High-Fat Diets for Diet-Induced Obesity (DIO) Models

2017- Brief Scientific Literature Review
Hyeran Jang, Ph.D, Scientist, Research Diets, Inc.

Genetic and environmental factors play a role in the development of obesity, and diet is one of the main environmental factors that contribute to obesity and its related metabolic diseases. Human studies have shown that increased fat intake is associated with body weight gain which can lead to obesity and other related metabolic diseases. As such, animal rodent models are useful tools to determine the mechanistic aspects of obesity and to develop therapeutic approaches as they will readily gain weight when fed high-fat diets (1, 2). Here, we discuss important factors to consider when designing a diet-induced obesity study using animal models.

Matched Formulas

When planning a diet-induced obesity study, the composition of the high-fat diet deserves special attention. All too often in the literature, one will find that diets used in the experiments are not well matched, thereby introducing a number of confounding factors. For example, in many cases a grain-based (GB) diet is used as a low-fat "control" diet for a purified high-fat diet. GB diets contain plant-derived ingredients which are subject to fluctuations in the growing season and will vary in composition at the time of harvest. Thus, the nutritional composition of GB diet formulas may differ based on the types of ingredients used during manufacturing. Purified ingredients, on the other hand, are highly refined and contain one primary nutrient (i.e. corn starch for carbohydrate, soybean oil for fat). These ingredients have little variability and therefore provide consistency between batches. There are numerous differences between GB and purified diets, introducing countless variables during the data analysis, thus making it difficult to interpret the results when these diets are used together in a study (3). In addition, GB diets contain plant-based compounds such as phytoestrogens which have been shown to reduce the degree of weight gain (4) compared to purified diets. For these reasons, a properly matched control diet should be low in fat (and higher in carbohydrate) while matched in every other way to the high-fat diet. In practical terms, since most high fat diets being used today are made with purified ingredients, this means using a properly matched, low-fat purified ingredient diet as the control and not a GB diet.

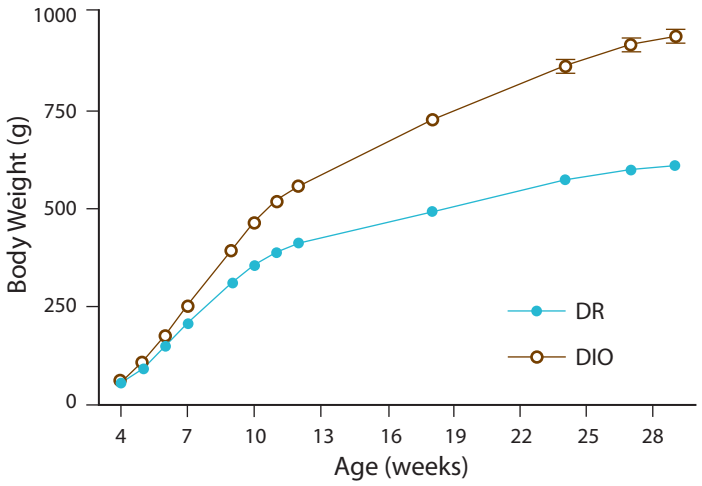

FIGURE 1. Growth rate of DIO (n = 12) and DR (n = 12) rats fed D12451 HFD (45 kcal% fat) diet used in meal analysis. Values are means ± SEM. Body weights are significantly different at all time points ($p < 0.05$). Graphic representation - for details see reference (34).

Calories from Fat

High-fat diets used in laboratory research typically contain approximately 32% to 60% of calories from fat. From a nutritional perspective, a human diet of 60 kcal% fat would be considered extreme and physiologically irrelevant. That said, diets with 60 kcal% fat are commonly used to induce obesity in rodents when it is desired to promote weight gain in a short time since animals tend to gain more weight faster (5, 6), thereby allowing researchers to establish obesity-related disease models quickly and to screen their test compounds in a shorter period of time. Thus, arguments may be made for choosing to use either a very high-fat diet for rapid weight gain or a more moderate fat diet for slower weight gain to mimic human dietary fat consumption. It should also be noted that when studying the effects of a drug, bioactive food compound, nutraceutical, or genetic modification on obesity, it may be more difficult to prevent or reverse the effects of a very high-fat diet with the dietary/genetic modification, whereas it might be possible to see the effects of a therapy when using a diet containing a lower percentage of fat (i.e. 45 kcal%).

Type of Fat

The type of fat used for the research should be considered when choosing a high-fat diet for an animal study because the fatty acid composition of the diet can affect study outcomes. Many high-fat diets used in laboratory animal research typically contain high saturated fat sources such as lard, beef tallow, coconut oil, or milk fat, or trans-fat such as hydrogenated vegetable oils, and these diets are quite capable of inducing obesity and metabolic diseases in susceptible strains (7-10). In contrast, oils rich in n-3 fatty acids and monounsaturated fatty acids (MUFAs) have been studied for their health benefits. For example, it has been shown that in animals fed similar amounts of fat, those fed diets containing fish oil did not gain as much weight (11-13) and were more insulin sensitive (14, 15) compared to those fed diets with more saturated fat. Also, a diet rich in n-3 fatty acids and MUFAs has shown to attenuate hepatic steatosis and alter hepatic phospholipid fatty acid profile in diet-induced obese rats (16). Since fatty acids can affect phenotype through a variety of mechanisms such as expression of genes involved in energy regulation and insulin function, eicosanoid production, cytokine production, membrane permeability, and alternation of gut microbiota (17-22), it is important to include information about the type and level of fat used in a study in order to allow other researchers to compare the resulting data.

Animal Models

While most rodents tend to become obese on high-fat diets, there can be variable responses in weight gain, glucose tolerance, insulin resistance, blood lipid profiles and other parameters depending on the strain. Some inbred mouse strains such as the C57BL/6J or AKR/J mice are more susceptible to obesity when fed high-fat diets (23). However, strains that exhibit similar levels of weight gain may show different responses for other parameters. For example, when fed a 58 kcal% fat diet, C57BL/6J mice and AKR/J mice will have similar degrees of weight gain, but C57BL/6J mice are more glucose intolerant compared to AKR/J mice (23). Other strains are simply more resistant to obesity, such as the SWR/J, A/J and BALB/c mice (24-29). Even within the same strain, different phenotypical responses to high-fat diets have been observed between animals bred in different facilities (30).

Rat models including outbred Sprague-Dawley and Wistar rats are popular strains to study obesity as they readily gain weight on high-fat diets. Interestingly, these strains are known to have a variable weight gain response to high-fat diets (31, 32), with some animals rapidly gaining weight while others gain only as much weight as those fed a low-fat diet (33, 34). This variation in weight gain is thought to mimic the diverse spectrum of human obesity and is an attractive model for some researchers. In fact, Sprague-Dawley rats have been selectively bred over time to study the genetic traits of animals where the obese or lean phenotype on a high-fat diet is known from birth (33). Additionally, and in contrast to a C57BL/6J mouse model, body weight gains in these rat strains are often not very different between 45 and 60 kcal% fat diets, something researchers should consider when selecting diets for these strains (35, 36). Another strain, the F344xBrown Norway rat, has been used as an obesity model for human aging since the animals gain weight until about 30 months of age, then level off, which is similar to the weight gain pattern in the average person (37).

There has been a growing body of literature using rodents as models of human obesity, even though there are many confounding factors including species, strain, age of the animals, type of diet, level of fat, and type of control diet. Fortunately, there is a growing discussion about these issues which will help scientists design studies with tighter controlled conditions and therefore improve our understanding of obesity and related diseases.

Rodent models of diet-induced obesity continue to be widely used, valuable tools to study the mechanisms of human obesity. When designing a research study using animal models to analyze the mechanisms of human obesity, two key considerations should govern the discussion. The first factor to consider is the animal model itself- the benefits and limitations that a specific animal model will provide the study. Researchers need to also pay careful attention to the diets they choose in order to meaningfully interpret their data. Of key importance when considering the diet component in any high-fat diet (or other nutritional intervention) study is the use of a properly matched control diet which allows the researcher to assign reasons for phenotypic differences to specific dietary variables (38).

The "Original" High-Fat Diets

Research Diets, Inc. formulated the "original" high-fat diet for diet induced obesity (DIO) studies in 1996. Today, our high-fat diets are the research standard for DIO mice worldwide.

(DIO) Formulas

Product #	D12451		D12492	
	gm%	kcal%	gm%	kcal%
Protein	24	20	26	20
Carbohydrate	41	35	26	20
Fat	24	45	35	60
Total		100		100
kcal/gm	4.73		5.24	
Ingredient	**gm**	**kcal**	**gm**	**kcal**
Casein, 80 Mesh	200	800	200	800
L-Cystine	3	12	3	12
Corn Starch	72.8	291	0	0
Maltodextrin 10	100	400	125	500
Sucrose	172.8	691	68.8	275
Cellulose, BW200	50	0	50	0
Soybean Oil	25	225	25	225
Lard	177.5	1598	245	2205
Mineral Mix S10026	10	0	10	0
DiCalcium Phosphate	13	0	13	0
Calcium Carbonate	5.5	0	5.5	0
Potassium Citrate, 1 H2O	16.5	0	16.5	0
Vitamin Mix V10001	10	40	10	40
Choline Bitartrate	2	0	2	0
FD&C Red Dye #40	0.05	0		
FD&C Blue Dye #1			0.05	0
Total	**858.15**	**4057**	**773.85**	**4057**

Formulated by E. A. Ulman, Ph.D., Research Diets, Inc., 1/18/96 and 8/26/98. Contact us for matched control diets.

Incorporate Test Compounds

Research Diets, Inc. will incorporate your test compound into pelleted diets for simple, safe dosing. Feeding test compounds eliminates dosing related stress to the animal, eliminates vehicle effects, and saves time and labor. Consult with one of our scientists on the formula, determine the dosage required and the diet will be produced and shipped in 5 to 7 business days.

OpenSource DIETS®

Report ▸ Repeat ▸ Revise

Scientists Helping Scientists Control Their Research

. . . Let's start the conversation

References - Obesity

1. Buettner R., Scholmerich J. and Bollheimer L.C. High-fat diets: modeling the metabolic disorders of human obesity in rodents. Obesity (Silver Spring) 15: 798-808, 2007.
2. Van Heek M, Compton D.S., France CF, Tedesco RP, Fawzi AB, Graziano MP, Sybertz EJ, Strader CD and Davis HR, Jr. Diet-induced obese mice develop peripheral, but not central, resistance to leptin. J Clin Invest 99: 385-390, 1997.
3. Warden C.H. and Fisler J.S. Comparisons of diets used in animal models of high-fat feeding. Cell Metab 7: 277, 2008.
4. Cederroth C.R., Vinciguerra M., Kuhne F., Madani R., Doerge D.R., Visser T.J., Foti M., Rohner-Jeanrenaud F., Vassalli J.D. and Nef S. A phytoestrogen-rich diet increases energy expenditure and decreases adiposity in mice. Environ Health Perspect 115: 1467-1473, 2007.
5. Jiang L, Wang Q, Yu Y, Zhao F, Huang P, Zeng R, Qi RZ, Li W, Liu Y. Leptin contributes to the adaptive responses of mice to high-fat diet intake through suppressing the lipogenic pathway. PLoS One. 4:e6884, 2009.
6. Johnston S.L., Souter D.M., Tolkamp B.J., Gordon I.J., Illius A.W., Kyriazakis I. and Speakman J.R. Intake compensates for resting metabolic rate variation in female C57BL/6J mice fed high-fat diets. Obesity (Silver Spring) 15: 600-606, 2007.
7. Moschonas DP, Piperi C, Korkolopoulou P, Levidou G, Kavantzas N, Trigka EA, Vlachos I, Arapostathi C, Perrea D, Mitropoulos D, Diamanti-Kandarakis E, Papavassiliou AG. Impact of diet-induced obesity in male mouse reproductive system: The role of advanced glycation end product-receptor for advanced glycation end product axis. Exp Biol Med (Maywood). 239:937-947, 2014.
8. Marin V, Rosso N, Dal Ben M, Raseni A, Boschelle M, Degrassi C, Nemeckova I, Nachtigal P, Avellini C, Tiribelli C, Gazzin S. An Animal Model for the Juvenile Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis. PLoS One. 11:e0158817, 2016.
9. Bruce-Keller AJ, White CL, Gupta S, Knight AG, Pistell PJ, Ingram DK, Morrison CD, Keller JN. NOX activity in brain aging: exacerbation by high fat diet. Free Radic Biol Med. 49(1):22-30, 2010.
10. Trevaskis JL, Griffin PS, Wittmer C, Neuschwander-Tetri BA, Brunt EM, Dolman CS, Erickson MR, Napora J, Parkes DG, Roth JD. Glucagon-like peptide-1 receptor agonism improves metabolic, biochemical, and histopathological indices of nonalcoholic steatohepatitis in mice. Am J Physiol Gastrointest Liver Physiol. 302:G762-72, 2012.
11. Ikemoto S, Takahashi M, Tsunoda N, Maruyama K, Itakura H and Ezaki O. High-fat diet-induced hyperglycemia and obesity in mice: differential effects of dietary oils. Metabolism 45: 1539-1546, 1996.
12. Wang H, Storlien LH and Huang XF. Effects of dietary fat types on body fatness, leptin, and ARC leptin receptor, NPY, and AgRP mRNA expression. Am J Physiol Endocrinol Metab 282: E1352-E1359, 2002.
13. Svahn SL, Grahnemo L, Pálsdóttir V, Nookaew I, Wendt K, Gabrielsson B, Schéle E, Benrick A, Andersson N, Nilsson S, Johansson ME, Jansson JO. Dietary Polyunsatu rated Fatty Acids Increase Survival and Decrease Bacterial Load during Septic Staphylococcus aureus Infection and Improve Neutrophil Function in Mice. Infect Immun. 83:514–521, 2015.
14. Buettner R, Parhofer KG, Woenckhaus M, Wrede CE, Kunz-Schughart LA, Scholmerich J and Bollheimer LC. Defining high-fat-diet rat models: metabolic and molecular effects of different fat types. J Mol Endocrinol 36: 485-501, 2006.
15. Ford NA, Rossi EL, Barnett K, Yang P, Bowers LW, Hidaka BH, Kimler BF, Carlson SE, Shureiqi I, deGraffenried LA, Fabian CJ, Hursting SD. Omega-3-Acid Ethyl Esters Block the Protumorigenic Effects of Obesity in Mouse Models of Postmenopausal Basal-like and Claudin-Low Breast Cancer. Cancer Prev Res (Phila). 8:796-806, 2015
16. Hanke D, Zahradka P, Mohankumar SK, Clark JL, Taylor CG. A diet high in α-linolenic acid and monounsaturated fatty acids attenuates hepatic steatosis and alters hepatic phospholipid fatty acid profile in diet-induced obese rats. Prostaglandins Leukot Essent Fatty Acids. 89:391-401, 2013.
17. Clarke SD. Polyunsaturated fatty acid regulation of gene transcription: a mechanism to improve energy balance and insulin resistance. Br J Nutr. 83:S59-66, 2000
18. Giudetti AM, Cagnazzo R. Beneficial effects of n-3 PUFA on chronic airway inflammatory diseases. Prostaglandins Other Lipid Mediat. 99:57-67, 2012.
19. Liu HQ, Qiu Y, Mu Y, Zhang XJ, Liu L, Hou XH, Zhang L, Xu XN, Ji AL, Cao R, Yang RH, Wang F. A high ratio of dietary n-3/n-6 polyunsaturated fatty acids improves obesity-linked inflammation and insulin resistance through suppressing activation of TLR4 in SD rats. Nutr Res. 33:849-58, 2013.
20. Hsueh HW, Zhou Z, Whelan J, Allen KG, Moustaid-Moussa N, Kim H, Claycombe KJ. Stearidonic and eicosapentaenoic acids inhibit interleukin-6 expression in ob/ob mouse adipose stem cells via Toll-like receptor-2-mediated pathways. J Nutr. 141:1260-6, 2011.
21. Camuesco D1, Gálvez J, Nieto A, Comalada M, Rodríguez-Cabezas ME, Concha A, Xaus J, Zarzuelo A. Dietary olive oil supplemented with fish oil, rich in EPA and DHA (n-3) polyunsaturated fatty acids, attenuates colonic inflammation in rats with DSS-induced colitis. J Nutr. 135:687-94, 2005.
22. Caesar R, Tremaroli V, Kovatcheva-Datchary P, Cani PD, Bäckhed F. Crosstalk between Gut Microbiota and Dietary Lipids Aggravates WAT Inflammation through TLR Signaling. Cell Metab. 22:658-68, 2015.
23. Rossmeisl M, Rim JS, Koza RA and Kozak LP. Variation in type 2 diabetes--related traits in mouse strains susceptible to diet-induced obesity. Diabetes 52: 1958-1966, 2003.
24. Surwit RS, Feinglos MN, Rodin J, Sutherland A, Petro AE, Opara EC, Kuhn CM and Rebuffe-Scrive M. Differential effects of fat and sucrose on the development of obesity and diabetes in C57BL/6J and A/J mice. Metabolism 44: 645-651, 1995.
25. Prpic V, Watson PM, Frampton IC, Sabol MA, Jezek GE and Gettys TW. Adaptive changes in adipocyte gene expression differ in AKR/J and SWR/J mice during diet-induced obesity. J Nutr 132: 3325-3332, 2002.
26. Biga PR, Froehlich JM, Greenlee KJ, Galt NJ, Meyer BM and Christensen DJ. Gelatinases impart susceptibility to high-fat diet-induced obesity in mice. J Nutr Biochem. 24:1462-8, 2013
27. Jiang T, Wang Z, Proctor G, Moskowitz S, Liebman SE, Rogers T, Lucia MS, Li J and Levi M. Diet-induced obesity in C57BL/6J mice causes increased renal lipid accumulation and glomerulosclerosis via a sterol regulatory element-binding protein-1c-dependent pathway. J Biol Chem. 280:32317-25, 2005.
28. Gallou-Kabani C, Vigé A, Gross MS, Rabès JP, Boileau C, Larue-Achagiotis C, Tomé D, Jais JP and Junien C. C57BL/6J and A/J mice fed a high-fat diet delineate components of metabolic syndrome. Obesity (Silver Spring). 15:1996-2005, 2007.
29. Neyrinck AM, Van Hée VF, Bindels LB, De Backer F, Cani PD and Delzenne NM. Polyphenol-rich extract of pomegranate peel alleviates tissue inflammation and hypercholesterolaemia in high-fat diet-induced obese mice: potential implication of the gut microbiota. Br J Nutr. 109:802-9, 2013.
30. Pecoraro N., Ginsberg A.B., Warne J.P., Gomez F., la Fleur S.E. and Dallman M.F. Diverse basal and stress-related phenotypes of Sprague Dawley rats from three vendors. Physiol Behav 89: 598-610, 2006.
31. Lauterio TJ1, Bond JP, Ulman EA. Development and characterization of a purified diet to identify obesity-susceptible and resistant rat populations. J Nutr. 124:2172-8, 1994.
32. Chang S, Graham B, Yakubu F, Lin D, Peters JC, Hill JO. Metabolic differences between obesity-prone and obesity-resistant rats. Am J Physiol. 259:R1103-10, 1990.
33. Levin BE, Dunn-Meynell AA, Balkan B and Keesey RE. Selective breeding for diet-induced obesity and resistance in Sprague-Dawley rats. Am J Physiol 273: R725-R730, 1997.
34. Farley C, Cook JA, Spar BD, Austin TM and Kowalski TJ. Meal pattern analysis of diet-induced obesity in susceptible and resistant rats. Obes Res 11: 845-851, 2003.
35. Wilson CR, Tran MK, Salazar KL, Young ME, Taegtmeyer H. Western diet, but not high fat diet, causes derangements of fatty acid metabolism and contractile dysfunction in the heart of Wistar rats. Biochem J. 406:457-67, 2007.
36. Kondoh T, Torii K. MSG intake suppresses weight gain, fat deposition, and plasma leptin levels in male Sprague-Dawley rats. Physiol Behav. 95:135-44, 2008.
37. Scarpace P.J., Matheny M., Moore R.L. and Tumer N. Impaired leptin responsiveness in aged rats. Diabetes 49: 431-435, 2000.

RESEARCH DIETS INC.

OpenSource DIETS®

BioDAQ® INTAKE MONITOR

20 Jules Lane | New Brunswick, NJ 08901 USA | Tel: 732.247.2390 Fax: 732.247.2340

www.researchdiets.com | info@researchdiets.com