

## REVIEW

# Modeling insulin resistance in rodents by alterations in diet: what have high-fat and high-calorie diets revealed?

Lewin Small,<sup>1</sup> Amanda E. Brandon,<sup>1,2</sup> Nigel Turner,<sup>3</sup> and Gregory J. Cooney<sup>1,2</sup>

<sup>1</sup>Diabetes and Metabolism Division, Garvan Institute, Sydney, New South Wales, Australia; <sup>2</sup>Sydney Medical School, Charles Perkins Centre, The University of Sydney, New South Wales, Australia; and <sup>3</sup>Department of Pharmacology, School of Medical Science, University of New South Wales, Sydney, New South Wales, Australia

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**Small L, Brandon AE, Turner N, Cooney GJ.** Modeling insulin resistance in rodents by alterations in diet: what have high-fat and high-calorie diets revealed? *Am J Physiol Endocrinol Metab* 314: E251–E265, 2018. First published November 7, 2017; doi:10.1152/ajpendo.00337.2017.—For over half a century, researchers have been feeding different diets to rodents to examine the effects of macronutrients on whole body and tissue insulin action. During this period, the number of different diets and the source of macronutrients employed have grown dramatically. Because of the large heterogeneity in both the source and percentage of different macronutrients used for studies, it is not surprising that different high-calorie diets do not produce the same changes in insulin action. Despite this, diverse high-calorie diets continue to be employed in an attempt to generate a “generic” insulin resistance. The high-fat diet in particular varies greatly between studies with regard to the source, complexity, and ratio of dietary fat, carbohydrate, and protein. This review examines the range of rodent dietary models and methods for assessing insulin action. In almost all studies reviewed, rodents fed diets that had more than 45% of dietary energy as fat or simple carbohydrates had reduced whole body insulin action compared with chow. However, different high-calorie diets produced significantly different effects in liver, muscle, and whole body insulin action when insulin action was measured by the hyperinsulinemic-euglycemic clamp method. Rodent dietary models remain an important tool for exploring potential mechanisms of insulin resistance, but more attention needs to be given to the total macronutrient content and composition when interpreting dietary effects on insulin action.

diet composition; diet-induced obesity; hyperinsulinemic-euglycemic clamp; insulin resistance; rodent models

## INTRODUCTION

Metabolic conditions associated with nutrient overconsumption, such as obesity, insulin resistance, type 2 diabetes, non-alcoholic steatohepatitis, and dyslipidemia, present major challenges for the healthcare sector. Basic and clinical research that advances knowledge in this field is necessary for our understanding of metabolic disease. Animal models, and in particular rodent models, play a crucial role in the study of the complex pathologies caused by nutrient overconsumption and obesity. Although there are many surrogate measures of insulin action, including glucose tolerance tests, insulin tolerance tests, homeostatic model assessment-insulin resistance, and insulin-signaling phospho-immunoblots, hyperinsulinemic-euglycemic clamp data are considered the most robust way to directly

compare insulin sensitivity within and between studies in animals and humans. This review examines the effect of diets on insulin action in rodent models of diet-induced obesity (DIO) by primarily reviewing investigations in which insulin action was directly measured systemically by the hyperinsulinemic-euglycemic clamp and/or peripherally by glucose tracer uptake at matched insulin levels. The review also focuses on liver and skeletal muscle, which are considered responsible for the majority of insulin-stimulated glucose clearance in rodents and humans (84). This review complements and extends some excellent other reviews on dietary modulation of insulin action (156, 157) and on the rodent high-fat diet (HFD) model in general (21, 61).

## RODENT MODELS OF INSULIN RESISTANCE

The most commonly used rodent models of obesity and the metabolic syndrome are either monogenic or diet induced. Monogenic models of obesity, such as rodents with a defect in leptin production (*ob/ob* mice) or its receptor [*db/db* mice

Address for reprint requests and other correspondence: G. Cooney, Univ. of Sydney, Charles Perkins Ctr., D17, Sydney Medical School, Sydney, NSW, 2006 (e-mail: gregory.cooney@sydney.edu.au).

(*fa/fa*) Zucker fatty rats] (183), are extensively used, as they generate animals with pronounced hyperphagia and consequently severe obesity. However, because of germline deletions/mutations in these genes, these animals have many physiological differences from wild-type rodents, including alterations in the microvasculature (191) and nervous system (50) and fertility problems (96). Therefore, the manifestations of metabolic dysfunction in leptin or leptin receptor-deficient rodents may not fully reflect metabolic disease etiology in humans wherein congenital leptin deficiency is exceedingly rare (126). There are also several gene knockout mouse models of insulin resistance, mostly mice with deletions/mutations in genes coding for proteins in the insulin-signaling pathway or glucose transporters (111). Although these models provide vital information for mechanistic studies, they do not necessarily reflect the complexity and heterogeneity of the metabolic syndrome. Studies using polygenic models of rodent obesity in which rodents are selectively bred to produce pronounced hyperphagia and obesity, such as the New Zealand obese mouse (38, 131) and the Wellesley mouse (57), must also be interpreted with care for similar reasons and because of a lack of suitable “within strain” control animals to enable appropriate comparison between lean and obese animals. In contrast, the rodent DIO model has the advantage of having greater relevance to humans wherein overconsumption of calories invariably leads to increased fat mass and metabolic changes irrespective of genetic background (13). Additionally, the DIO model allows comparisons between genetically very similar or identical animals, which may reduce the potential variability of the study (51).

#### TISSUE-SPECIFIC INSULIN ACTION

Whole body glucose metabolism/insulin action is a sum of glucose metabolism in all the tissues of the body. However, not all tissues of the body contribute to glucose utilization to the same extent, and not all tissues are regulated by insulin in the same way. Arguably the most important tissues to insulin-regulated glucose metabolism are the muscle, liver, and adipose tissue.

**Muscle.** Impaired insulin-stimulated glucose uptake in skeletal muscle is one of the hallmarks of lipid-induced insulin resistance. Skeletal muscle makes up 25–40% of body mass (76), and, because of its relative size in man and most animals, muscle is considered to be a major tissue for the disposal of both glucose (74) and fatty acids (55). Under hyperinsulinemic-euglycemic clamp conditions, it has been calculated that skeletal muscle accounts for up to 80% of the total glucose disposal (44) and ~40% of glucose disposal after an oral glucose meal (73, 81). Skeletal muscle is also responsible for between 20 and 30% of resting energy expenditure (195). Additionally, muscle is capable of taking up and disposing of large amounts of glucose during and after exercise (137), which can have a major impact on glucose homeostasis and positive implications for metabolic health (17, 18).

There are multiple theories about the mechanisms that may be responsible for diet-induced insulin resistance in muscle. Excess intramyocellular lipid (IMCL) content has been proposed to be a mediator, as many reports show a strong negative correlation with whole body and skeletal muscle insulin sensitivity in humans and rodents (82, 89). However, this is not

always the case (49), and, interestingly, in athletes who are very insulin sensitive, IMCL is high [the so-called athletes paradox (155)]. Although an increase in lipid content is most clearly displayed as elevated triacylglycerol (TAG) content, it is likely that TAGs may only act as a marker of dysfunctional muscle glucose metabolism. Accumulation of bioactive lipids or lipid intermediates, such as diacylglycerol (DAGs), ceramides, acylcarnitines, and/or acyl-CoAs, is more likely to be involved in the observed decrease of insulin sensitivity (2, 12, 66, 72). Increased intracellular DAG levels resulting from fat feeding have been shown to activate protein kinase C (PKC) signaling, leading to serine phosphorylation of insulin receptor substrate 1 (IRS-1). This prevents the phosphorylation of tyrosine residues on IRS-1, leading to a defect in canonical phosphatidylinositol-3 kinase/Akt signaling, reduced glucose transporter 4 (GLUT-4) translocation, and consequently reduced insulin-stimulated glucose uptake (52, 72, 193).

The DAG hypothesis of lipid-induced insulin resistance has gained considerable traction in the literature and has been reported to be present in the muscle of lipid-infused patients with type 2 diabetes (169). However, there are an increasing number of studies that provide conflicting evidence. These include genetic models with disruption of fatty acid metabolism, leading to rodents that have increased muscle DAG concentration that retain (148) or even increase (173) muscle insulin sensitivity. Similar to DAG, another family of bioactive lipid species, ceramides, are also thought to inhibit insulin signaling (33) and have been shown to interact with several intracellular messengers, including PKC isoforms, protein phosphatase 2A, as well as kinases involved in inflammation pathways, JNK and NF- $\kappa$ B (34, 163). Inhibiting ceramide synthesis has been shown to protect against glucocorticoid, DIO, and saturated fat-induced insulin resistance in rodents (66). Similar to the investigations in rodent models of insulin resistance, the human literature correlating different lipid species with insulin sensitivity in muscle is equally divided on the importance of any specific lipids in the generation of insulin resistance (reviewed in detail in Ref. 12).

A dysfunction in the oxidative capacity of the mitochondria has also been suggested as a mechanism underlying skeletal muscle insulin resistance (175). However, other reports show no differences in mitochondrial function or indeed an increase in DIO rodent models and between obese and lean humans (45, 176). A build-up of muscle reactive oxygen species and activation of inflammatory pathways by circulating cytokines or intracellular lipids have also been proposed (186). Because of the multiple levels of regulation of glucose uptake and disposal in muscle, it is likely that the range of muscle insulin sensitivity in humans may be due to a combination of defects in extracellular glucose delivery (blood flow, microvascular recruitment), transport (glucose transporter number, activity, and translocation), and phosphorylation (hexokinase activity) (185). Therefore, we believe that insulin action in muscle may be negatively affected by multiple different metabolites/mechanisms as discussed above. Clearly, our understanding of the mechanisms involved in diet-induced, skeletal muscle insulin resistance remains incomplete despite the detailed analysis of the molecular mechanisms involved in skeletal muscle insulin action outlined in several review articles (1, 43, 69, 103, 142, 143, 177).

*Liver.* Hepatic insulin resistance, most commonly defined as the failure of insulin to suppress hepatic glucose production (HGP), is one of the first pathologies observed in DIO models of insulin resistance (86, 141, 179). This is consistent with short-term overfeeding studies in humans that attributed a rapid loss of whole body insulin sensitivity to defects in control of HGP (19, 36). The exact cellular mechanisms behind lipid-induced hepatic insulin resistance are still debated; however, it is clear that the development of nonalcoholic fatty liver disease (NAFLD) is strongly associated with a loss of the ability of insulin to inhibit glucose output. Similar to lipid-induced insulin resistance in muscle, one of the main theories suggested to explain this change in hepatic insulin sensitivity focuses on accumulation of bioactive lipid species. In this scenario, the activation of PKC- $\epsilon$  by hepatic DAG accumulation results in the inhibition of hepatic insulin signaling and subsequent increased expression and activation of gluconeogenic enzymes (127) although the time course for this sequence of events does not necessarily fit with the rapid ability (within minutes) of insulin to shut down glucose output from the liver. Liver ceramide content has also been implicated and has been reported to have a negative correlation with hepatic insulin action (118). Despite the many studies suggesting a causative role for liver lipid in systemic insulin resistance, some researchers have suggested that hepatic insulin resistance may precede NAFLD (53).

In addition to carbohydrate metabolism, the liver plays a crucial role in fatty acid metabolism. This includes the uptake, oxidation, and de novo synthesis of fatty acids, as well as packaging of lipids into lipoproteins for export and storage in other tissues (130). Lipogenesis and triglyceride synthesis in the liver are regulated by the transcription factor SREBP1c, which is activated by insulin (15). In the normal liver, stimulation of the insulin-signaling pathway leads to the phosphorylation of FOXO1 and activation of SREBP1c, leading to a transcriptional program to reduce glucose production and increase triglyceride synthesis. However, in the insulin-resistant liver, there is a loss of suppression of glucose production without decreases in triglyceride synthesis despite these processes being regulated by the same insulin-signaling pathway. This has led some researchers to the conclusion that there may be selective insulin resistance for different metabolic pathways in the liver (16). Because of the central role of the hepatocyte mitochondria in both the oxidation and synthesis of glucose and lipid, it is not surprising that mitochondrial function can be substantially altered in the insulin-resistant liver (37). Interestingly, in mouse models of NAFLD, there is a reported increase in the mitochondrial oxidative capacity of the liver (77, 78). Clearly, the liver has a crucial role in regulating systemic glucose and fatty acid metabolism in both the fasting and postprandial state (84).

*Adipose tissue.* Although white adipose tissue (WAT) can contribute a significant portion to our body mass, particularly in obese individuals (54), it does not have a major impact on whole body glucose disposal (54, 81, 88). In lean humans, adipose tissue is responsible for ~3% of the clearance of an oral glucose load (84). WAT also plays a relatively small role in the whole body oxidation of fatty acids; instead it acts as more of a storage organ, releasing free fatty acids during fasting or starvation for use by other tissues, such as heart and muscle (149). Despite its relative small contribution to glucose clear-

ance, there is growing evidence that disruption of WAT development and remodeling can have significant consequences systemically. This may be due to the emerging role of WAT as a key endocrine organ, responsible for the production of metabolic regulatory hormones, such as leptin and adiponectin (165).

In contrast to WAT, brown adipose tissue (BAT) is a very metabolically active tissue that plays a role in thermoregulation. BAT has a large capacity for glucose uptake and fatty acid oxidation and has significant expression of uncoupling protein (UCP)-1, a unique protein able to dissipate the electrochemical gradient across the inner mitochondrial membrane, resulting in a direct conversion of chemical energy to heat (26). However, because of the low abundance of BAT found in humans (estimates range between 60 and 100 g), the contribution of BAT to whole body glucose homeostasis remains low, at least when not activated by cold exposure (93).

#### DIETS USED IN OBESITY/DIABETES RESEARCH

*The HFD.* Altering rodent diets to produce and/or exacerbate obesity and metabolic syndrome has been a common tool used by researchers dating back to the mid-20th century. Early studies promoted a HFD as a way to induce obesity, hyperglycemia, and insulin resistance, and this type of diet has subsequently become a widely used tool in modeling the metabolic syndrome (59, 88, 144, 168). Although extensively used in diabetes and obesity research, the composition and fat content of so-called HFDs differ considerably, with relative fat fractions varying from between 20 and 95%, with fat derived from multiple sources, including animals (lard, tallow), plants (olive, safflower, corn, coconut), and fish (21). Although HFD studies in rodents generally constrain the amount of dietary fat to between 45 and 60% of energy intake, there is an increasing field of literature looking at the effect of very-high-fat diets (VHFDs) (80–95% dietary energy as fat) on metabolic health similar to low-carbohydrate, ketogenic diets in humans (71). In rodents, the evidence indicates that, although VHFDs generally seem to reduce body weight gain [although not always (91)], they also reduce systemic and particularly hepatic insulin sensitivity (10, 79, 91).

Because the source of fat used in HFDs can vary, it is important to keep in mind that feeding rodents diverse fatty acid species has been demonstrated to lead to different metabolic outcomes. This is outlined in Table 1, a review of studies investigating insulin sensitivity by hyperinsulinemic-euglycemic clamp of rodents fed varying diets (high fat and refined carbohydrates). In rats, diets high in saturated fatty acids (SFAs) have been shown to cause a greater degree of insulin resistance than diets high in monounsaturated fatty acid (MUFA) and polyunsaturated fatty acid (PUFA) (20, 158). Different SFA subtypes may also differ in their effects on insulin action with some evidence showing a greater effect of stearate (181). There is also evidence from rodents fed a mixed fatty acid diet that different fatty acid species may have tissue-specific effects on insulin action (190). In mice, diets containing predominantly PUFA reportedly produce lower levels of muscle TAG and DAG than ones with higher levels of SFA and MUFA (172); however, this does not necessarily translate to a difference in insulin sensitivity (125). Interestingly, supplementing HFD with omega-3 fatty acids seems to

Table 1. Rodent hyperinsulinemic-euglycemic clamp studies comparing the effects of dietary content

Predominant Energy Source	Citation	Rodent Sex/Strain/Age or Weight#	Diet (energy % of macronutrient)	Control/Comparative Diet	Length of Diet, days	Muscle Glucose Uptake, % control	Hepatic Glucose Production <sup>†</sup> , Δ % control	Glucose Infusion Rate, % control
Saturated fat*	(158)	Male Wistar rats (age 54 days)	Tallow (59% fat, 20% carb, 21% protein)	Standard chow (12% fat, 65% carb, 23% protein)	30	27 (RQ)	40	43
	(116)	Female C57BL/6J mice (age 6 wk)	Lard (60% fat, 20% carb, 20% protein) (Research Diets no. D12492)	Sucrose, starch (10% fat, 70% carb, 35% sucrose, 20% protein) (Research Diets no. D12450B)	56	NR	NR	55
	(56)	Male C57BL/6J mice (age 7–8 wk)	Lard (60% fat, 20% carb, 20% protein) (Research Diets no. D12492)	Standard chow (energy not given)	10	NR	31	55
	(41)	Male C57BL/6J mice (age 12 wk)	Long-chain triacylglycerol (75% palmitate) (source not reported) (45% fat, 30% carb, 25% protein)	Standard chow (12% fat, 61% carb, 27% protein)	56	NR	31	40
	(79)	Male C57BL/6J mice (age 7 wk)	Lard (95.1% fat, 0.4% carb, 4.5% protein) (Bio-Serv no. F3666)	Standard chow (17% fat, 60% carb, 23% protein)	35	123 (Q)	28	44
	(10)	Male Wistar rats (age 12 wk)	Tallow (78.7% fat, 2.2% carb, 19.1% protein)	Starch (semipurified) 16.7% fat, 64.3% carb, 19% protein	28	NR	84	40
	(10)	Male Wistar rats (age 12 wk)	Tallow (92.8% fat, 1.7% carb, 5.5% protein)	Starch (semipurified) 16.7% fat, 64.3% carb, 19% protein	28	NR	115	20
	(178)	Male Wistar rats (age 8 wk)	Hydrogenated coconut oil (59% fat, 20% carb, 21% protein)	Standard chow (12% fat, 65% carb, 23% protein)	35	90 (RQ)	13	82
	(188)	Male Wistar rats (~280 g start of study)	Low-fat basal diet supplemented with octanoic- (70%)/decanoic (30%) acid	Standard chow (energy not given)	28	NR	NR	90
	(116)	Female C57BL/6J mice (age 6 wk)	Hydrogenated coconut oil (58% fat, 25.5% carb, 13% sucrose, 16.4% protein) (Research Diets no. D12331)	Sucrose, starch (10% fat, 70% carb, 35% sucrose, 20% protein) (Research Diets no. D12450B)	56	NR	NR	78
High fat, high sucrose (Surwit)	(41)	Male C57BL/6J mice (age 12 wk)	Medium-chain triacylglycerol (source not reported) (45% fat, 30% carb, 25% protein)	Standard chow (12% fat, 61% carb, 27% protein)	56	NR	18	41
	(181)	Male C57BL/6J mice (age 14 wk)	Lard (45% fat, 35% carb, 17.5% sucrose, 20% protein) (Research Diets no. D12451)	Sucrose, starch (10% fat, 70% carb, 35% sucrose, 20% protein) (Research Diets no. D12450B)	35	NR	40 (Difference in suppression)	28
	(179)	Male C57BL/6J mice (age 8–12 wk)	Cocoa butter (43% fat, 40% carb, 32% sucrose, 17% protein) (Specialty Feeds no. SF01-028)	Standard chow (5% fat, 72% carb, 23% protein)	7, 21, 42, 112	112, 64, 48, 54 (Q)	23, 38, 39, 38	69, 42, 44, 38
Monounsaturated fat	(158)	Male Wistar rats (age 54 days)	Olive oil (59% fat, 20% carb, 21% protein)	Standard chow (12% fat, 65% carb, 23% protein)	30	68 (RQ)	14	63

Continued

Table 1.—Continued

Predominant Energy Source	Citation	Rodent Sex/Strain/Age or Weight#	Diet (energy % of macronutrient)	Control/Comparative Diet	Length of Diet, days	Muscle Glucose Uptake, % control	Hepatic Glucose Production <sup>†</sup> , Δ % control	Glucose Infusion Rate, % control	
Polyunsaturated fat	(88)	Male Wistar rats (age 90–120 days)	Safflower oil (60% fat, 20% carb, 20% protein)	Standard chow (12% fat, 65% carb, 23% protein)	22	57 (RQ)	NR	66	
	(159)	Male Wistar rats (age 60 days)	Safflower oil (59% fat, 20% carb, 21% protein)	Standard chow (12% fat, 65% carb, 23% protein)	29	58 (RG)	34	48	
	(158)	Male Wistar rats (age 54 days)	Safflower oil (59% fat, 20% carb, 21% protein)	Standard chow (12% fat, 65% carb, 23% protein)	30	38 (RQ)	22	50	
	(86)	Male Wistar rats (300–380 g final weight)	Safflower oil (59% fat, 20% carb, 21% protein)	Cornstarch (10% fat, 69% carb, 21% protein)	3, 21	79 (RQ) (3 days only)	43, 37	41, 54	
	(30)	Male Wistar rats (age 2 mo)	Safflower oil (59% fat, 20% carb, 21% protein)	Standard chow (10% fat, 65% carb, 25% protein)	300	49 (RQ)	45	32	
	(178)	Male Wistar rats (age 8 wk)	Safflower oil (59% fat, 20% carb, 21% protein)	Standard chow (12% fat, 65% carb, 23% protein)	35	57 (RQ)	21	56	
	(119)	Male Sprague-Dawley rats (age 3, 8, 16, 56 wk)	Corn oil (45% fat, 35% carb, 20% protein)	Cornstarch (12% fat, 68% carb, 20% protein)	35	57, 60, 50, 117 (S)	NR	R <sub>d</sub> (72, 75, 77, 90)	
	(112)	Male Sw/129 mice (age 10–12 wk)	Safflower oil (59% fat, carb, protein not reported)	Standard chow (7% fat, carb, protein not reported)	14	116 (Q)	69	48	
	Marine oils	(158)	Male Wistar rats (age 54 days)	Safflower oil, fish oil (59% fat, 18% fish oil, 20% carb, 21% protein)	Standard chow (12% fat, 65% carb, 23% protein)	30	95 (RQ)	−3	94
		(112)	Male Sw/129 mice (age 10–12 wk)	Safflower oil, fish oil (59% fat, 22% fish oil, carb, protein not reported)	Standard chow (7% fat, carb, protein not reported)	14	150 (Q)	24	75
		(159)	Male Wistar rats (age 60 days)	Safflower oil, fish oil (59% fat, 12% tuna oil, 20% carb, 21% protein)	Standard chow (12% fat, 65% carb, 23% protein)	29	100 (RG)	5	94
Fructose/sucrose	(83)	Male Wistar rats (age 6 wk)	Sucrose (10% fat, 63% carb, 63% sucrose, 27% protein)	Standard chow (13% fat, 61% carb, 26% protein)	28	NR	11	105	
	(170)	Male Wistar rats (260 g)	Fructose (10% fat, 69% carb, 34.5% fructose, 21% protein)	Glucose (10% fat, 69% carb, 34.5% glucose, 21% protein)	30	50 (RQ)	NR	63	
(116)	Female C57BL/6J mice (age 6 wk)	Sucrose (11% fat, 73% carb, 60% sucrose, 16.4% protein) (Research Diets no. D12450B)	Sucrose, starch (10% fat, 70% carb, 35% sucrose, 20% protein) (Research Diets no. D12450B)	56	NR	NR	105		
(121)	Male Wistar rats (180 g)	Sucrose (12% fat, 68% carb, 68% sucrose, 20% protein)	Cornstarch (12% fat, 68% carb, 20% protein)	56	NR	63	48		
(120)	Male Wistar rats (200–220 g)	Sucrose (12% fat, 68% carb, 68% sucrose, 20% protein)	Cornstarch (12% fat, 68% carb, 20% protein)	7, 14, 35, 56	NR	38, 65, 68, 71	60, 47, 40, 40		
(119)	Male Sprague-Dawley rats (age 3, 8, 16, 56 wk)	Sucrose (12% fat, 68% carb, 68% sucrose, 20% protein)	Cornstarch (12% fat, 68% carb, 20% protein)	35	100, 74, 57, 91 (S)	NR	R <sub>d</sub> (97, 84, 78, 87)		

Continued

Table 1.—Continued

Predominant Energy Source	Citation	Rodent Sex/Strain/Age or Weight#	Diet (energy % of macronutrient)	Control/Comparative Diet	Length of Diet, days	Muscle Glucose Uptake, % control	Hepatic Glucose Production <sup>†</sup> , Δ % control	Glucose Infusion Rate, % control
	(39)	Male Sprague-Dawley rats (age 12 wk)	Fructose (12% fat, 66% carb, 66% fructose, 22% protein)	Standard chow (4% fat, 72% carb, 24% protein)	56	NR	NR	55

The studies in this table were identified by searching for “hyperinsulinemic-euglycemic clamp in mice/frats” in addition to each dietary subtype (for example “high-sucrose/fructose diet”). Studies focusing on transgenic rodent lines or pharmaceutical intervention were generally excluded because of a primary focus on comparisons between genotype or drug. Additionally, because of many of the studies controlling for energy intake either through pair feeding or isocaloric diets, we have not included body weight gain. Reporting insulin levels during the clamp was not an exclusion criteria, as many of the studies were performed before this became commonplace. There is significant heterogeneity between clamp methodologies between groups, including rates of insulin infusion, anesthesia, fasting time, bleeding from the tail, vein, or artery, and glucose tracers used. These may all have effects on the rates gained from the experiment as described by Ayala et al. (4, 5). Consequently, glucose metabolic rates are shown as percent of the control diet, as the actual rates show significant disparity, making comparison between different studies more difficult. In studies in which data was presented in graphs and exact numbers were not reported, percentages were estimated from the graphs displayed and may vary slightly from the results obtained.  $R_d$ , rate of glucose disappearance; RQ, red quadriceps; Q, quadriceps; RG, red gastrocnemius; S, soleus; NR, not reported. #Age and weight at the start of study unless specified. \*Although lard and tallow contain high levels of saturated fat (38–50%), they can be higher in monounsaturated fatty acids. However, because of relatively high levels of saturated fat compared with other fatty acid sources (safflower oil, olive oil, corn oil), they have been grouped with saturated fats. †As many of the control groups had completely suppressed hepatic glucose production (HGP) ( $R_d = 0$ ), it was not possible to express HGP as simply percentage of control. Therefore, we calculated the difference in HGP between groups as a function of  $R_d$  in the following equation [(control diet  $GIR/R_d$ ) – (test diet  $GIR/R_d$ ) × 100]. A higher number indicates that the test diet has a higher rate of HGP as a percentage of  $R_d$ .

improve insulin sensitivity and muscle insulin action (97, 128, 158, 159), possibly through a peroxisome proliferator-activated receptor- $\alpha$ -dependent mechanism (112). Additionally, a HFD consisting predominantly of medium-chain SFAs (MCFA), such as lauric and capric acid (the predominant fatty acid species in coconut oil), do not seem to reduce insulin sensitivity as much as a HFD containing animal-derived long-chain SFAs (LCFA) (20, 164, 178, 188). This may be due to contrasting effects of these fatty acids on insulin-sensitive tissues, such as skeletal muscle (107) and liver (164). This is of particular interest because hydrogenated coconut oil has been commonly used as an SFA source for HFD and is found in the widely used, commercially available obesogenic “Surwit diet” (166, 167) (Research Diets D12330, D12331). However, other researchers have reported no difference in insulin sensitivity between mice fed a HFD predominantly of either MCFA or LCFA (41).

The mechanisms behind the differential effects of saturated and unsaturated fatty acids on insulin sensitivity are still debated and include alterations in plasma membrane phospholipid composition (122, 158, 187), transcriptional changes in fatty acid metabolism (35), inflammatory effects (151), as well as direct regulation of insulin signaling (33, 65, 107, 146, 161, 193). It is also clear that the rates of oxidation of different species of fatty acids vary quite significantly and that fatty acids that are more unsaturated and shorter seem to be oxidized faster than longer, more SFAs (46, 95). This may be relevant, as incomplete fatty acid oxidation and substrate competition between fatty acids and glucose (glucose/fatty acid cycle) have both been implicated as possible mechanisms for reduced insulin-stimulated glucose uptake in peripheral tissue (109, 134, 177).

*High-fat, high-sucrose diet.* In the late 1980s, Surwit et al. (167) published a DIO study on C57BL/6J using a high-fat, high-sucrose diet (HFHS). The authors concluded that the C57BL/6J strain of mice is genetically predisposed to DIO and that a mix of a high-fat, high-simple carbohydrate diet is sufficient to produce many of the pathophysiological changes of the metabolic syndrome. In a follow-up study, they showed that a HFHS diet generates higher weight gain and more pronounced hyperglycemia and hyperinsulinemia than a high-fat, low-carbohydrate diet (166). These two papers popularized the HFHS diet as a way of generating a more severe metabolic syndrome phenotype in the C57BL/6J model of DIO. The HFHS diet is widely used in rodent studies as a “Western style” diet because of high levels of both sucrose and fat and is thought to more closely resemble a high-energy human diet rather than HFDs and VHFDs of 60% or greater calories from fat. There are presently limited data on direct comparisons between the more traditional HFD and the Surwit HFHS diet effects on insulin action although Omar et al. (116) have reported that, in C57BL/6J mice, the HFHS is not as effective as a more traditional HFD in suppressing whole body insulin action under hyperinsulinemic-euglycemic clamp conditions.

*Cafeteria and “choice” diets.* The use of a nonpurified “cafeteria” diet, in which a mix of energy-dense, high-fat and high-sugar foods that are regularly consumed by humans (cake, cookies, chips, and processed meats) has been gaining traction as a more physiologically relevant model of the human Western diet. The cafeteria diet has been reported to generate more pronounced obesity than a regular HFD (63, 140), and adding

a greater degree of food choices seems to increase food intake and change feeding behavior (104). Recently, Diepenbroek et al. (48) investigated the effect of different choice diets (animals received access to a combination of chow, beef tallow, and 30% sucrose solution) on insulin sensitivity in rats after 1 wk of diet. They found that animals who only had access to chow and tallow had the greatest reduction in HGP, whereas rats with access to all three foods were substantially hyperphagic and had the lowest whole body glucose disposal. Because of the present lack of studies using cafeteria and choice diets, no major conclusion can be drawn about the comparative effects of a more conventional HFD and these diets on insulin action. Additionally, the cafeteria diet may make energy intake measurements harder to perform.

**High-carbohydrate diets.** Although not as widely used as HFD in rodent DIO models, diets high in refined simple carbohydrates have been used successfully to model some elements of the metabolic syndrome, in particular hypertriglyceridemia and insulin resistance. Sprague-Dawley and Wistar rats have been shown to become insulin resistant after 4–8 wk of either high-sucrose or -fructose diets (60–70% sucrose or fructose as a percentage of total calories) (39, 119, 121, 145, 160). Pagliassotti et al. (120) reported that in, as little as 1 wk of high-sucrose feeding, Wistar rats show evidence of whole body insulin resistance driven by reduced hepatic glucose suppression. There are fewer studies investigating systemic insulin resistance in mice fed diets high in simple carbohydrates although high-sucrose/fructose feeding has been shown to reduce glucose tolerance compared with mice fed a diet high in complex carbohydrates (105, 135, 139, 162). However, others have reported no difference in glucose disposal under hyperinsulinemic-euglycemic clamp conditions (116).

Although the induction of whole body insulin resistance by high-sucrose/fructose feeding is not as well established in rodents as the HFD model of insulin resistance, it is clear that other hallmarks of the metabolic syndrome, such as obesity, hypertriglyceridemia, and NAFLD, all of which correlate with insulin resistance in rodents and humans, can be quite pronounced (6, 127). Interestingly, the fructose moiety of the sucrose molecule seems to be the main driver of the loss in insulin action possibly because of its preferential metabolism in the liver and the subsequent increase in liver lipids as a result (6, 170, 171). The molecular mechanisms behind insulin resistance caused by dietary fructose are mainly focused on the strong hypertriglyceridemia and hepatic lipid accumulation explained in detail by Basciano et al. (6). Additionally, high-sucrose/fructose feeding may alter the trafficking dynamics of glucose transporters (174) and potentially trigger endoplasmic reticulum stress pathways (135). It is unclear whether insulin resistance derived from high-simple carbohydrate feeding is of a similar etiology to that derived from HFDs. Potentially, a chronic increase in insulin secretion or glucose oversupply may drive the insulin resistance similar to insulin resistance seen in glucose-infused rodents (14, 68). From the few comparative studies published, it seems likely that, in rodents, HFD and HFHS diets generate a greater degree of insulin resistance than high-sucrose/fructose diets (116) (Table 1).

Altering the source or complexity of more complex carbohydrates can also have implications on whole body insulin sensitivity. Replacing regular starch with resistant starch reduces digestion in the small intestine and increases bacterial

fermentation in the large intestine. Resistant starch is a modified starch that generally contains higher levels of amylose (one of the two main components of starch, the other being amylopectin) or more cross linkages within the starch structure. Rats fed a high-carbohydrate diet higher in resistant starches exhibited less weight gain and better insulin sensitivity than those on a simple starch diet (24, 64, 150).

**Altering dietary protein.** Historically, protein is generally kept consistent in rodent DIO models at ~20% of the dietary energy, and therefore there are relatively few studies that investigate insulin action in which dietary protein has been altered. Rossetti et al. (138) found that male Sprague-Dawley rats were significantly insulin resistant when fed very-high-protein diets (calorically 63.2% and 36.5% protein) because of both a decrease in peripheral glucose uptake and increased HGP. More recently, Solon-Biet et al. (153) explored the metabolic effects of varying dietary protein and showed that diets that were low in protein and high in carbohydrate were associated with improved glucose tolerance in mice despite the high-protein-fed mice being leaner. This investigation also indicated that, when faced with low levels of dietary protein, rodents compensate by overconsumption to reach their protein target. This has implications when diets that differ greatly in protein content are compared.

The source of protein in synthetic diets has also been shown to influence insulin action. Animals fed fish protein have been shown to have enhanced systemic insulin sensitivity compared with those fed primarily casein or soy (92), and protein from specific fish species such as salmon may particularly promote insulin sensitivity (129). Others have shown that, in combination with a high-sucrose diet, replacing the source of dietary protein from casein to soy has beneficial effects on insulin resistance and dyslipidemia (115). The reasons why proteins from different sources may have differential effects on insulin sensitivity remain poorly understood. Early work suggested a link with GLUT4 translocation in muscle (92). This may be due to the differential effect of specific amino acids on the amino acid-sensing kinases, mammalian target of rapamycin and S6 kinase, that have been shown to interact with the canonical insulin-signaling cascade (31, 180, 192). There is also emerging evidence that circulating levels of branched-chain amino acids (BCAA) correlate with impaired insulin signaling and action (75, 100, 113). Newgard et al. (113) found that rats fed a HFD supplemented with BCAA had similar glucose tolerance despite decreased adiposity compared with fat-fed controls; however, evidence of the effect of dietary BCAA on insulin action in rodents is limited.

#### GENERAL CONSIDERATIONS IN PLANNING A RODENT DIET STUDY

**Length of diets.** The length of time mice are exposed to different diets for DIO studies varies considerably with common DIO models being fed for between 4 to 16 wk to elicit observable differences in body and fat mass. The different pathologies of the metabolic syndrome occur at different times in this process, with insulin resistance reported to occur quite rapidly between 1 and 3 wk after commencing a HFD. After 1 wk of a HFD, hepatic insulin resistance is detectable through the lack of suppression of hepatic glucose output in a hyperinsulinemic-euglycemic clamp, whereas skeletal muscle insu-

lin resistance was not evident until 3 wk after the diet commenced (86, 124, 179). Visible differences in macrophage “crown-like” structure numbers in adipose tissue take longer to appear and become visible around 5 wk of HFD and continue to increase in number at 10 and 16 wk (94, 179). Adipose tissue inflammation may be responsible for further loss of insulin action after long-term fat feeding (94); however, it is unlikely to be responsible for early lipid-induced insulin resistance because of this timing discrepancy. Interestingly, multiple investigations have found that systemic insulin resistance in C57BL/6J mice as measured by glucose infusion rate during a hyperinsulinemic-euglycemic clamp decreases with fat feeding without further deterioration after 3 wk (124, 179). Pagliassotti et al. (120) found a similar result in high-sucrose-fed rats in which there was no further deterioration of systemic insulin sensitivity after 5 wk of high-sucrose feeding.

Although, a loss of insulin action can take weeks to be observed, there is some evidence suggesting that a proportion of lipid-induced insulin resistance can be reversed by relatively short periods of carbohydrate administration. This can be seen in fat-fed rats given a high-glucose meal the day before a hyperinsulinemic-euglycemic clamp (7, 114). A similar “glucose-priming” effect was seen in dogs administered a duodenal infusion of glucose the morning before a clamp (108). However, others have suggested that this insulin resistance is an adaptive response to high serum free fatty acid levels attributable to a functional glucose/fatty acid cycle and that muscle insulin resistance caused by fat-feeding cannot be reversed in the same way (60). Similarly, mice fed a HFD for 8 wk returned to normal glucose tolerance after a 7-day switch to chow despite having similar adiposity to HFD controls (85).

*Strain comparisons.* When using rodent DIO models it is not uncommon to extrapolate that the metabolic effects of a certain diet are relevant to all strains of mice. However, diverse strains of rodents have been shown to have different metabolic profiles and adapt in different ways to nutrient excess. For example, C57BL/6 mice are the strain used most in metabolism research; however, this strain exhibits smaller reduction in insulin sensitivity (measured by clamp) upon exposure to a HFD compared with the DBA strain (8). BALB/c mice, another common strain, seem to resist the effects of a HFD on glucose tolerance (106). There is also some evidence to suggest that there is a difference in glucose handling between Wistar and Sprague-Dawley strains of laboratory rat (102).

*Sex.* The majority of studies looking at dietary manipulation and metabolism are conducted in male mice. This is due in part to concerns about what impact the estrus cycle might be having on metabolic parameters in females independent of the dietary manipulation and because of the reported protective effect of female hormones on metabolism (25, 117, 136). It has been demonstrated that high-fat or high-sucrose feeding in female premenopausal rats does not produce the same glucose intolerance or insulin resistance as in male rats (3, 67). Increasing plasma free fatty acids using an intralipid infusion also has been shown to cause a decrease in insulin sensitivity in male but not female rats (62). This was suggested to be related to the fact that females have better oxidative stress responses (11, 23, 29), have more mitochondria (3, 80), have better respiratory capacity (80, 110), or that they have a greater capacity to expand fat stores (3). Whatever the reason, this protective effect is lost by removal of the ovaries (136).

*Palatability of diets.* An important consideration when undertaking diet studies is the palatability of the diets. This is especially the case when comparing diets that have different consistency or smell like starch-based diets with HFDs. A significant amount of evidence shows that different carbohydrate and fat formulations are differentially palatable in rodents (147). High-carbohydrate diets that are in a liquid or gel form produce more substantial hyperphagia and weight gain compared with pelleted or powdered dry diets (51, 132, 133), and even powdering food has been reported to negate the body weight changes observed between pelleted low-fat control diets and high-fat and Western diets (47). In the context of a particular diet promoting fat gain to allow examination of the metabolic complications of obesity, it is important to consider how difficult the diet is to consume, as this may not be dependent on the macronutrient content of the particular diet.

Choice of the most suitable control diet is also important. It is very common for a chow diet to be used as a low-fat control diet, as it is a cheaper alternative to a matched semipurified diet. However, the content of chow is often not well defined, and the sources of macronutrients used by different suppliers can vary because of availability and cost. Warden et al. (184) discuss the problems of using chow control diets. However, it is worth noting, as discussed above, that semipurified low-fat control diets generally using starch as the carbohydrate source can produce similar levels of obesity as a HFD if the diet is powdered (47). Because of the different physical properties of carbohydrates and lipids, it is possible that in a dried and pelleted form HFDs are significantly more palatable than high-starch diets.

*Iso-caloric diets.* Because of the differences in energy density between carbohydrate and fats (16 kJ/g carbohydrate, 37 kJ/g fat) (189), comparing HFD with low-fat control diets will result in a HFD that is more calorically dense than the control diet. For this reason, many investigators normalize the energy per gram of the diet by the addition of nondigestible ingredients such as cellulose or inulin. The benefits of this approach are that it provides a more accurate way in which to measure food intake as well as reducing the difference in food volume eaten by feeding diets with different energy densities. However, the effect of large amounts of nondigestible fiber may have effects on the microbiome (32), satiety, gastric emptying, and the incretin response (123) that must be taken into consideration when planning or analyzing results from any dietary study. Altering the diet by the addition of fiber to increase short-chain fatty acid production from gut fermentation has been shown to have beneficial effects on systemic insulin sensitivity (9). Another important key point in designing animal studies is that the diets meet the animal’s minimal nutrient requirements, especially for protein, vitamins, and minerals, to eliminate the possibility of overconsumption of the diet to fulfil needs for specific nutrients.

*Thermoneutrality.* Recently, there has been considerable discussion about the applicability to human diseases of studies using rodents housed at temperatures (19–24°C), which are more attuned to suiting the comfort of the human researchers than the comfort of the rodents. Mice expend a significant amount of energy on thermogenesis at temperatures of 19–24°C that can mask the development of metabolic and other phenotypes that might be central to the aims of the particular study (27). For example, in the case of UCP-1 knockout

animals, a paradoxical phenotype that showed a resistance to HFD was observed at 20°C, but not at 27°C, indicating the relevance of housing temperature to understand the role of UCP-1 in energy balance (98). In another example Castillo et al. (28) reported that mice with deletion of type 2 deiodinase (enzyme in thyroid hormone metabolism) have no phenotype at 22°C but became more glucose intolerant and obese at 30°C on a HFD. Therefore, many are advocating housing mice at “thermoneutral” temperatures (28–34°C), where they expend minimal energy on thermogenesis (99, 101). However, others have argued that mice with adequate nesting material that are group housed may have a much lower thermoneutral housing temperature, approximating 20–22°C (154).

**Hyperinsulinemic-euglycemic clamp procedure.** The hyperinsulinemic-euglycemic clamp in rats (22, 87) and mice (182) was adapted from the human procedure [pioneered by DeFronzo et al. (42)] and is considered the gold standard for assessing insulin sensitivity *in vivo*. In the human procedure, insulin is often infused sequentially at two different rates (2-step clamp), first a lower rate to quantify the contribution of HGP and then a higher rate in which it is assumed that HGP is completely suppressed to assess the contribution of the periphery. In comparison, the rodent model generally utilizes the infusion of radioactive glucose tracers to measure HGP (either by isotope dilution or disappearance of a tracer bolus) and therefore is generally conducted at only one rate of insulin infusion. However, it is worth considering that, at high insulin doses, HGP may be completely suppressed; therefore, when one is trying to discern differences in hepatic insulin sensitivity, it may be beneficial to utilize a lower insulin infusion rate (121, 152). Ayala et al. (4, 5) provide an in-depth investigation into these considerations when designing a clamp study in mice, including insulin doses, use of anesthesia, and site of blood sampling. Standard operating procedures for the hyperinsulinemic-euglycemic clamp in mice (5) and rats (70) have been described in detail. As with the other considerations outlined in this review, in the designing of clamp studies in rodents, some thought should be given to whether the primary outcome required from the procedure is accurate assessment of hepatic or peripheral insulin sensitivity.

## CONCLUSIONS

The heterogeneity of metabolic phenotypes reported in the literature for HFD models of DIO (outlined in Table 1) may be in part due to the disparity in percentage of fat content (ranging from ~45% all the way up to 95%) and the specific source of fat. There continues to be no standardized definition of a HFD; however, it is quite clear that diets with a fat content >40% promote systemic insulin resistance in all of the studies reviewed here (Table 1). These include both studies using chow and semipurified diets as a control. There may be an inverse relationship between the percentage of fat in the diet and insulin sensitivity; however, as the VHFDs generally have substantially reduced protein content, it can be hard to make a conclusion about the importance of the excess of one macronutrient over the lack of another. The evidence is less clear with the high-sucrose/fructose diets, which seem to have a clear negative effect on hepatic insulin sensitivity but may not have as strong an effect on peripheral glucose disposal as a more traditional HFD. A summarized graphical depiction of

the studies investigated in Table 1 comparing the peripheral and hepatic effects of varying diets on insulin sensitivity is illustrated in Fig. 1.

Clearly, the molecular mechanisms that govern insulin sensitivity in humans are still not well understood. We believe that human research in this field is of vital importance; however, because of the difficulties and ethical problems that result in giving unhealthy diets to humans for long periods of time, it is still almost impossible to conduct well-controlled dietary studies in humans that require one group to gain weight or impair metabolic health. This can result in particular research areas in which human data present particularly conflicting results, such as the effect of dietary sugar on insulin action. Although rodent experiments show clear detrimental effects of high dietary sucrose/fructose on insulin sensitivity, human studies have been much more mixed, potentially attributable to fears about leaving humans on unhealthy diets for long periods of time or to rodents having a higher dietary sugar percentage (40). The use of rodents to model the metabolic effect of diets on humans remains controversial, with some groups seeing no translatable potential (90). However, rodents remain a useful tool to investigate the mechanisms that drive insulin resistance, which we know is an evolutionary conserved phenomenon present in mammals and some nonmammal vertebrates (58, 194). Rat and mice dietary models investigating insulin action are therefore still required, as they have more relevance to human diet-induced metabolic syndrome than monogenic models of insulin resistance and provide important tools for the evaluation of novel therapeutic agents for insulin resistance and type 2 diabetes. However, the field is moving away from focusing solely on the idea that HFDs generate a generic and equivalent insulin resistance. An array of different diets that affect insulin

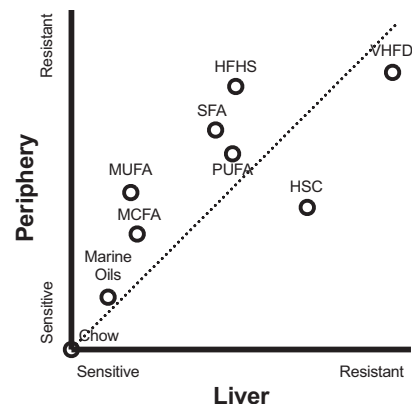


Fig. 1. A comparison of peripheral and liver insulin sensitivity between different diets. This graph is a visual depiction of the hepatic glucose production (HGP) and glucose infusion rate (GIR) values from Table 1, averaged between studies using the same broad diet classifications. The x and y axes rank diets based on their average HGP (liver) and GIR (periphery) from insulin sensitive to insulin resistant. As the HGP is a function of GIR and rate of glucose disappearance, this graph is not meant to describe whether a specific diet produces greater insulin resistance in the liver compared with the periphery; rather it is a comparison between different diets. The data depicted are an average between different investigations with varying dietary makeups, rodent strains, length of diets, and many other differences and should not be taken as a true comparative study [of which several exist in the literature (116, 158)]. VHFD, very-high-fat diet; HFHS, high fat, high sucrose; SFA, saturated fatty acids; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; HSC, high simple carbohydrate (sucrose/fructose); MCFA, medium-chain fatty acids.

action in both negative and positive ways are now being used, including variations in protein type and content to create a new dimension in the macronutrient composition of diets (153). These ongoing and future studies will hopefully provide a new perspective on the effects of diet on metabolic health in rodents, which may translate to better health outcomes in humans.

## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

## AUTHOR CONTRIBUTIONS

L.S. conceived and designed research; L.S. analyzed data; L.S. prepared figures; L.S., A.E.B., and G.J.C. drafted manuscript; L.S., A.E.B., N.T., and G.J.C. approved final version of manuscript; A.E.B., N.T., and G.J.C. edited and revised manuscript.

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