications	Signs of metabolic syndrome not affected by drug treatment
ob/ob mice	Temocapril (ACE inhibitor) and olmesartan (AT$_1$ receptor blocker) [37]	Reduced blood pressure and ventricular fibrosis	No change in body weight and blood glucose concentrations
	Resveratrol [76]	Reduced blood glucose, plasma insulin, adiponectin concentrations, improved glucose tolerance	No change in body weight and blood lipid concentrations
db/db mice	Aliskiren (renin inhibitor) [41]	Reduced blood pressure, cardiac fibrosis, macrophage infiltration in heart and coronary remodelling, improved endothelial function and glucose tolerance, increased pancreatic insulin content and beta cell mass, reduced pancreatic fibrosis	No change in body weight, visceral fat and liver weight
ZDF rats	Sitagliptin (DPP-4 inhibitor) [54]	Reduced body weight and blood pressure, reduced blood glucose, plasma triglyceride, plasma insulin and serum inflammatory markers, reduced pancreatic fibrosis and inflammation	No change in total cholesterol concentration
OLETF rats	Rosiglitazone (PPARγ agonist) [77]	Reduced blood glucose, plasma insulin and serum inflammatory markers	No change in body weight
GK rats	Levosimendan (calcium sensitiser) [78]	Reduced cardiac fibrosis and cardiac hypertrophy, improved ventricular function	No change in blood pressure
	Hesperidin [67]	Reduced serum insulin and blood glucose, serum triglyceride, serum total cholesterol concentrations, increased serum HDL-cholesterol and adiponectin concentrations	—
Alloxan	Cucurbita pepo peel extract [79]	Reduced blood glucose, plasma total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol and VLDL-cholesterol, increased plasma insulin concentrations	—
Streptozotocin	Quercetin [80]	Increase in body weight, reduced serum glucose concentrations and increased plasma insulin concentrations, pancreatic beta cell protection	—
Fructose-induced metabolic syndrome	Lipoic acid [81]	Reduced blood pressure, blood glucose and plasma insulin concentrations, improved renal function	—
Sucrose-induced metabolic syndrome	Hippophae rhamnoides (sea buckthorn) seed extract [82]	Reduced blood pressure, reduced plasma concentrations of triglycerides, total cholesterol and free fatty acids, increased plasma HDL-cholesterol concentrations	No change in body weight, blood glucose and plasma insulin concentrations
High fat-induced metabolic syndrome	Enalapril (ACE inhibitor) [83]	Reduced body weight, epididymal fat pads and plasma insulin concentrations, increased plasma leptin and cholesterol concentrations, improved vascular relaxation	No change in blood glucose, plasma triglyceride and plasma free fatty acids concentrations, glucose tolerance
High fructose, high fat-induced metabolic syndrome	Purple carrot juice [84]	Reduced body weight gain, improved glucose tolerance, reduced plasma triglycerides, total cholesterol, free fatty acids concentrations, reduced plasma inflammatory marker, improved ventricular function, reduced cardiac fibrosis and stiffness, reduced blood pressure, improved vascular relaxation, attenuation of fatty liver	—
High sucrose, high fat-induced metabolic syndrome	Piperine [85]	Reduced body weight, reduced abdominal fat pads	No change in blood glucose, plasma triglyceride, plasma total cholesterol and free fatty acid concentrations

ACE - Angiotensin converting enzyme, AT - Angiotensin, ZDF - Zucker diabetic fatty, DPP-4 - dipeptidyl peptidase-4, OLETF - Otsuka Long-Evans Tokushima Fatty, PPAR - peroxisome proliferator-activated receptor, GK - Goto-Kakizaki.

of chitooligosaccharides for 8 weeks [98]. While these models may be suitable for studies in type 2 diabetes [99], the key signs of hypertension and obesity necessary for the metabolic syndrome were not reported.

10. Diet-Induced Metabolic Syndrome

Diet plays an important role in growth and development as a source of nutrition, but the composition of the diet decides its nutritional status. The modern diet, especially in Western countries, is rich in carbohydrates such as fructose and sucrose as well as saturated fat. This increased calorific intake has been associated with many diet-induced complications including metabolic syndrome, cardiovascular diseases and nonalcoholic fatty liver disease [100, 101]. Combinations of carbohydrate and fat-rich dietary components have been used in rodents to mimic these signs and symptoms of human metabolic syndrome.

11. Fructose-Induced Metabolic Syndrome

Fructose has become an important and pervasive ingredient in Western diets [102, 103]. The world average per capita daily fructose intake increased by 16% between 1986 and 2007 [103]. Together with the increase in consumption of fructose in the diet over the last fifty years, there has been a proportionate increase in the incidence of obesity [104]. The main sources of fructose in the diet are sucrose, high-fructose corn syrup, fruits and honey. Unlike glucose, high-fructose feeding to rodents induced the development of symptoms of metabolic syndrome including high blood pressure, insulin resistance, impaired glucose tolerance and dyslipidemia [102, 105]. Fructose feeding induced ventricular dilatation, ventricular hypertrophy, decreased ventricular contractile function, infiltration of inflammatory cells in heart and hepatic steatosis [106, 107]. In the liver, fructose feeding induced both microvesicular and macrovesicular steatosis with periportal fibrosis and lobular inflammation [108]. Fructose has been reported to induce obesity [109] but this was not confirmed [106]. Fructose feeding in rats caused renal tubular injury, collagen deposition in interstitium and increased macrophage infiltration along with proliferation and hyperplasia of renal proximal tubules [110] as well as leptin resistance without changes in body weight and adiposity [111]. Increases in plasma uric acid and plasma triglyceride concentrations have been reported without changes in plasma cholesterol concentrations [112, 113].

Fructose, unlike glucose, did not elicit insulin secretion from pancreatic β-cells, possibly due to the absence of the fructose transporter (GLUT5) on pancreatic β-cells [104]. Fructose also lacks the ability to stimulate the secretion of leptin [104] whereas it has the ability to activate *de novo* lipogenesis in the liver (Figure 3) [114]. During metabolism, fructose bypasses the rate-limiting step, the reaction catalysed by phosphofructokinase, leading to uncontrolled supply of carbon skeleton for lipogenesis in liver [115].

12. Sucrose-Induced Metabolic Syndrome

Sucrose is a dietary source of fructose [103], thus sucrose feeding has been used to mimic human metabolic syndrome in animal models. Similar to fructose, sucrose feeding has shown variable results, especially with obesity [116, 117]. As with fructose, sucrose induced lipogenesis in rats along with increased plasma concentrations of insulin, leptin, triglycerides, glucose and free fatty acids, and impaired glucose tolerance [118, 119]. Sucrose feeding in rats led to an insulin-resistant state with no change in fasting plasma insulin and glucose concentrations, but higher postprandial plasma concentrations of insulin and glucose [117]. Sucrose feeding increased systolic blood pressure in rats with increased left ventricular mass but without cardiac fibrosis [120] and caused development of hepatic steatosis [121]. No changes were seen in kidneys of rats fed with high-sucrose diet [122].

13. High Fat-Induced Metabolic Syndrome

High-fat diets have been used to model obesity, dyslipidaemia and insulin resistance in rodents for many decades. The complications developed by high-fat diets resemble the human metabolic syndrome and these complications may extend to cardiac hypertrophy, cardiac fibrosis, myocardial necrosis and hepatic steatosis [123–126]. High-fat diet feeding in mice increased systolic blood pressure and induced endothelial dysfunction [126]. High-fat diet-fed mice also showed albuminuria, increased glomerular tuft area, mesangial expansion, renal lipid accumulation, collagen deposition in glomeruli and increased infiltration of macrophages in renal medulla [127]. Different types of high-fat diets have been used with fat fractions ranging between 20% and 60% energy as fat as either animal-derived fats, such as lard or beef tallow, or plant oils such as olive or coconut oil [125]. Long-term feeding of rats (60% of energy) and mice (35% fat wt/wt) with high-fat diet increased body weight compared to standard chow-fed controls [128, 129]. Although the increase in body weight was significant after as little as 2 weeks, the diet-induced phenotype became apparent after more than 4 weeks of high-fat diet feeding [128]. Long-term feeding with both animal and plant fat-enriched diets eventually led to moderate hyperglycaemia and impaired glucose tolerance in most rat and mouse strains [130, 131].

Lard, coconut oil and olive oil (42% of energy content) increased body weight, deposition of liver triglycerides, plasma triglyceride and free fatty acid concentrations and plasma insulin concentrations and decreased plasma adiponectin concentrations [125]. Lard and olive oil but not coconut oil decreased insulin sensitivity [125]. Lard, coconut oil and olive oil caused hepatic steatosis with no signs of inflammation and fibrosis in any of the groups [125]. Beef tallow when used as fat source (40% of energy) increased plasma insulin and leptin concentrations with increased plasma lipid concentrations and hepatic steatosis [132]. Although high-fat diet induces most of the symptoms of human metabolic syndrome in rodents, it does not resemble the diet causing metabolic syndrome and associated
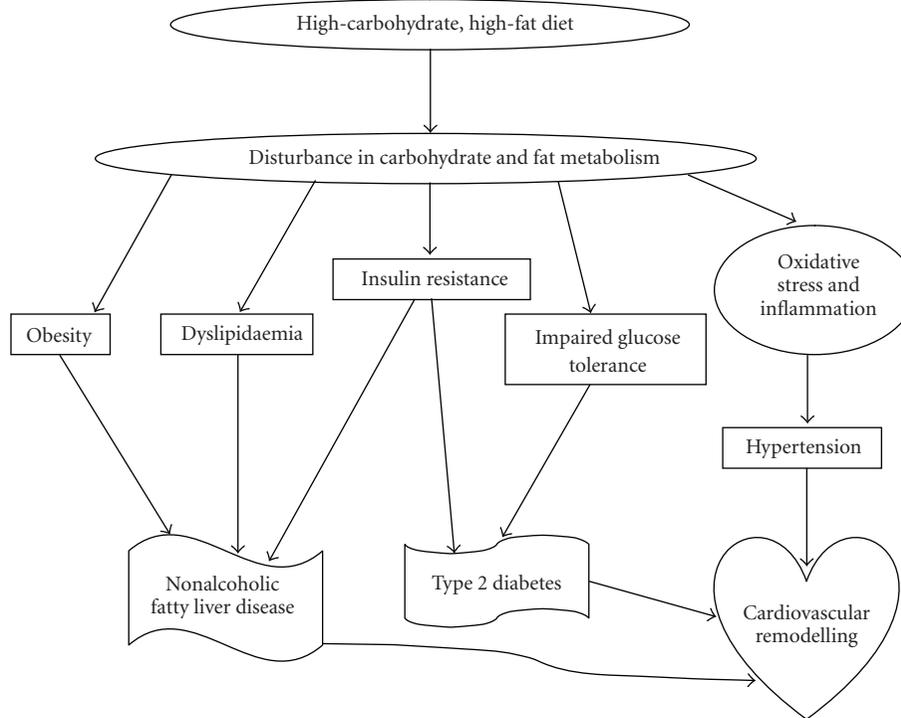
Figure 3: Metabolism of fructose.

complications, as the human diet is more complex than a high-fat diet.

14. High Carbohydrate-, High Fat-Induced Metabolic Syndrome

A diet high in carbohydrates together with fat, either of animal or plant origin, mimics the human diet more closely. This combined diet should induce metabolic syndrome in rodents (Figure 4). Different combinations and amounts of carbohydrates and fats have been used in different studies [133–136]. The common carbohydrates used are fructose and sucrose whereas the source of fat varies in different studies.

Different combinations of sucrose and fat have been used to induce signs of metabolic syndrome. Sucrose content varied between 10% and 30% whereas fat content in this diet group varied between 20% and 40% [137–139]. Rodents fed on high-sucrose, high-fat diet had increased body weight, abdominal fat deposition, hyperinsulinaemia, hyperglycaemia and hyperleptinaemia [137, 138]. Sucrose and fat in combination also caused hepatic steatosis and increased hepatic lipogenic enzymes [139].

Fructose and fat have been used in combination to induce metabolic syndrome. The fructose content varies between 10% and 60%, either in the diet or drinking water or both, whereas the fat content varies between 20% and 60% [133, 140–143]. Fructose and fat feeding increased body weight and the plasma concentrations of triglycerides, cholesterol, free fatty acids and leptin [133, 140]. The combination of fructose and fat also caused hyperinsulinaemia, insulin

resistance, impaired glucose tolerance, increased abdominal fat deposition, hepatic steatosis and inflammation [133, 140]. The rats fed with the high-fructose, high-fat diet showed cardiac hypertrophy, increased ventricular stiffness, ventricular dilatation, cardiac inflammation and fibrosis, hypertension, decreased cardiac function and endothelial dysfunction along with mild renal damage and increased pancreatic islet mass [133].

Since high-carbohydrate, high-fat diet-fed rodents develop all the complications present in human metabolic syndrome and the diet is similar to human diets (sometimes called a "cafeteria diet"), this model is probably the best model to study the human metabolic syndrome. Pharmaceutical and nutraceutical preparations can be tested for treatment of diet-induced human metabolic syndrome in this high-carbohydrate, high-fat diet-fed model.

15. Obesity-Resistant Rat Strain

The interaction of genes with the diet is crucial for the induction of obesity in rodents and humans as shown by the studies with diet-induced obese (DIO) and diet-resistant (DR) rats [144, 145]. DR rats, even when fed with high-fat diet, did not produce the signs of metabolic syndrome, whereas DIO rats clearly showed those signs [144, 145]. The signs shown by DIO rats and not shown by DR rats included increases in body weight and body fat, impairment of glucose tolerance, dyslipidaemia, hyperinsulinaemia and hyperleptinaemia [144, 145]. However, these signs are similar to many control rats and mice fed standard rodent food that are sedentary, obese and develop impaired glucose tolerance, described as "metabolically morbid" [146].

FIGURE 4: High-carbohydrate, high-fat diet-induced metabolic syndrome.

16. Fatty Liver Disease

Nonalcoholic steatohepatitis is now recognized as a complication of metabolic syndrome [147]. The most important model of nonalcoholic steatohepatitis is the methionine- and choline-deficient diet-fed rat. This special diet produced hepatic steatosis and fibrosis, increased hepatic triglycerides, increased serum activities of transaminases and alkaline phosphatase and increased serum concentrations of total bilirubin [148, 149]. Methionine- and choline-deficient diet-fed rats showed extreme reduction in body weight and liver weight along with decreased serum triglyceride and total protein concentrations [148, 149]. Although these rats develop nonalcoholic steatohepatitis, they do not show the other signs of metabolic syndrome.

17. High-Fat Diet-Fed Spontaneously Hypertensive Rats

Spontaneously hypertensive rats (SHRs) are the most widely used genetic model of human hypertension [22]. High-fat feeding to SHRs led to an increased body weight compared to SHRs fed on normal chow diet [150]. High-fat-fed SHRs also showed renal inflammation and albuminuria but did not show changes in plasma concentrations of total cholesterol, triglycerides and insulin, although plasma concentrations of free fatty acids were higher in high-fat-fed SHRs compared to normal diet-fed SHRs [150]. There was no change in systolic blood pressure with high-fat feeding in SHRs [151]. High-fat-fed SHRs also showed impaired glucose tolerance

[152]. Although high-fat-fed SHRs show some symptoms of metabolic syndrome, they have genetically induced rather than diet-induced hypertension. Since human hypertension is not monogenetic, this model should not be considered appropriate as a model of the metabolic syndrome.

18. Nile Grass Rats

Apart from laboratory animals, wild rodents have been tested for the development of diabetes and obesity with laboratory diets. The Nile rat (African grass rat; *Arvicanthis niloticus*) and sand rat (*Psammomys obesus*) are two examples. These rats do not develop diabetes in the wild, but diabetes was induced when these rats were kept under laboratory conditions on chow diet [153]. These rats show hyperglycaemia and dyslipidaemia after 1 year of age [154]. They also develop liver steatosis, abdominal fat deposition, hypertension and hyperinsulinaemia [153, 154]. These rats show promise for metabolic syndrome research, even though these signs develop when fed on normal diet rather than the high-carbohydrate, high-fat diet in humans. This is similar to the concept of metabolically morbid rodents fed a normal diet [146].

19. Useful Treatment Strategies in Metabolic Syndrome Research

These rodent models have been used to characterize responses to many interventions. Success has been variable but some treatments have attenuated most of the signs

of the metabolic syndrome. These treatment strategies clearly indicate that it is possible to inhibit the progression of metabolic syndrome and associated complications and maybe to reverse them. Some of the responses to treatments in different rodent models have been described in Table 2.

20. Conclusion

Pharmaceutical and nutraceutical preparations are required to decrease morbidity and mortality in chronic diseases such as metabolic syndrome. These preparations need to be tested for efficacy in an appropriate rodent model. Thus, different animal models have been developed for this purpose. While many rodent models display some of the signs of the metabolic syndrome, few models can adequately mimic the range of signs that characterise this syndrome in humans. In particular, the presence of inflammation has often not been tested or defined. Further, many models rely on genetic changes to induce symptoms even though the human disease is usually diet induced. It is our opinion that chronic consumption of a high-carbohydrate, high-fat diet by normal rodents provides an adequate rodent model to mimic the human metabolic syndrome and for testing potential therapeutic interventions.

Conflict of Interests

The authors declare no conflict of interests.

Acknowledgments

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