

Diet-Induced Metabolic Syndrome in Rodent Models

A discussion of how diets made from purified ingredients influence the phenotypes of the MS in commonly used rodent models.

**Angela M. Gajda, MS, Michael A. Pellizzon, Ph.D.,
Matthew R. Ricci, Ph.D. and Edward A. Ulman, Ph.D.**

A quick look at a crowd of people shows that many of our fellow humans are carrying around too much excess weight. The prevalence of obesity is at epidemic levels in the developed world, and obesity may be the root cause of or precursor to other diseases such as insulin resistance, abnormal blood lipid levels (hypertriglyceridemia and reduced high density lipoprotein cholesterol), and hypertension (high blood pressure). The term 'metabolic syndrome' (MS) is used to describe the simultaneous occurrence of these diseases and people with the MS are at increased risk for type 2 diabetes, cardiovascular disease, cancer, and non-alcoholic fatty liver disease. It is estimated that individuals with the MS spend over \$4000 per year in treatment and to make matters worse, the prevalence of the MS is growing at an alarming rate, even in obese children.

Like many diseases, the risk of developing the MS will depend upon the interaction of one's genes and their environment. Since the genetic make-up, or genotype of the human population has not changed over the past several decades, we must look to the environment as the main cause of the increase in metabolic disease during this time frame. To be sure, decreased daily physical exercise (and fewer calories expended) plays an important causal role. Research has shown that increased exercise can ameliorate or even reverse the progression of diseases that make up the MS.

On the other side of the energy balance equation is the food that we eat. From an evolutionary point of view, it has been argued that obesity and other 'diseases of excess' are in fact the natural outcome of eating too many calories. During the evolutionary process, because the food supply

was not stable and periods of starvation were common, it was advantageous to have genes that allowed for the efficient storage of excess calories as fat, given the uncertainty of when the next meal would come. In our present society, the problem is that we still have those 'thrifty genes' but also have a variety of foods that are high in saturated fat, simple sugars, and salt. Unfortunately for us, many of these foods are inexpensive and highly accessible (not to mention very tasty), and we find them easy to consume in excess, leading to disease and most likely early death. On the flip side of caloric intake coin is the very interesting finding that long-term restriction of calories prolongs the lifespan.¹ This concept that nutrients can change our biology or phenotype, called nutriphenomics, is very important and brings together many disciplines — physiology, endocrinology, and molecular biology to name a few — in the pursuit of how the nutrients we eat can affect biological outcomes.

The costs of treating the MS are clearly growing, and it is no surprise that the research community is seeking animal models that mimic the human phenotype so that potential therapies can be tested. Because of the pivotal role that diet plays in causing the MS in humans, most metabolic disease animal models do (and we believe should) use diet as a way to precipitate this syndrome. Though this was not the case decades ago, today, most diet-driven animal disease models are generated using open source, purified ingredient diets. The open source nature of purified ingredient diets allows researchers around the world to compare data from different studies, since the diet formulas are generally freely available to the public (this is in contrast to chow diets, which are generally 'closed,' meaning the formulas are gen-

erally kept secret). In addition, purified ingredient diets have very little variability from batch to batch (compared to chows), and so help to minimize data variability. Since the ingredients used are so highly refined, purified diets lack the hundreds of plant-derived phytochemicals that are found in grain-based chow diets. Some of these compounds, in particular the phytoestrogens, are known to affect disease progression² and so are usually unwanted variables. Finally, purified ingredient diet formulas can be easily modified so that researchers can intentionally and specifically change one ingredient at a time, allowing them to study the effects of large or small changes in the nutritional quantity and quality of the diet. Because of these advantages (being able to report, repeat, and revise the diets), most metabolic disease animal research uses (and in fact requires) purified ingredient diets. For an expanded discussion of diets, see our previous article in this publication.³ In this brief review, we discuss how diets made from purified ingredients influence the phenotypes of the MS in commonly used rodent models.

High-Fat Diets for Diet-Induced Obesity Models

In order to gain a greater understanding of human obesity, rats and mice are commonly used models as they will readily gain weight when provided with a high-fat diet and also develop other risk factors associated with the MS.

Numerous high-fat rodent diets are available from commercial vendors. Not all high-fat diets are the same, since both the level and source of fat may differ between diets. While most obesity research is being conducted with purified ingredient diets, some studies use a mixture of chow plus added fat. This can lead to nutritional inadequacies, since as more and more fat is added to a chow, the other nutrients (protein, vitamins, minerals, and fiber) are diluted. The addition of too much fat can actually render the final diet protein deficient, which is clearly not the intention when feeding a high-fat diet.

When choosing a purified ingredient diet with elevated fat, the level of fat in the diet should be taken into consideration. While these terms do not have strict definitions, low-fat diets (LFD) have about 10% of

Brief Summary of Diet-Induced Metabolic Disease Models

Type of Diet	Strain	Phenotype	Comments	References
Purified ingredient diet, 30-60 kcal% fat with various fat sources	SD rat, Wistar rat	Obesity	BW differences between DR and DIO rats apparent between 2-10 weeks on diet. Fat type can impact weight gain.	4, 15, 16
Chow with added fat to equal 48 kcal% fat	ZDF rat	Obesity and diabetes	Males develop diabetes on standard chow, but disease is more robust on higher fat diets. Females require diet with at least 48 kcal% fat to develop diabetes.	18, 19
Purified ingredient diet, 45-60 kcal% fat with various fat sources	C57BL/6 mice	Obesity/hyperglycemia	BW differences between high fat and low fat diets groups appear as early as 1 week on diet. Hyperglycemia occurs around 4 weeks.	11, 21
Purified ingredient diet, 10 or 58 kcal% fat with various fat and CHO sources	A/J mice	Obesity resistance	Do not become obese despite caloric intake similar to C57BL/6 mice.	21, 22
Purified ingredient diet, 10 or 58 kcal% fat with various fat and CHO sources	AKR mice	Obesity and insulin resistance	Become obese on high fat diets. They are more glucose tolerant but more insulin resistant, compared to C57BL/6 mice.	11, 22
Purified ingredient diet, 32 kcal% fat	SD rat	Hypertension	Hypertension and obesity developed after 10 weeks on high fat diet.	66
Purified ingredient diet, 8% NaCl	Dahl SS rat	Hypertension	Hypertension developed after 2-4 weeks on diet.	59-62
Purified ingredient diet, 60% fructose	SD rat, Wistar rat	Hypertension	Hypertension developed after 6-8 weeks on diet.	67
Purified ingredient diet, 60 - 70 kcal% Sucrose	SD rat, Wistar rat	IR/hypertriglyceridemia	Both IR and hypertriglyceridemia after 2 weeks on diet.	47,48
Purified ingredient diet, 60 - 70 kcal% Fructose	Golden Syrian Hamster	IR/hypertriglyceridemia	Both IR and hypertriglyceridemia after 2 weeks on diet.	54
Purified ingredient diet, high saturated fat, 1% cholesterol, 0.25% cholic acid	C57BL/6 mice	Atherosclerosis/ Hypercholesterolemia	Hypercholesterolemia and mild atherosclerosis after 14-18 weeks on diet.	26, 27
Purified ingredient diet, 0.1 - 1.25% cholesterol	LDL receptor KO, apolipoprotein E KO	Atherosclerosis/ Hypercholesterolemia	Hypercholesterolemia and atherosclerosis after 12 weeks on diet.	29-31
Purified ingredient diet, high in saturated fat, 0.05 - 1% cholesterol	Golden Syrian Hamster	Atherosclerosis/ Hypercholesterolemia	Hypercholesterolemia and atherosclerotic after 6 weeks on diet.	38, 40
Purified ingredient diet, high saturated fat, ~0.3% cholesterol	Hartley Guinea Pigs	Atherosclerosis/ Hypercholesterolemia	Hypercholesterolemia and atherosclerosis after 12 weeks on diet.	43, 44

the calories coming from fat, high-fat diets (HFD) have about 30-50% of the calories coming from fat, and very high-fat diets (VHFD) generally contain greater than 50 kcal% fat. For comparison, most low-fat chow diets contain 10-12% of the calories from fat. To induce obesity, both HFD and VHFD are used, and there is a dose-response for body weight as a function of dietary fat.⁴ When studying the influence of a drug, nutraceutical, or gene mutation on obesity, one must consider that it may be more difficult to reverse the drive to obesity on a VHFD, whereas something like compound efficacy may be more detectable when used in conjunction with a HFD.

The source of dietary fat is also important. As one researcher has said, "Oils ain't oils,"⁵ meaning all fats are not equal in terms of the phenotype they produce. For example, when rodents were fed purified ingredient diets with similar amounts of fat, those fed diets with fish oil did not gain as much weight and were more insulin sensitive compared to those fed saturated fats (SF).⁶⁻⁸ However, not all studies support this and it may depend on dietary fat level and gender.^{6,9}

Most rodents tend to become obese on HFD and VHFD, but there can be variable responses in glucose tolerance, insulin resistance (IR), triglycerides (TG), and other parameters depending on the strain and gender.^{10,11} and source of dietary fat.⁶⁻⁸ Outbred Sprague-Dawley and Wistar rats have a variable response to a HFD (32 or 45 kcal% fat) such that some animals rapidly gain excess weight while others gain only as much weight as they would on a LFD. At first, this research was done with chow-based diets¹² but purified ingredient diets were developed¹³ which now researchers commonly use to separate the rats into diet-induced obese (DIO) and diet-resistant (DR) groups.¹⁴⁻¹⁶ Furthermore, the outbred Sprague-Dawley DIO and DR rats have been selectively bred over time such that their future body weight response to a HFD is known in utero, allowing the researcher to look early in life (prior to the onset of obesity) for genetic traits that may later predispose them to their DIO or DR phenotypes.^{10,17} For researchers interested in an obesity and type 2 diabetes rat model, the inbred obese Zucker diabetic fatty (ZDF) rat is available. The males become obese and diabetic on a LFD, but HFD feeding promotes more robust disease. The female ZDF rat is unique in that while they are obese, they do not develop diabetes unless fed a diet (in this case, chow-based) containing 48 kcal% fat.¹⁸ The prolonged period of insulin sensitivity prior to the onset of diet-induced diabetes allows the researcher more time to study

female ZDF rat in a pre-diabetic state.¹⁹

Different strains of mice show variability in weight gain on a purified ingredient VHFD (~60% by energy).²⁰ Some inbred strains such as the C57BL/6 or AKR mouse are quite susceptible to obesity on a VHFD,¹¹ while mice of the A/J and SWR/J strains tend to be resistant to obesity.^{21,22} However, strains that may exhibit similar levels of obesity may have varied metabolic responses. For example, C57BL/6 mice will become obese on a VHFD and are more glucose intolerant while obese AKR mice become more insulin resistant.¹¹

Diets High in SF and Cholesterol for Hypercholesterolemia and Atherosclerosis

Humans with the MS are more prone to developing atherosclerotic cardiovascular disease (ASCVD). It is believed that an increased intake of SF and cholesterol, which raise the levels of circulating total cholesterol (TC) and low density lipoproteins (LDL-C),^{23,24} increases the risk of ASCVD. As with humans, a purified ingredient HFD (with much as SF), and cholesterol (~0.2% by weight), commonly referred to as a 'Western diet,' can elevate TC and LDL-C and in turn cause atherosclerosis in certain rodent models.

Careful choice of the animal model is always crucial for any experiment and a good example of this is seen with the diet-induced development of atherosclerosis in rodents. Normal mice and rats have traditionally not been ideal models of cardiovascular disease research since they typically have very low levels of TC and LDL-C but high levels of high density lipoprotein cholesterol (HDL-C). This is in contrast to humans in whom the reverse is true. The ability of rats and mice to maintain their cholesterol profile (which is thought to be athero-protective) even in the face of high-cholesterol diets²⁵ means that very little actual atherosclerosis develops. In order to 'force' the atherosclerosis phenotype on normal rats and mice, it is usually necessary to combine high concentrations of dietary cholesterol with 0.25%-0.5% cholic acid (a bile acid which promotes fat and cholesterol absorption from the intestine).^{26, 27} Researchers should be aware that since cholic acid can also promote liver inflammation, decrease bile acid production, and alter circulating TG and HDL-C,^{26,28,29} it may independently affect the development of atherosclerosis.

The ability to change the genetic make-up of mice and produce 'transgenic' or 'knockout' mice has allowed for the development of many interesting and useful disease models. Genetically modified

mice such as those with mutations that slow the removal of LDL-C from the blood have led to more 'human-like' models which can show significant elevations in circulating LDL-C. These models in turn can develop mature atherosclerotic lesions when fed purified ingredient high cholesterol diets without the need for dietary cholic acid.²⁹ Some of these knockout mouse models (such as the LDL receptor knockout and the Apolipoprotein E knockout) can be very responsive to elevations in dietary cholesterol (0.15% - 1.25%) and can have significant elevations in both plasma LDL-C and atherosclerotic lesions after being fed for 12 weeks.²⁹⁻³² Even in these susceptible knockout mice, the source of fat can be used to further modify the phenotype to the researcher's advantage. For example, diets high in monounsaturated fats (i.e. olive oil) promoted more atherosclerosis than those high in SF (i.e. coconut oil) and polyunsaturated fats (PF) (i.e. corn oil, safflower oil) in LDL receptor knockout mice.³³

Another model of atherosclerosis that has been used frequently is the Golden Syrian hamster. Like rats and mice, these animals normally have high levels of HDL-C, but in contrast, dietary cholesterol (~0.1%) can significantly elevate LDL-C and like humans, SF can increase these levels further.^{34,35} The combination of high dietary SF and cholesterol is commonly used to promote atherosclerosis in these animals³⁶⁻³⁸ and atherosclerotic lesions similar to those found in humans can be found after prolonged feeding periods.³⁹ Actually, cholesterol itself may not always be necessary for this phenotype, since a purified diet with no cholesterol but high concentrations of SF (as hydrogenated coconut oil) can promote more aortic cholesterol accumulation compared to a diet with both cocoa butter and 0.15% cholesterol.⁴⁰ This was despite the fact that both groups had similar levels of LDL-C, suggesting that the type of fat may play an important role in atherosclerosis formation in the hamster.

Guinea pigs are often used for lipid research, since unlike rats, mice, and hamsters, they begin with a cholesterol profile similar to humans (higher in LDL and lower levels of HDL-C), and also possess other human-like traits of cholesterol metabolism.⁴¹ As with hamsters, diets high in SF will elevate TC and LDL-C levels relative to those fed high levels of PF; the addition of cholesterol can promote further elevations.⁴² Atherosclerotic lesions and aortic cholesterol accumulation can develop when high levels (~0.33%) of dietary cholesterol are fed.^{43,44}

High Fructose/Sucrose Diets for Hypertriglyceridemia and Insulin Resistance in Rodents

Because it is so sweet and inexpensive, high fructose corn syrup (HFCS) is used in many processed foods which humans eat and recent surveys in humans have suggested that carbohydrate intake is on the rise. As we have learned over the past few decades, an increased intake of refined carbohydrates, such as HFCS and the disaccharide sucrose (which is composed of fructose + glucose), is associated with increased weight gain, elevated circulating TG levels, and insulin resistance (IR) in humans and animal models.^{45,46} In rodent models, purified diets containing high fructose or sucrose elevate TG and glucose production in the liver and this increased availability of nutrients ultimately leads to IR and hypertriglyceridemia.^{45,46} Typically, low-fat chow diets contain about 4% sucrose and < 0.5% free fructose. Low-fat purified diets can contain higher levels of sucrose and this will depend heavily on the formula being used.

The Sprague-Dawley and Wistar rat are established models of sucrose-induced IR and hypertriglyceridemia.⁴⁷⁻⁴⁹ Both of these phenotypes can develop within two weeks when these animals are fed a diet containing 65% sucrose (by weight) relative to one with 65% corn starch.⁴⁷ It seems that the fructose component of sucrose is largely responsible for the hypertriglyceridemia and IR produced by high sucrose diets.⁵⁰⁻⁵² Unless fed for a prolonged period of time, these high fructose/sucrose diets do not appear to lead to excessive weight gain.⁵³

Similar to rats, hamsters fed high fructose diets (~60% of energy) may develop IR and elevations in TG after only two weeks compared to diets low in fructose.^{54,55} Interestingly, hamsters fed high-sucrose diets did not have elevated TG levels and developed only mild IR relative to those fed diets high in fructose.⁵⁴ Since sucrose is one-half fructose, it appears that the level of dietary fructose is quite important in the rapid development of IR and elevated TG in hamsters.

In contrast to rats and hamsters, the mouse is used less frequently as a model for sucrose/fructose-induced IR and hypertriglyceridemia. The response to high fructose/sucrose diets is very strain-dependent in the mouse⁵⁶ and commonly used strains like the C57BL/6 mouse either do not develop IR or develop IR slowly.^{56,57} However, the mouse genome is easier to manipulate than that of the rat and several knockout models (that are prone

to develop atherosclerosis) do show TG responses to high dietary fructose.⁵⁸

Diets High In Sodium (and Fructose) For Hypertension

The causes of hypertension in humans are not fully understood but are correlated with sodium chloride (NaCl) intake, obesity, insulin resistance and of course, genetics. The rat is the historically preferred small animal model for diet-induced hypertension, perhaps because of its size, the amount of physiological data available, and robust blood pressure response that some strains present.

Both the level of dietary NaCl and the background diet are important in generating a hypertensive phenotype in the rat. Typical purified ingredient diets contain about 0.1% Na, while chow diets contain about 0.3-0.4% Na. Both types of diets have been modified to contain increased NaCl to study hypertension. The Dahl salt-sensitive rat shows a significant rise in blood pressure within 2-4 weeks after being fed a purified diet containing 8% NaCl.⁵⁹⁻⁶² Lower levels of NaCl (4%) will still raise blood pressure⁶³ and this is reported to occur at a slower rate.¹⁹ This rise in blood pressure can be attenuated by the addition of extra vitamin E to the diet.⁶⁴ Similar to findings in humans, hypertension due to an 8% NaCl diet can be prevented by supplementing the diet with extra potassium,⁵⁹ suggesting that diets low in potassium may aid in the promotion of hypertension. Thus, diet can be used to both induce and attenuate hypertension in the Dahl SS rat.

The diet to which the NaCl is added also affects the level of hypertension and concurrent kidney damage. When 4% NaCl was added to both a chow diet and a purified ingredient diet, Dahl SS rats fed the purified diet had higher blood pressure and more renal damage compared to chow-fed rats.⁶⁵ Of equal interest is the finding that offspring from parents who were fed the 4% NaCl purified diet had higher blood pressures regardless of the diet they were fed after weaning, suggesting that the diet fed to the mother during pregnancy can promote hypertension in the offspring. How does the background diet (chow vs. purified) affect the outcome in this case? The reasons are not clear but may be related to fundamental differences between chows and purified diets in their protein sources, presence or absence of phytochemicals, level and type of fiber, carbohydrate type, and/or the level of minerals such as potassium.

Outbred rat strains such as the Sprague-Dawley

(which is in widespread use for obesity research) can develop hypertension on high NaCl diets, and this usually occurs over a longer time period (compared to Dahl SS rats) or concurrent with the development of obesity.⁶⁶ Interestingly, diets with normal levels of NaCl but high in fructose (around 60% of calories) will also increase blood pressure^{67,68} and produce signs of kidney damage in both Sprague-Dawley and Wistar rats.⁶⁷⁻⁶⁹ Such high fructose diets also cause IR⁶⁹ (see section on high fructose diets) and this may in fact have a role in causing the hypertension.⁷⁰

Even in a spontaneous rat model of hypertension, (such as the spontaneously hypertensive rat [SHR] which will develop hypertension on a variety of diets), diet can be used to modify the onset or degree of this disease. For example, dietary supplementation with antioxidants (such as vitamins E and C) can lower blood pressure in stroke-prone, SHR.⁷¹

As mentioned earlier, the mouse is not as widely used for the study of diet-induced hypertension. Inbred mice such as the C57BL/6 can develop elevated blood pressure on purified diets high in NaCl (8%), though the time frame for this appears to be on the order of several months.⁷²

It should be clear that in order to develop and study an animal model of the MS, special diets are needed. Purified ingredient diets are ideally suited to this task, since they can be intentionally modified to meet researcher's needs, contain little to no extraneous compounds, and have very little variation from batch to batch. Though it is well-known to most researchers, it is worth stating that no phenotype is guaranteed and that careful choice of the species/strain and adequate control over environmental variables will be extremely important in generating and repeating data. In this article, we have briefly covered only some of the disease models that can be induced by diet. What should be clear is that while some dietary factors promote one specific phenotype (i.e. sodium induces hypertension), others may promote multiple phenotypes. Examples include the use of high-fat diets to induce obesity, IR, and hyperglycemia and using high fructose diets to promote IR, hypertriglyceridemia, and hypertension. This simultaneous development of disease should not be very surprising given the complex interactions and causal relationships between these diseases. At present, diet-driven animal models of the MS are still developing and there may not be one single model that will satisfy all metabolic disease research needs.

However, the demand for a diet-driven MS animal model is relatively new. Ongoing research using different species/strains along with existing and new purified ingredient diet formulations should lead to the development of more and more useful MS phenotypes.

Angela M. Gajda, M.S. is Project Development and Management Specialist for Research Diets, Inc. She can be reached at Gajda@ResearchDiets.com.

Michael A. Pellizzon, Ph.D. is Project Manager and Scientist for Research Diets, Inc. He can be reached at Pellizzon@ResearchDiets.com.

Matthew R. Ricci, Ph.D. is Vice-President, Science Director of Research Diets, Inc. He can be reached at Ricci@ResearchDiets.com.

Edward A. Ulman, Ph.D. is President of Research Diets, Inc. He can be reached at Ulman@ResearchDiets.com.

Research Diets, Inc. 20 Jules Lane, New Brunswick, NJ 08901
www.ResearchDiets.com

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