High-fat diet-induced obesity in animal models

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Epidemiological studies have shown a positive relationship between dietary fat intake and obesity. Since rats and mice show a similar relationship, they are considered an appropriate model for studying dietary obesity. The present paper describes the history of using high-fat diets to induce obesity in animals, aims to clarify the consequences of changing the amount and type of dietary fats on weight gain, body composition and adipose tissue cellularity, and explores the contribution of genetics and sex, as well as the biochemical basis and the roles of hormones such as leptin, insulin and ghrelin in animal models of dietary obesity. The major factors that contribute to dietary obesity – hyperphagia, energy density and post-ingestive effects of the dietary fat – are discussed. Other factors that affect dietary obesity including feeding rhythmicity, social factors and stress are highlighted. Finally, we comment on the reversibility of high-fat diet-induced obesity.

Dietary obesity: Rats: Mice: High-fat diet

Introduction

Obesity is considered to be a major risk factor for chronic diseases such as CHD and hypertension, type 2 diabetes, and some types of cancer[1]. Its prevalence is increasing, with 400 million obese and 1·6 billion overweight adults around the world[1]. Although genetics plays a role in the regulation of body weight, body size and body composition and the metabolic response to feeding in humans[2–6] and in animals[7,8], the increase in worldwide obesity in a short period of time cannot be explained by genetics; there are individual differences in genetic susceptibility to environmental factors such as diet[2,6,9–11].

Dietary fat intake often has been claimed as responsible for the increase in adiposity. Human studies have shown that high-fat diets ($\geq 30\%$ of energy from fat) can easily induce obesity[10,12–15]. Epidemiological studies conducted in countries such as China, Canada and the USA have shown that, when the average amount of fat in the diet increases, the incidence of obesity also increases[16–19]. This has led to a worldwide effort to decrease the amount of fat in the human diet.

Diets rich in fat not only induce obesity in humans but also make animals obese[20–22]. In both rats[23,24] and mice[25,26] a positive relationship has been found between the level of fat in the diet and body weight or fat gain. In the scientific literature it was first shown that rats consuming diets containing high proportions of fat gained weight faster than those on diets containing minimal amounts of fat[27,28].

In 1949, obesity was induced for the first time in rats by *ad libitum* feeding of a semi-liquid palatable diet[29]. Then in 1953, Fenton & Dowling used high-fat diets with fat at 50% of total energy in weanling mice to induce obesity; they called it nutritional obesity[30] but the model was later renamed as dietary obesity[31].

Since under-reporting is an important bias in epidemiological studies on diet and obesity in human subjects[32–34], animal models have been widely utilised for experiments on dietary obesity[7,8,35,36]. Usually high-fat diets within the range of 30–78% of total energy intake are used[21] – either by adding a particular fat to the animal's diet or using an assortment of fat- and sugar-rich supermarket foods (cafeteria diet) – for studying obesity in rats[24,37–46] and mice[25,47–52]. The use of high-carbohydrate–low-fat diets has not been found as efficient as high-fat–low-carbohydrate diets in inducing obesity[24,41,53].

It has been reported that despite the growing problem of obesity, Canadians and Americans are eating less fat than a generation ago[54,55]. This shows that the increasing rate of obesity cannot be totally explained by high intakes of fat in the diet, suggesting that the type of fat may also play a role, although the results of the studies in human subjects and animals have not been conclusive[56]. Some studies have reported that not all fats are obesogenic and the dietary fatty acid profile rather than the amount of energy from fat is an important variable in developing dietary obesity[25,47,57–60], but there is some controversy on this matter since there are

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reports showing non-significant differences in final body weight and/or body-weight gain of the animals consuming various fatty acids[53,61−66].

Other factors that may contribute to obesity induced by a diet rich in fat include failure to adjust oxidation of fat to the extra fat in the diet[15], increase in adipose tissue lipoprotein lipase activity[67], increased meal size and decreased meal frequency[68], as well as overconsumption of energy attributed to high energy density of the diet[69−72], orosensory characteristics of fats and poorly satiating properties of the high-fat diets[22,69,70]. Reviews of dietary obesity describe potential mechanisms of body weight and food intake regulation involving the central nervous system – mainly the hypothalamus – neuropeptides such as ghrelin and neuropeptide Y, and hormones such as insulin and leptin[73,74]. Adipose tissue *per se* is considered to be an endocrine organ that secretes cytokines such as IL-6 and TNFα; thus obesity could possibly be regarded as a chronic inflammatory disease[73−76].

Obesity occurs when energy uptake surpasses energy expenditure in the individual animal and so the stores of energy in body fat are enlarged, particularly in adipose tissues. Obesity involves both or either an increase in the number of adipocytes (hyperplasia) and their size (hypertrophy)[10,77,78]. Initially it was hypothesised that adipocyte number was determined in early childhood and that the obesity developed during adulthood was a result of an increase in adipocyte size[79,80]. However, it is now known that hyperplasia is an ongoing event not limited to childhood. At any stage of life when adipocytes enlarge to the point of hypertrophy, they release factors such as TNFα and insulin-like growth factor that stimulate hyperplasia of the adipocytes[76,77,81]. Conversely, recent studies on reversal of obesity in human subjects have found decreases not only in the size of the fat cells but also in their number: the loss of weight is followed by apopotosis of adipocytes[78,81].

This paper summarises the present literature on factors that can play a role in the development of obesity and explores mechanisms that have been proposed for obesity induced by a diet rich in fat. The adequacy of the paradigm of high-fat diets in animal models of human obesity will be discussed. The possibility of reversing dietary obesity in animal models will be explored. Physical activity is another important factor in obesity; however, the present paper focuses on dietary factors only. Some reviews have been published about diverse areas of dietary obesity that have been cited in this introduction but the aim of the present review is to summarise the range of relevant results and to provide a conclusive coverage of the different aspects of obesity from high-fat diets in non-human species.

Assessment of dietary obesity

In animal models, as in humans, obesity can be assessed by criteria based on (1) gain of body weight or the Lee obesity index and/or (2) increase of body fat content. However, standard thresholds for obesity have not been developed like BMI in human beings. In most studies, the degree of obesity has been evaluated by comparing body weight (or fat) of the experimental group fed a high-fat or energy-dense diet with control animals that show normal growth while fed chow or low-fat diets[20,24,41,42,45,82]. Researchers that have attempted to do so differed in the values that are 10−25 % greater body weight than age-matched control rats fed chow (normal pattern of body-weight gain) as moderate obesity[41,42] and greater than 40 % as severe obesity[82].

The Lee index for assessing obesity in rats is similar to BMI in humans. It was defined by Lee in 1929[83] as the cube root of body weight (g) divided by the naso−anal length (cm) and multiplied by 1000. Lee considered values greater than 310 as an indicator of obesity. Since then some researchers have used the Lee index to assess the levels of obesity in rats[44,84−88]. Reliable correlations were found in some studies between the Lee index and fat content of the body[86,89−91].

In human subjects body composition assessment with methods such as air displacement plethysmography or dual-energy X-ray absorptiometry gives a more precise idea of the degree of obesity than do anthropometric measurements alone[92,93]. For example, children and adolescent males have smaller fat mass than females of a similar BMI, and this difference is more pronounced in the older age group; and so the relationship between BMI and the direct measures of adiposity is influenced by factors such as sex and age[92]. Dual-energy X-ray absorptiometry is also used in rats for assessing body composition[24,94]. In rats fed diets high in fat, a linear increase in body fat with increasing body weight has been shown[25,45]. However, results of the study of Woods *et al.* [42] showed that measuring body fat is a more sensitive criterion for assessing obesity in animals, since rats fed a high-fat diet (40 % of energy) for 10 weeks displayed a 10 % increase in total body weight but a 35−40 % increase in total body fat compared with the animals fed a low-fat diet.

In models of dietary obesity, animals are classified as prone and resistant based on their body weight, body-weight gain, body fat, or noradrenaline concentrations in urine. Tulipano *et al.* [95] categorised Sprague−Dawley rats fed a high-fat diet based on their final body weight, with rats in the highest quartile designated as obesity prone and those in the lowest quartile assigned as obesity resistant. In some studies upper (prone) and lower (resistant) tertiles of body-weight gain[46,51,96] or body fat[97] of the animals fed high-fat diets have been used for this classification. Before developing obesity while fed with chow, prone and resistant animals have also been identified based on high and low levels of urinary noradrenaline, respectively[98,99].

High-fat diets

Energy density

In humans, a significant positive relationship has been found between the amount of dietary energy from fat and the proportion of the population who are overweight (in epidemiological studies), and in clinical studies between the level of dietary fat and body-weight gain as well as between the reduction in the dietary fat and weight loss[16,17,19,100]. These associations have also been shown in animal studies[23−26,101]. This relationship in humans or in animal

models of more dietary fat leading to greater obesity shows that the fat content of the diet is an important factor in energy balance. In general, diets containing more than 30 % of total energy as fat lead to the development of obesity.

Researchers have induced obesity by diets having different percentages and sources of fats in rats[24,31,37–45,53,82,102–105], mice[25,47–52,60] and hamsters[106]. Furthermore, the characteristics of the diets used have differed within and between laboratories in macronutrient composition, energy density and orosensory properties. In many animal studies the composition of the control diet was not shown or a non-purified chow control diet was used. This could have confounding effects arising from comparisons made with the high-fat diets.

Since the original observations of dietary obesity, obesity has been induced in animals by diets containing fat as low as 13 % of total energy in a high-energy diet[41] (Table 1; line 26) (which is more than the rat's requirement for fat: 5 %) to as high as 85 % of energy[37] (Table 1; line 1). Several researchers have reviewed the amount of fat required to induce obesity in animals. The most recent review was by Buettner et al.[21] who summarised studies conducted between 1997 and 2007, and concluded that the best method to induce obesity in animals was to use semi-purified high-fat diets containing animal fats at 40 % of energy, with a low amount of n-3 fatty acids and a low amount of plant oils rich in n-6 and n-9 fatty acids.

Interestingly, some recent studies have indicated that the development of obesity is prevented in humans and rats when the increase in dietary fat is accompanied by an increase in protein (high protein:carbohydrate and low carbohydrate:fat ratios)[107–109]. This has been related to greater satiety with high-protein diets, lower insulin levels with low-carbohydrate diets and the energy required to convert amino acids in glucose compounds for gluconeogenesis[107]. High-protein diets were also found to increase cholecystokinin and decrease plasma levels of the orexigenic hormone ghrelin[110,111], reduce gastric emptying[111] and increase central nervous system leptin sensitivity[109,112]. Moreover, high-protein diets resulted in a decrease in fatty acid synthase enzyme activity in the liver that reduces hepatic lipogenesis[107]. The increase in circulating amino acids per se is a satiety signal and inhibits food intake through suppressing the gene expression of agouti-related protein (a neuropeptide in the brain that increases appetite)[110,113]. However, Huang et al.[114] showed that increasing the dietary protein:carbohydrate ratio could not reduce the degree of obesity when obesity had already been induced in high-fat diet-fed mice (at 40 % of energy). Therefore they suggested that these diets might be efficient in preventing obesity but may not reverse obesity once established.

In the human diet, an increase in dietary fat is usually accompanied by a decrease in carbohydrate while the protein is relatively constant (for example, fat 35–45 %, carbohydrate 45–55 %, protein 15–20 %). This is why a presumably positive relationship between the level of fat of the diet and degree of obesity is usually found in epidemiological studies without controlling for dietary protein level.

Dietary profile of fatty acids

Fatty acid composition of the diet may play an important role in body-weight regulation and cellularity of adipose tissue (fat cell volume and number)[56,59,115,116]. Studies in human subjects have shown that SFA are more obesogenic than PUFA[57,58,117–119]. This idea has been supported by animal studies by showing either greater accumulation of body fat[43,47,120–122] (Table 1; lines 19, 21, 16, 18 and 37, respectively) or higher body weight[25,47,60,122] (Table 1; lines 11, 21, 33 and 18, respectively) on feeding with diets moderate or rich in SFA. A study conducted by Ellis et al.[53] in 3-week-old female Sprague–Dawley rats comparing diets rich in low-SFA maize oil or high-SFA coconut oil (40 % of total energy) for 8 weeks found higher fat cell number in animals fed coconut oil and greater fat cell size in the rats fed maize oil. Since hypertrophy of adipocytes is a prerequisite for hyperplasia, those results show that more severe form of obesity developed from feeding a diet high in SFA.

The obesogenic effect of SFA can be explained by the fact that SFA are poorly used for energy, and so remain to be acylated into TAG and stored in adipose tissue, whereas PUFA and MUFA are readily used for energy and so stored less[59]. In other words, the effective energy content of a diet is greater when the fats in it are high in SFA. In addition, the rate of oxidation of SFA decreases with increase of carbon chain length[57]. Furthermore, unlike MUFA and PUFA, SFA decrease RMR and diet-induced thermogenesis[116,118,123–125]. Moussavi et al.[56] suggested that PUFA suppress the expression of lipogenic transcription genes while MUFA and SFA do not.

Another possible mechanism is that saturation of fatty acids decreases their suppressive effect on dietary intake: thus fats and oils containing high proportions of linoleic acid are more satiating than fats and oils rich in oleic or stearic acid[13,117,126]. PUFA inhibit appetite more strongly than MUFA or SFA through an increase in the release of cholecystokinin which augments other signals of satiety[117,126]. Another study, however, failed to confirm that SFA induced less satiety than MUFA[127].

A study in adult male Wistar rats showed that feeding high-fat diets (60 % of energy) for 8 weeks resulted in greater intrathoracic fat mass in animals fed a SFA-rich diet (cocoa butter) and greater intra-abdominal and epididymal fat mass in those fed PUFA (safflower-seed oil)[61] (Table 1; line 38). There are also reports of studies that did not show any specific effect of SFA and PUFA on body weight or fat mass[64,128] (Table 1; lines 17 and 25, respectively).

Short-chain ($C2:0–C4:0$) and medium-chain ($C6:0–C12:0$) fatty acids are directly transported to the liver via the portal system, are not dependent upon carnitine for entering the mitochondria and therefore are oxidised more and deposited less in adipose tissue than long-chain fatty acids ($C14:0–C24:0$)[56,129,130]. Short-chain and medium-chain fatty acids also increase diet-induced thermogenesis and energy expenditure[56,130]. The lower obesogenic effect of medium-chain TAG, which are composed of medium-chain fatty acids, was shown in many studies. Isoenergetic diets (with fat at 12 % of total energy) containing olive oil or medium-chain fatty acid (octanoic acid) offered for 23 d to

Table 1. Studies of high-fat diet-induced obesity (DIO) in animal models

Reference	Species, strain, sex, weight, age	Diet composition						Changes in body weight and dietary intake						Line no.
		DIO diet	Amount of fat		Control diet	Amount of fat		Duration (weeks)	Final/daily body weight (g)	Body-weight gain (g)	Body fat (g)	Food intake (g)	Energy intake	
			g/100 g diet	% of total energy		g/100 g diet	% of total energy							
Mickelsen *et al.* (1955)[37]	Rats, Osborne–Mendel, male, 300 g, adult	g/100 g 60 Crisco® (Proctor & Gamble, Cincinnati, OH, USA) 25 casein 7 sucrose 1 starch 4 mineral salts 3 cottonseed oil containing: 2 vitamin A and D 1 vitamin E	63	85	g/100 g 30 casein 61 sucrose 2 starch 4 mineral salts 3 cottonseed oil containing: 2 vitamin A and D 1 vitamin E	3	7	41	i	nr	–	–	–	1
Schemmel *et al.* (1969)[45]	Rats, Osborne–Mendel, male and female, 57·5 ± 6·4 g (female), 51·6 ± 3·1 g (male), 3·5 weeks	g/100 g 60 Crisco® 25 casein liver 2 liver powder 0·25 DL-methionine 5 mineral mix 2·2 vitamin mix 0·01 auremycin 2 fibre	60	78	Grain	nr	nr	65	i	nr	Total i	–	–	2
Herberg *et al.* (1974)[49]	Mice, NMRI, male, 19·2 ± 0·2 g (DIO diet), 19·3 ± 0·2 g (control diet), 4 weeks	g/100 g 38 soya oil 24 casein 10 starch 16 sucrose 5 powdered cellulose 1 vitamin mix 6 mineral mix	38	63	g/100 g 20 protein 30 oatmeal 24 whole meal 13 flour 7 wheat 2·2 sweet whey 2·5 distillers solubles 0·2 vitamin mix 1·1 mineral mix	6·2	13	11–12	i	i	Epididymal and subcutaneous i	d	kcal 0	3
Lemonnier *et al.* (1975)[50]	Mice, Swiss, male and female, nr, weaning	g/100 g 53 lard % of energy 72 lipid 22 protein 6 carbohydrate	53	72	% of total energy 9 lipid 22 protein 69 carbohydrate	4·5	9		i	nr	Genital i	–	–	4
Sclafani & Springer (1976)[228]	Rats, CFE, female, 234–239 g, 17 weeks	g/100 g 33 Crisco® 67 Purina chow + sweetened condensed milk + palatable supermarket foods: chocolate chip cookies, salami, banana, marshmallows, milk chocolate, peanut butter	>33	>52·5	Purina chow (company not specified)	4·5	9·6	8–9	nr	i	–	–	–	5

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Table 1. *Continued*

Reference	Species, strain, sex, weight, age	DIO diet	Amount of fat g/100 g diet	Amount of fat % of total energy	Control diet	Amount of fat g/100 g diet	Amount of fat % of total energy	Duration (weeks)	Final/daily body weight (g)	Body-weight gain (g)	Body fat (g)	Food intake (g)	Energy intake	Line no.
Sclafani & Gorman (1977)[44]	Rats, CFE, male and female, 308 g and 12 weeks (male), 233 g and 13 weeks (female)	Purina chow + supermarket foods: marshmallows, cheese puffs, sugar-coated cereal, chocolate cookies, peanut butter, bologna, sweetened condensed milk	nr	nr	Purina chow (company not specified)	4·5	9·6	8·5	nr	i	–	–	–	6
Faust et al. (1978)[103]	Rats, Sprague–Dawley and Osborne–Mendel, male, nr, 17 weeks	g/100 g 55 Crisco® 25 casein 13 dextrose 4 mineral salts 2·82 vitamin mix 0·12 L-cystine 0·06 L-cysteine	55	76	Purina chow (company not specified)	4·5	9·6	8·5	i (both strains)	nr	Retroperitoneal and gonadal i (both strains)	–	–	7
Oscai (1982)[38]	Rats, Wistar, female, nr, weaning	g/100 g 4·84 maize oil 18·16 lard 18 casein 49·5 sucrose 2 brewer's yeast 2 liver powder 4 Hegsted salt mixture 1·5 vitamin mix	23	42	Purina chow (Ralston Purina, Nestlé Purina PetCare, St Louis, MO, USA)	4·5	9·6	58	i	nr	Total i	nr	–	8
Wade (1982)[106]	Hamsters, golden, male and female, 80–110 g, nr	Two parts Purina chow (Purina Rodent Chow, no. 5001) One part vegetable shortening (company not specified)	>33	>52·5	Purina chow (Purina Rodent Chow, no. 5001)	4·5	9·6	4	nr	i	Total i	nr	kcal 0	9
Bourgeois et al. (1983)[25]	Mice, NMRI, male and female, nr, 4 weeks	g/100 g 5 lard 3·2 bran 0·3 DL-methionine 4·3 mineral mix 2·4 vitamin mix 14 casein 70·8 wheat flour	5	6·9	g/100 g 78·5 wheat flour 12·1 casein 3 bran 0·4 DL-methionine 2·1 vitamin mix 3·9 mineral mix	3	6·1	13	0	nr	Retroperitoneal and parametrial 0	–	–	10
		10 lard 3·5 bran 0·2 DL-methionine 4·6 mineral mix 2·5 vitamin mix 17 casein 62 wheat flour	10	26·8					i (female only)	nr	0	–	–	
		20 lard 3·9 bran 0·1 DL-methionine 5·2 mineral mix 2·9 vitamin mix 21·9 casein 45·5 wheat flour	20	43·5					i	nr	i	–	–	

Reference	Animals	High-fat diet	Fat (g/100 g)	Energy (%)	Control diet				Body weight	Energy intake	Adipose tissue			Ref.
		30 lard / 4·2 bran / 0·05 DL-methionine / 5·6 mineral mix / 3·1 vitamin mix / 27 casein / 30·1 wheat flour	30	55·9					i	nr	i	–	–	
Bourgeois *et al.* (1983)[25]	Mice, NMRI, male and female, nr, 4 weeks	g/100 g			g/100 g						Retroperitoneal and para-metrial			
		30 lard / 4·2 bran / 0·05 DL-methionine / 5·6 mineral mix / 3·1 vitamin mix / 27 casein / 30·1 wheat flour	30	55·9	78·5 wheat flour / 12·1 casein / 3 bran / 0·4 DL-methionine / 2·1 vitamin mix / 3·9 mineral mix	3	6·1	13	i	nr	i / i *v.* beef tallow (male only) / d *v.* beef tallow (female only)	–	–	11
		30 beef tallow / 4·2 bran / 0·05 DL-methionine / 5·6 mineral mix / 3·1 vitamin mix / 27 casein / 30·1 wheat flour	30	55·9					i *v.* sunflower-seed oil (female only)	nr	d *v.* lard, soya-bean oil (male only) / i *v.* lard, soya-bean oil, sunflower-seed oil (female only)	–	–	
		30 soyabean oil / 4·2 bran / 0·05 DL-methionine / 5·6 mineral mix / 3·1 vitamin mix / 27 casein / 30·1 wheat flour	30	55·9					i	nr	i / i *v.* beef tallow (male only) / d *v.* beef tallow (female only)	–	–	
		30 sunflower-seed oil / 4·2 bran / 0·05 DL-methionine / 5·6 mineral mix / 3·1 vitamin mix / 27 casein / 30·1 wheat flour	30	55·9					d *v.* beef tallow (female only)	nr	i / i *v.* beef tallow (male only)	–	–	
Cunnane *et al.* (1986)[48]	Mice, *ob/ob* and *in/in*, male, 22 g (*in/in*), 36 g (*ob/ob*), 6 weeks	g/100 g									Epididymal			
		10 evening primrose oil / 20 casein / 60 sucrose / 5·5 cellulose / 3·5 mineral mix / 1 vitamin mix	10	21	Purina chow (Jackson laboratory, no. 5001)	4·5	9·6	16	0 / i *v.* cod liver oil (*ob/ob* only)	0 / d *v.* cod liver oil (*in/in* only)	0 *v.* cod liver oil	0	–	12
		10 cod liver oil / 20 casein / 60 sucrose / 5·5 cellulose / 3·5 mineral mix / 1 vitamin mix							0 / d *v.* evening primrose oil (*ob/ob* only)	0 / d *v.* evening primrose oil (*in/in* only)	0 *v.* evening primrose oil	0	–	
Chang *et al.* (1990)[40]	Rats, Wistar, female, nr, nr	g/100 g			g/100 g						Retroperitoneal and para-metrial		kcal	
		32·70 maize oil / 29·20 casein / 12·20 sucrose / 12·15 dextrin / 6·30 solka floc / 2 vitamin mix / 5 mineral mix / 0·30 DL-methionine / 0·15 choline chloride	32	60	8·2 maize oil / 22 casein / 29·35 sucrose / 28 dextrin / 6·30 Solkafloc / 2 vitamin mix / 5 mineral mix / 0·20 DL-methionine / 0·15 choline chloride	8·2	20	5	0 (obesity resistant only) / i (obesity prone only) / i (obesity prone *v.* obesity resistant)	i (obesity prone *v.* obesity resistant)	i (obesity prone *v.* obesity resistant)	nr	i (obesity prone *v.* obesity resistant)	13
Su & Jones (1993)[66]	Rats, Sprague–Dawley, male, 65–85 g, nr	g/100 g									Total			
		22·4 fish oil / 27·8 maize starch / 11·2 sucrose / 22·4 casein / 6·19 cellulose / 1·24 vitamin mix / 8·65 mineral mix	22·4	42	nr	nr	nr	12	0 *v.* other DIO diets	0 *v.* other DIO diets	d *v.* beef tallow and olive oil	0 *v.* other DIO diets	nr	14

Table 1. *Continued*

Reference	Species, strain, sex, weight, age	DIO diet	Amount of fat g/100 g diet	% of total energy	Control diet	g/100 g diet	% of total energy	Duration (weeks)	Final/daily body weight (g)	Body-weight gain (g)	Body fat (g)	Food intake (g)	Energy intake	Line no.
		22·4 safflower-seed oil 27·8 maize starch 11·2 sucrose 22·4 casein 6·19 cellulose 1·24 vitamin mix 8·65 mineral mix	22·4	42					0 v. other DIO diets	0 v. other DIO diets	0 v. other groups	0 v. other DIO diets	nr	
		22·4 olive oil 27·8 maize starch 11·2 sucrose 22·4 casein 6·19 cellulose 1·24 vitamin mix 8·65 mineral mix	22·4	42					0 v. other DIO diets	0 v. other DIO diets	i v. fish oil	0 v. other DIO diets	nr	
		22·4 beef tallow 27·8 maize starch 11·2 sucrose 22·4 casein 6·19 cellulose 1·24 vitamin mix 8·65 mineral mix	22·4	42					0 v. other DIO diets	0 v. other DIO diets	i v. fish oil	0 v. other DIO diets	nr	
Hill *et al.* (1993)[63]	Rats, Wistar, male, 300 g, 13–17 weeks	g/100 g									Total		kcal	
		18·2 maize oil 1·3 safflower-seed oil 20 casein 16·2 sucrose 16·2 maize starch 0·3 DL-methionine 5 fibre 1 vitamin mix 3·5 mineral mix	19·5	45	nr	nr	nr	25	0 v. other DIO diets	nr	i v. fish oil	–	0 v. other DIO diets	15
		18·2 lard 1·3 safflower-seed oil 20 casein 16·2 sucrose 16·2 maize starch 0·3 DL-methionine 5 fibre 1 vitamin mix 3·5 mineral mix	19·5	45					0 v. other DIO diets	nr	i v. fish oil	–	i v. fish oil	
		18·2 fish oil 1·3 safflower-seed oil 20 casein 16·2 sucrose 16·2 maize starch 0·3 DL-methionine 5 fibre 1 vitamin mix 3·5 mineral mix	19·5	45					0 v. other DIO diets	nr	d v. maize oil and lard	–	d v. lard	
Shillabeer & Lau (1994)[120]	Rats, Sprague–Dawley, male, 50–60 g, 4 weeks	% of total energy									Epididymal, and inguinal		kcal	
		59 beef tallow 21 carbohydrate 20 protein	38	45	Purina chow (company not specified)	4·5	9·6	26	0 0 v. other DIO diets	nr	i 0 v. other DIO diets	nr	0 v. other DIO diets	16
		59 safflower-seed oil 21 carbohydrate 20 protein	38	45					0 0 v. other DIO diets	nr	0 0 v. other DIO diets	nr	0 v. other DIO diets	
		5 beef tallow 75 carbohydrate 20 protein	2·2	5					0 0 v. other DIO diets	nr	0 0 v. other DIO diets	nr	0 v. other DIO diets	
Jones *et al.* (1995)[64]	Rats, Sprague–Dawley, male, 193 ± 9·1 g, nr	g/100 g												

19 beef tallow 31·2 maize starch 11·2 sucrose 22·4 casein 6·2 cellulose 1·2 vitamin mix 8·6 mineral mix	20	40	nr	nr	nr	10	0 v. other DIO diets	nr	–	–	nr	17
19 fish oil 31·2 maize starch 11·2 sucrose 22·4 casein 6·2 cellulose 1·2 vitamin mix 8·6 mineral mix	20	40					0 v. other DIO diets	nr	–	–	nr	
19 olive oil 31·2 maize starch 11·2 sucrose 22·4 casein 6·2 cellulose 1·2 vitamin mix 8·6 mineral mix	20	40					0 v. other DIO diets	nr	–	–	nr	
19 safflower-seed oil 31·2 maize starch 11·2 sucrose 22·4 casein 6·2 cellulose 1·2 vitamin mix 8·6 mineral mix g/100 g	20	40					0 v. other DIO diets	nr	–	–	nr	

Takeuchi et al. (1995)[122] — Rats, Sprague–Dawley, male, 95–97 g, 4 weeks — Epididymal, perinephrial and mesenteric — kJ

20 lard 39·8 maize starch 24 casein 5 sucrose 5 cellulose 1·2 vitamin mix 4·2 mineral mix 0·4 DL-methionine 0·3 choline 0·002 α-tocopherol	20	39·4	nr	nr	nr	12	i v. high-oleic safflower-seed oil and linseed oil	nr	i v. high-oleic safflower-seed oil, safflower-seed oil and linseed oil	nr	0 v. other DIO diets	18
20 high-oleic safflower-seed oil 39·8 maize starch 24 casein 5 sucrose 5 cellulose 1·2 vitamin mix 4·2 mineral mix 0·4 DL-methionine 0·3 choline 0·002 α-tocopherol	20	39·4					d v. lard	nr	d v. lard	nr	0 v. other DIO diets	
20 safflower-seed oil 39·8 maize starch 24 casein 5 sucrose 5 cellulose 1·2 vitamin mix 4·2 mineral mix 0·4 DL-methionine 0·3 choline 0·002 α-tocopherol	20	39·4					0 v. other DIO diets	nr	d v. lard	nr	0 v. other DIO diets	
20 linseed oil 39·8 maize starch 24 casein 5 sucrose 5 cellulose 1·2 vitamin mix 4·2 mineral mix 0·4 DL-methionine 0·3 choline 0·002 α-tocopherol g/100 g	20	39·4					d v. lard	nr	d v. lard	nr	0 v. other DIO diets	

Yaqoob et al. (1995)[43] — Rats, Lewis, male, 65–85 g, 3 weeks — g/100 g — Epididymal — kcal

Table 1. *Continued*

Reference	Species, strain, sex, weight, age	DIO diet	Amount of fat — g/100 g diet	Amount of fat — % of total energy	Control diet	Amount of fat — g/100 g diet	Amount of fat — % of total energy	Duration (weeks)	Final/daily body weight (g)	Body-weight gain (g)	Body fat (g)	Food intake (g)	Energy intake	Line no.
		20 coconut oil 1 maize oil 0·0004 cholesterol 20 protein 49·5 carbohydrate 5 non-nutritive bulk 0·12 vitamin E	21	40·5	14·6 protein 48·4 carbohydrate 18·6 non-nutritive bulk 0·01 vitamin E 2·4 unspecified oil 0·0001 cholesterol	2·4	6	10	i	i	i i *v.* other DIO diets	i 0 *v.* other DIO diets	d *v.* olive oil, evening primrose oil, fish oil, control	19
		20 olive oil 1 maize oil 0·0004 cholesterol 20 protein 49·5 carbohydrate 5 non-nutritive bulk 0·12 vitamin E	21	40·5					i d *v.* fish oil	i d *v.* fish oil	i d *v.* coconut oil	i 0 *v.* other DIO diets	i *v.* coconut oil	
		20 safflower-seed oil 1 maize oil 0·0004 cholesterol 20 protein 49·5 carbohydrate 5 non-nutritive bulk 0·12 vitamin E	21	40·5					i	i	i d *v.* coconut oil i *v.* evening primerose oil, fish oil	i 0 *v.* other DIO diets	0 *v.* other DIO diets	
		20 evening primrose oil 1 maize oil 0·0004 cholesterol 20 protein 49·5 carbohydrate 5 non-nutritive bulk 0·12 vitamin E	21	40·5					i d *v.* fish oil	i d *v.* fish oil	i d *v.* coconut oil, safflower-seed oil	i 0 *v.* other DIO diets	i *v.* coconut oil	
		20 fish oil 1 maize oil 0·0004 cholesterol 20 protein 49·5 carbohydrate 5 non-nutritive bulk 0·12 vitamin E	21	40·5					i i *v.* olive oil and evening primrose oil	i i *v.* olive oil and evening prim-rose oil	i d *v.* coconut oil, safflower-seed oil	i 0 *v.* other DIO diets	i *v.* coconut oil	
Ikemoto *et al.* (1996)[52]	Mice, C57BL/6J, female, nr, 7 weeks	g/100 g			g/100 g						Parametrial		kcal	
		32 palm oil 33·1 casein 17·6 sucrose 1·4 vitamin mix 9·8 mineral mix 5·6 cellulose powder 0·5 DL-methionine	32	60	4 safflower-seed oil 23·7 casein 10 sucrose 50 starch 1 vitamin mix 7 mineral 4 cellulose powder 0·4 DL-methionine	4	11	19	i	i	i	nr	0 d *v.* fish oil	20
		32 lard 33·1 casein 17·6 sucrose 1·4 vitamin mix 9·8 mineral mix 5·6 cellulose powder 0·5 DL-methionine	32	60					i	i	i	nr	0 i *v.* perilla oil	
		32 fish oil 33·1 casein 17·6 sucrose 1·4 vitamin mix 9·8 mineral mix 5·6 cellulose powder 0·5 DL-methionine	32	60					0	0	0	nr	i i *v.* palm oil, rapeseed oil, perilla oil	
		32 perilla oil 33·1 casein 17·6 sucrose 1·4 vitamin mix 9·8 mineral mix 5·6 cellulose powder 0·5 DL-methionine	32	60					i	i	i	nr	0 d *v.* lard, saf-flower-seed oil, fish oil	

Reference	Animal model	High-fat diet			Control diet					Outcomes						
		32 rapeseed oil; 33·1 casein; 17·6 sucrose; 1·4 vitamin mix; 9·8 mineral mix; 5·6 cellulose powder; 0·5 DL-methionine	32	60	4 safflower-seed oil; 23·7 casein; 10 sucrose; 50 starch; 1 vitamin mix; 7 mineral mix; 4 cellulose powder; 0·4 DL-methionine					i	i	i	nr	0 / d v. fish oil		
		32 soyabean oil; 33·1 casein; 17·6 sucrose; 1·4 vitamin mix; 9·8 mineral mix; 5·6 cellulose powder; 0·5 DL-methionine	32	60						i	i	i	nr	0		
		32 safflower-seed oil; 33·1 casein; 17·6 sucrose; 1·4 vitamin mix; 9·8 mineral mix; 5·6 cellulose powder; 0·5 DL-methionine	32	60						i	i	i	nr	0 / i v. perilla oil		
Bell et al. (1997)[47]	Mice, Swiss Albino, female, nr, 6 weeks	g/100 g			g/100 g							Retroperitoneal			kJ	
		14·4 beef fat; 6 maize oil; 24·1 casein; 0·4 DL-methionine; 25·3 maize starch; 18·1 sucrose; 6 cellulose; 1·2 vitamin mix; 4·2 mineral mix; 0·2 choline; 0·004 butylated hydroxytoluene	20·5	40·8	5 maize oil; 20 casein; 0·3 DL-methionine; 50 maize starch; 15 sucrose; 5 cellulose; 1 vitamin mix; 3·5 mineral mix; 0·2 choline; 0·001 butylated hydroxytoluene	5	11·5	8		i / i v. rapeseed oil	nr	i / i v. rapeseed oil	nr	0	21	
		14·4 rapeseed oil; 6 maize oil; 24·1 casein; 0·4 DL-methionine; 25·3 maize starch; 18·1 sucrose; 6 cellulose; 1·2 vitamin mix; 4·2 mineral mix; 0·2 choline; 0·004 butylated hydroxytoluene	20·5	40·8						0 / d v. beef fat	nr	0 / d v. beef fat	nr	0		
Okuno et al. (1997)[65]	Rats, Sprague–Dawley, male, nr, 4 weeks	g/100 g										Epididymal and perirenal				
		12 beef tallow; 20 casein; 59 sucrose; 4 cellulose; 0·15 choline chloride; 4 mineral mix; 1 vitamin mix	12	26·2	nr	nr	nr	12		0 v. other DIO diets	nr	i v. perilla oil	0 v. other DIO diets	nr	22	
		12 olive oil; 20 casein; 59 sucrose; 4 cellulose; 0·15 choline chloride; 4 mineral mix; 1 vitamin mix	12	26·2						0 v. other DIO diets	nr	i v. perilla oil	0 v. other DIO diets	nr		
		12 safflower-seed oil; 20 casein; 59 sucrose; 4 cellulose; 0·15 choline chloride; 4 mineral mix; 1 vitamin mix	12	26·2						0 v. other DIO diets	nr	0 v. other DIO diets	0 v. other DIO diets	nr		
		12 perilla oil; 20 casein; 59 sucrose; 4 cellulose; 0·15 choline chloride; 4 mineral mix; 1 vitamin mix	12	26·2						0 v. other DIO diets	nr	d v. beef tallow, olive oil	0 v. other DIO diets	nr		

Table 1. *Continued*

Reference	Species, strain, sex, weight, age	DIO diet	Amount of fat g/100 g diet	Amount of fat % of total energy	Control diet	g/100 g diet	% of total energy	Duration (weeks)	Final/daily body weight (g)	Body-weight gain (g)	Body fat (g)	Food intake (g)	Energy intake	Line no.
Cha & Jones (1998)[62]	Rats, Sprague–Dawley, male, 209 ± 6·5 g, nr	g/100 g									Perirenal			
		20 fish oil 15 casein 45 maize starch 10 sucrose 5 cellulose 3·5 mineral mix 1 vitamin mix 0·18 L-cystine 0·25 choline bitartrate 0·004 tert-butylhydroqui-none	20	36	nr	nr	nr	10	0 v. other DIO diets	nr	d v. safflower-seed oil, beef tallow	0 v. other DIO diets	nr	23
		20 safflower-seed oil 15 casein 45 maize starch 10 sucrose 5 cellulose 3·5 mineral mix 1 vitamin mix 0·18 L-cystine 0·25 choline bitartrate 0·004 tert-butylhydroqui-none	20	36					0 v. other DIO diets	nr	i v. beef tallow, fish oil	0 v. other DIO diets	nr	
		20 beef tallow 15 casein 45 maize starch 10 sucrose 5 cellulose 3·5 mineral mix 1 vitamin mix 0·18 L-cystine 0·25 choline bitartrate 0·004 tert-butylhydroqui-none	20	36					0 v. other DIO diets	nr	i v. fish oil d v. safflower-seed oil	0 v. other DIO diets	nr	
Loh et al. (1998)[104]	Rats, Zucker, genetically obese and lean, male, lean: 112–113 g, obese: 132–136 g, 5 weeks	g/100 g			g/100 g						Total		kcal	
		35·8 soyabean oil 23·5 casein 2·7 sucrose 15 maize starch 17·9 fibre 1 vitamin mix 3·5 mineral mix 0·3 L-cysteine 0·25 choline chloride	35·8	65	6·85 soyabean 19·5 casein 53·6 sucrose 10 maize starch 5 fibre 1 vitamin mix 3·5 mineral mix 0·3 L-cysteine 0·25 choline chloride	6·8	15	8	0	0 d v. palm olein (only in obese)	0 d v. palm olein (only in obese)	nr	i (only in obese)	24
		30 palm olein 5·8 soyabean oil 23·5 casein 2·7 sucrose 15 maize starch 17·9 fibre 1 vitamin mix 3·5 mineral mix 0·3 L-cysteine 0·25 choline chloride	35·8	65					i (only in obese)	i (only in obese) i v. soyabean oil (only in obese)	i (only in obese) i v. soya-bean oil (only in obese)	nr	i (only in obese)	
George et al. (2000)[128]	Mice, C57B/6J, female, nr, 9–10 weeks	g/100 g												
		Cocoa butter	17·5	nr	Purina chow (Purina Rodent Laboratory Chow, no. 5001)	8·25	nr	15	0 0 v. safflower-seed oil	nr	–	nr	nr	25

Reference	Animal model	High-fat diet			Control diet				Body weight		Fat depot		Energy intake	
		Safflower-seed oil	17·5	nr					0 0 v. cocoa butter	nr	–	nr	nr	
Harrold et al. (2000)[41]	Rats, Wistar, male, 150 g, 6 weeks	g/100 g 33 Nestlé condensed milk 7 sucrose 33 ground pellet	6·3	13	Standard pellet (CRM Biosure, Cambridge, UK) % of total energy 9 fat 65 carbohydrate 24 protein	4·3	9·2	8	i (high weight-gainers only) 0 (low weight-gainers only) i (high v. low weight-gainers)	i (high weight-gainers only) 0 (low weight-gainers only) i (high v. low weight-gainers)	Epididymal and perirenal i (high v. low weight-gainers)	nr	kJ i (high v. low weight-gainers)	26
Ainslie et al. (2000)[39]	Rats, Wistar, female, 223–233 g, 20–22 weeks	10 ml fat emulsion (Intralipid; Kabi Pharmacia, AB, Stockholm) + non-purified laboratory diet (not specified)	20	36	Non-purified diet (not specified)	3	6·5	14	i	nr	Abdominal, infrarenal and subcutaneous i	nr	kJ i	27
Ghibaudi et al. (2002)[24]	Rats, Sprague–Dawley, male, 50–60 g, weaning	% of total energy 45 fat 35 carbohydrate 20 protein (D12451; Research Diets, New Brunswick, NJ, USA) 32 fat 51 carbohydrate 17 protein (D12266; Research Diets)	26 17	45 32	% of total energy 10 fat 70 carbohydrate 20 protein (D12450B; Research Diets)	4·6	10	26	i 0	i 0	Total i 0	nr	kcal i 0	28
Levin & Dunn-Meynell (2002)[82]	Rats, Sprague–Dawley (DIO and DR), male, DR: 282–327 g, DIO: 368–402 g, 10–12 weeks	g/100 g 8 maize oil 44 sweetened condensed milk 48 Purina chow (Purina Rat Chow, no. 5008) % of total energy 31 fat 48 carbohydrate 21 protein	16·6	31	Purina chow (Purina Rat Chow, no. 5008)	4·5	9·6	10	i (Only in DIO) d v. Ensure®	i (Only in DIO) d v. Ensure®	Epididymal, retroperitoneal, perirenal and mesenteric i (Only in DIO) d v. Ensure®	nr	kcal 0 d v. Ensure®	29
		DIO diet + chocolate-flavoured liquid diet (Ensure®; Ross Products Division, Medical Supplies Depot, AL, USA) % of total energy 22 fat 64 carbohydrate 14 protein	11·1	22					i i v. DIO diet	i i v. DIO diet	i i v. DIO diet	nr	i i v. DIO diet	
Levin & Dunn-Meynell (2002)[46]	Rats, Sprague–Dawley (DIO and DR), male, 300–425 g, nr	g/100 g 8 maize oil 44 sweetened condensed milk 48 Purina chow (Purina Rat Chow, no. 5001) % of total energy 31 fat 48 carbohydrate 21 protein	16·6	31	nr	nr	nr	4	i v. DR	nr	Total i v. DR	nr	nr	30
Ellis et al. (2002)[53]	Rats, Sprague–Dawley, female, 61 g, 3 weeks	g/100 g			g/100 g						Total, % change		kcal	

Table 1. *Continued*

Reference	Species, strain, sex, weight, age	DIO diet	Amount of fat g/100 g diet	Amount of fat % of total energy	Control diet	g/100 g diet	% of total energy	Duration (weeks)	Final/daily body weight (g)	Body-weight gain (g)	Body fat (g)	Food intake (g)	Energy intake	Line no.
		20 maize oil 22·6 casein 45·4 dextrin 0·5 DL-methionine 1·5 vitamin mix 3 mineral mix 4 cellulose	20	40	2·4 maize oil 18·2 casein 70·5 dextrose 0·4 DL-methionine 1·5 vitamin mix 3 mineral mix 4 cellulose	2·4	6	8	i i *v.* coconut oil (only in low-fat diet)	i i *v.* coconut oil (only in low-fat diet)	i i *v.* coconut oil (only in low-fat diet)	nr	0	31
		20 rapeseed oil 22·6 casein 45·4 dextrin 0·5 DL-methionine 1·5 vitamin mix 3 mineral mix 4 cellulose	20	40	2·4 rapeseed oil 18·2 casein 70·5 dextrose 0·4 DL-methionine 1·5 vitamin mix 3 mineral mix 4 cellulose	2·4	6		i	i i *v.* coconut oil (only in low-fat diet)	i i *v.* coconut oil (only in low-fat diet)	nr	0	
		20 coconut oil 22·6 casein 45·4 dextrin 0·5 DL-methionine 1·5 vitamin mix 3 mineral mix 4 cellulose	20	40	2·4 coconut oil 18·2 casein 70·5 dextrose 0·4 DL-methionine 1·5 vitamin mix 3 mineral mix 4 cellulose	2·4	6		i d *v.* maize oil (only in low-fat diets)	i d *v.* rapeseed oil, maize oil (only in low-fat diets)	i d *v.* rapeseed oil, maize oil (only in low-fat diets)	nr	0	
Rolland *et al.* (2002)[105]	Rats, Zucker (lean and obese), male, obese: 227 ± 12 g; lean: 196 ± 12 g, 6 weeks	g/100 g									Total			
		17·1 butter 54·4 starch 20·4 casein 2 cellulose 5 mineral mix 1 vitamin mix 0·15 methionine	17·1	30	nr	nr	nr	11	i *v.* soyabean oil (only in obese) d *v.* soyabean oil (only in lean)	nr	i *v.* soyabean oil (only in obese)	i *v.* soyabean oil	nr	32
		14·1 soyabean oil 56·5 starch 21·2 casein 2 cellulose 5 mineral mix 1 vitamin mix 0·15 methionine	14·7	27					d *v.* butter (only in obese) i *v.* butter (only in lean)	nr	d *v.* butter (only in obese)		nr	
Wang *et al.* (2002)[60]	Mice, C57BL/6J, male, nr, 3 weeks	g/100 g			g/100 g						Epididymal, perirenal and inguinal		kJ	
		16·9 beef tallow 16·9 maize starch 8·5 sucrose 25·4 casein 1·9 gelatin 5·1 bran 6·7 mineral mix 1·3 vitamin mix 0·3 methionine	16·9	58	4·1 safflower-seed oil 43·8 maize starch 23·9 sucrose 18·8 casein 1·4 gelatin 3·8 bran 5 mineral mix 0·97 vitamin mix 0·23 methionine	4·1	10	7	nr	nr	i i *v.* fish oil	d *v.* high-fat safflower-seed oil (week 5–7)	i 0 *v.* other DIO diets	33
		16·9 safflower-seed oil 16·9 maize starch 8·5 sucrose 25·4 casein 1·9 gelatin 5·1 bran 6·7 mineral mix 1·3 vitamin mix 0·3 methionine	16·9	58	4·1 safflower-seed oil 43·8 maize starch 23·9 sucrose 18·8 casein 1·4 gelatin 3·8 bran 5 mineral mix 0·97 vitamin mix 0·23 methionine	4·1	10	7	nr	nr	0	i *v.* high-fat beef tallow (week 5–7)	i 0 *v.* other DIO diets	

Reference	Animals	HF diet			Control diet									
		16·9 fish oil 16·9 maize starch 8·5 sucrose 25·4 casein 1·9 gelatin 5·1 bran 6·7 mineral mix 1·3 vitamin mix 0·3 methionine	16·9	58					nr	nr	d d v. beef tallow	nr	i 0 v. other DIO diets	
Jen et al. (2003)[102]	Rats, Wistar, female, nr, 3 weeks	g/100 g			g/100 g						Abdominal fat		kcal	
		40 soyabean oil 26 casein 0·65 maize starch 0·217 maltodextrin 20 maltose dextrin 6·5 cellulose 0·008 butylhydroquinone 4·5 salt mix 1·3 vitamin mix 0·039 vitamin E 0·39 L-cystine 0·325 choline bitartrate	40	65·4	7 soyabean oil 20 casein 32·1 maize starch 10·72 maltodextrin 20 maltose dextrin 5 cellulose 0·008 butylhydroquinone 3·5 salt mix 1 vitamin mix 0·03 vitamin E 0·3 L-cystine 0·25 choline bitartrate	7	15·9	6	i i v. fish oil	nr	i i v. fish oil	nr	0 d v. palm oil	34
		33 palm oil 7 soyabean oil 26 casein 0·65 maize starch 0·217 maltodextrin 20 maltose dextrin 6·5 cellulose 0·008 butylhydroquinone 4·5 salt mix 1·3 vitamin mix 0·039 vitamin E 0·39 L-cystine 0·325 choline bitartrate	40	65·4					i i v. fish oil	nr	i i v. fish oil	nr	i i v. soyabean oil, fish oil	
		33 fish oil 7 soyabean oil 26 casein 0·65 maize starch 0·217 maltodextrin 20 maltose dextrin 6·5 cellulose 0·008 butylhydroquinone 4·5 salt mix 1·3 vitamin mix 0·039 vitamin E 0·39 L-cystine 0·325 choline bitartrate	40	65·4					0 d v. soyabean oil, palm oil	nr	0 d v. soyabean oil, palm oil	nr	0 d v. palm oil	
Woods et al. (2003)[42]	Rats, Long–Evans, male and female, 250–350 g, 9–10 weeks	g/100 g			g/100 g						Total		kJ	
		19 butter oil 1 soyabean oil 16·4 casein 30·3 maize starch 11·5 dextrose 8·9 sucrose 5·8 cellulose 5·2 mineral mix 1·17 vitamin mix 0·21 L-cystine 0·29 choline bitartrate	20	40	3 butter oil 1 soyabean oil 14 casein 45·5 maize starch 15·5 dextrose 10 sucrose 5 cellulose 4·5 mineral mix 1 vitamin mix 0·18 L-cystine 0·25 choline bitartrate	4	8	10	i	nr	i	nr	i	35
Huang et al. (2004)[51]	Mice, C57BL/6J, male, nr, 3 weeks	% of total energy			% of total energy								kcal	
		59 fat 14 carbohydrate 27 protein (not specified)	38·9	59	10 fat 63 carbohydrate 27 protein (company not specified)	4·6	10	13	nr	i (only in obesity prone)	–	nr	i	36
Silva et al. (2006)[121]	Rats, Wistar, male, nr, 3 weeks	g/100 g									Epididymal			

Table 1. *Continued*

Reference	Species, strain, sex, weight, age	DIO diet	Amount of fat g/100 g diet	Amount of fat % of total energy	Control diet	Amount of fat g/100 g diet	Amount of fat % of total energy	Duration (weeks)	Final/daily body weight (g)	Body-weight gain (g)	Body fat (g)	Food intake (g)	Energy intake	Line no.
		7 soyabean oil 15 casein 67·9 maize starch 5 cellulose 3·5 mineral mix 1 vitamin mix 1·8 L-cystine 0·25 choline	7	16	nr			3–4	d v. palm oil and hydrogenated vegetable oil	nr	d v. palm oil and hydrogenated vegetable oil	0 v. other DIO diets (starting week 3)	–	37
		5 palm oil 2 soyabean oil 15 casein 67·9 maize starch 5 cellulose 3·5 mineral mix 1 vitamin mix 1·8 L-cystine 0·25 choline	7	16	nr			3–4	i v. soya oil and rapeseed oil	nr	i v. soya oil, rapeseed oil and hydrogenated vegetable oil	0 v. other DIO diets (starting week 3)	–	
		6 rapeseed oil 1 soyabean oil 15 casein 67·9 maize starch 5 cellulose 3·5 mineral mix 1 vitamin mix 1·8 L-cystine 0·25 choline	7	16					d v. palm oil and hydrogenated vegetable oil	nr	d v. palm oil and hydrogenated vegetable oil	0 v. other DIO diets (starting week 3)	–	
		6 hydrogenated vegetable oil 1 soyabean oil 15 casein 67·9 maize starch 5 cellulose 3·5 mineral mix 1 vitamin mix 1·8 L-cystine 0·25 choline	7	16					i v. soya oil and rapeseed oil	nr	i v. soya oil and rapeseed oil d v. palm oil	0 v. other DIO diets (starting week 3)	–	
Okere et al. (2006)[61]	Rats, Wistar, male, 329 ± 9·7 g, 8–9 weeks										Abdominal, epididymal and intra-thoracic		kcal	
		Cocoa butter (Research Diets, New Brunswick, NJ, USA)	nr	60	Purina chow (Teklad)	4·7	10	8	0 0 v. other DIO diet	0 0 v. other DIO diet	i i v. safflower-seed oil (intra-thoracic) d d v. safflower-seed oil (epididymal and abdominal)	nr	0 0 v. other DIO diet	38
		Safflower-seed oil (Research Diets, New Brunswick, NJ, USA)	nr	60					0 0 v. other DIO diet	0 0 v. other DIO diet	0 i v. cocoa butter (epididymal and abdominal) d v. coca butter (intra-thoracic fat)	nr	0 0 v. other DIO diet	

nr, Not reported; i, increase *v.* control diet or as specified; 0, no change or difference *v.* control diet or as specified; –, not measured; d, decrease *v.* control diet or as specified; DR, dietary obesity resistant.

overweight adult female Wistar rats led to a lower final weight and fat mass in medium-chain fatty acid-fed animals[131]. Similarly, lower body weight and fat gain were found in adult male Sprague–Dawley rats fed medium-chain TAG-rich high-fat diets (at 50 % of energy) for 8 weeks than in rats fed high-fat diets based on long-chain fatty acids[132]. Other studies in animals[133–135] and in human subjects[136,137] reported similar findings.

The location of the terminal double bond of PUFA may affect their action. Diets rich in n-3 fatty acids have been shown to prevent obesity better than other subclasses of PUFA[56,116]. This effect has been reported in studies in human subjects[57,138,139], mice[48,60] and rats[62,63,65,66,102]. In most of the animal studies lower fat deposition in subjects fed n-3 fatty acids was shown despite comparable food and energy intake among the groups[48,60,62,65,66] (Table 1; lines 12, 33, 23, 22 and 14, respectively); therefore this effect can be related to the metabolic effects of n-3 fats. Suggested mechanisms involved in this effect of n-3 PUFA are: (1) low expression of lipogenic transcription genes with diets high in n-3 PUFA[59,60,116,118]; (2) increased concentrations of thromboxane A$_2$, leukotriene B$_4$ and some cytokines that are elevated by an increase in n-6 PUFA intake and decrease in n-3 PUFA, and a low dietary n-6:n-3 ratio is beneficial for preventing them[140]; (3) inhibition of PG synthesis by n-3 PUFA leading to suppression of terminal differentiation of adipocytes[65].

The configuration of the double bonds of PUFA may also affect the development of obesity. Conjugated fatty acids are PUFA that have at least one double bond separated by one single bond. Conjugated linoleic acid was shown to prevent obesity, and this effect has been attributed to: lower energy intake by decreasing the expression of neuropeptide Y and agouti-related protein, increased diet-induced thermogenesis, decreased pre-adipocyte differentiation via decreasing the expression of PPARγ which is a key factor for adipogenesis, and decreased lipogenesis through decreasing lipoprotein lipase activity and fatty acid synthase expression[141,142]. The antiobesity effect of conjugated linoleic acid was reported in studies conducted in rodents[143,144] and human subjects[145,146]. However, animal[147] and human[148] studies have found that feeding conjugated linoleic acid-rich diets might also lead to insulin resistance.

The studies mentioned varied in species, strain, age and/or sex of the animals used, which may explain some divergences among the results. Using different fats or fatty acids at various percentages of animal or plant origin and in a wide range of durations might have affected the results as well. For example, in a diet containing 40 %[47] or 58 %[60] energy as beef tallow (48 % SFA and 52 % PUFA), the percentages of SFA and PUFA would be 19 and 21 % (in the 40 % diet) and 28 and 30 % (in the 58 % diet), respectively. These percentages might have been high enough to reveal the obesogenic effect of SFA when used for a 7–8-week period. The source of fat (plant origin v. animal origin) also might have affected the results, for example, because SFA of plant origin might not be as effective as SFA of animal origin in developing obesity. Indeed, SFA of plant origin mainly contain medium-chain fatty acids (lauric acid in coconut oil and palm kernel oil)

rather than long-chain fatty acids which are abundant in fats of animal origin[149].

Taken together, the findings indicate that rats and mice are appropriate models for studying the effects of various fatty acids in developing obesity.

Physiological mechanisms of high-fat diet-induced obesity

Food efficiency and diet-induced thermogenesis

Some reports have attributed obesity induced by high-fat diets to their high food efficiency (g body-weight gain per kJ food consumed). Energy from fat has a larger effect on body-weight gain than has energy from non-fat sources[12,14,22,49,106,150,151]. Diet-induced thermogenesis is the energy for digesting, absorbing and storing nutrients and produces a loss of energy for the body which is 2–3 % for fats, 25–30 % for proteins and 6–8 % for carbohydrates. Therefore, the efficiency of nutrient utilisation differs among macronutrients and fats have an efficiency of 97–98 %, whereas efficiency is 70–75 % for proteins and 92–94 % for carbohydrates[10,12,22,112]. In addition, it costs energy to build long-chain fatty acids from glucose or amino acids, whereas dietary fat contains long-chain fatty acid pre-formed.

Energy density

Some studies have shown that a fat-rich diet induces obesity by increasing energy intake[24,38,39,41,42]. If weight of intake is not increased at least in proportion, this implicates the high energy density of high-fat diets.

Individuals with *ad libitum* access to diets with different energy densities ate the same amount of food by weight (in a meal or over a few days)[72,152–155]. On the other hand, after 2 weeks of exposure, subjects learned to compensate for the higher energy density of the diet, and ate less weight of food[156]. Rats and mice have been labelled as hyperphagic when fed a fat-rich diet, which was based on animals ingesting more energy and not necessarily weight of food[24,39,42,51]. Although in the mentioned studies, the wieght of food ingested was not always reported, rats might have attempted to adjust their intake according to the energy density of the fat-rich diet. While some of the high-fat diets were less dense in other macronutrients and micronutrients, rats could not fully adjust for the extra dietary energy while ingesting a minimal amount of the high-fat diet to meet their requirements (for example, 5 % protein for maintenance and 15 % for growth)[157] with carrying extra energy. Therefore, high-fat diets used to induce obesity in animal models should meet macronutrient and micronutrient requirements of the animals, so that hyperphagia can be better interpreted.

Satiating effects of fat

Weaker satiety signals from fat than from carbohydrates and proteins have been suggested to play a role in over-consumption of energy from fat-rich diets[69,70,158,159]. To clarify if the hyperphagia from fat-rich diets is due to their post-ingestive effect, rats were administered by gastric self-infusion for 16 d isoenergetic high-fat (59·9 % of

energy) and high-carbohydrate (fat: 16·7 % of energy) liquid diets[160]. Rats self-infused more energy per d of the high-fat diet than of the high-carbohydrate diet; thus, when orosensory effects are minimised, hyperphagia on high-fat diets remains. Poorly satiating post-ingestive effects of fat produced more frequent meals and resulted in large meals[160].

Post-ingestive effect of nutrients also may increase food intake by conditioning sensory preference[159]. In a 9 d study, adult female Sprague–Dawley rats were infused intragastrically with isoenergetic high-fat (59·6 % of energy) and high-carbohydrate (14·6 % of energy) diets paired with different flavours (cherry, grape or strawberry). The rats drank substantially more (38 %) of the solution paired with the infusion of the high-fat diet than the solution paired with the infusion of the high-carbohydrate diet, hence the post-ingestive effect of the diets high in fat enhances preference for the sensory features of high-fat diets[159].

Various mechanisms have been suggested for a reduction in satiety signals with high-fat feeding and attenuation of suppression of energy intake by high-fat diets. These include: (1) attenuated enterogastric inhibition of gastric emtpying and secretion of satiety hormones (cholecysto-kinin, peptide YY (PYY) and glucagon-like peptide-1) which are normally stimulated by the presence of fat in the small intestine, and thus decrease late satiety[161,162]; (2) inhibition of fatty acid oxidation[163,164], so that high-fat diets lower the rate of oxidation of fatty acids, hence they may increase intake; (3) insensitivity to the food intake reducing the effect of apoA-IV, which is a peptide that decreases meal size[165,166]. Low-energy-dense diets have greater volume and so induce more stomach distension than diets with higher energy density[13].

Hormones

Signals from adipose tissue (leptin, adiponectin and resistin), stomach (ghrelin and obestatin), pancreas (insulin) and intestine (cholecystokinin, PYY and incretins including glucagon-like peptide-1 and gastric-inhibitory peptide) are sent to the brain to regulate energy balance[167–169]. The present review reports the most extensively studied hormonal effects on energy balance (by reducing energy expenditure or increasing energy intake) associated with high-fat feeding.

Leptin. Leptin, first identified in 1994 by Rockefeller University scientists, is an important hormone in the control of food intake and body weight[170]. It is as an obese gene product produced by adipose tissue, generally in proportion to fat mass, with rises in plasma levels resulting in a decrease in food intake and increase in energy expenditure[170–174]. Plasma leptin levels display a circadian rhythm. In humans, leptin is increased during the night and peak values are reached at about 24.00 hours, while minimum values are found at midday[175,176]. Studies in human subjects have shown that obesity is associated with higher concentrations of plasma leptin[176]. Moreover, in healthy men, leptin levels increased in response to a high-fat meal; however, no differential effects among fatty acid chain length or saturation were reported[177].

Laboratory rats have similar circadian variations of plasma leptin, although maximum levels are reached in the middle of their active phase (at night) and minimum levels in the middle of their resting phase (daytime)[178,179]. In a study in weanling male and female normal FVB mice, 12 weeks of feeding a high-fat diet (Western diet, Teklad Adjusted Calories Western-Type Diet, no. 88 187, fat at 40 % of total energy; Harlan-Teklad, Madison, WI, USA) produced 2·6- to 4·6-fold elevation in plasma leptin levels (measured between 09.00 and 11.00 hours) relative to control mice fed chow, but intake of energy was not less than that of the chow-fed controls[180]. Higher leptin levels were also found after a 2 h high-fat meal at dark onset compared with pre-meal levels in adult male obesity-prone Sprague–Dawley rats[181].

In adult male Osborne–Mendel rats, adapted to a high-fat diet (56 % of energy) for 2 weeks, no reduction in food intake at 2, 4, 6 and 24 h following intraperitoneal injection of leptin (0·5 mg/kg body weight) after an overnight fast was found[182]. In contrast, when the rats had been adapted to a low-fat diet, the injection suppressed the food intake at all time points. Thus, the intake response to peripheral leptin was impaired by chronically high levels of fat intake[182]. Harrold et al.[41] found hyperleptinaemia after 1 week of feeding adult male Wistar rats a raised level of energy as fat (13 % of energy). Levin & Dunn-Meynell[46] showed that when adult male Sprague–Dawley rats were fed a high-fat diet (31 % of energy) for 1 week and were then switched to 3 weeks of chow feeding, leptin levels (time of sampling not mentioned) were higher in rats that were prone to developing obesity on the high-fat diet than in rats that were resistant to dietary obesity despite having comparable body weights. Both obesity-prone and -resistant Sprague–Dawley rats fed high-fat diets (at 20 % of total energy) showed resistance to the anorectic effect of centrally administered leptin (10 μg; intracerebroventricular; ICV), while control animals fed a low-fat diet (3 % of total energy) decreased their energy intake following leptin adminis-tration[95]. However, in another study resistant animals did not show compromised responsiveness to the food-lowering effect of leptin when fed high-fat diets[183]. Overall, these results indicate that high-fat feeding induces hyperleptinae-mia and leptin resistance and that this effect is independent of obesity-induced leptin resistance.

The mechanism thought to be involved in hyperleptinae-mia and leptin resistance on the high-fat diet involves hypothalamic leptin receptors and their signalling path-ways[180]. Animals susceptible to dietary obesity have reduced hypothalamic leptin receptor gene expression and show an early leptin response to an increase in dietary fat[184].

In contrast to this, Ainslie et al.[39] showed that female hooded Wistar rats aged between 20 and 22 weeks fed a high-fat diet (36 % of energy) for 4 weeks had significantly lower plasma leptin levels (measured after an overnight fast) than control rats fed low-fat diets (6·5 % of energy)[39]. A more recent study showed that adult male Sprague–Dawley rats fed a high-fat diet (60 % of energy) for 2 weeks were hypersensitive to the food intake-lowering effect of ICV administration of leptin (3 μg); however, after 5 weeks on the high-fat diet, rats became insensitive to this effect of injected leptin[185]. Another study in weanling C57BL/6J

mice led to similar conclusions[186]. The researchers suggested that early in high-fat feeding, animals are sensitive to the food-lowering effect of leptin but despite the reduction in food intake animals become fat as a result of the increase in food efficiency, leading to an increase in plasma leptin levels that is followed by insensitivity to its action[186]. This implies that leptin resistance after long-term feeding on a high-fat diet is an effect of the obese state rather than the cause of obesity development.

Animal studies found that the fatty acid composition of a high-fat diet may influence leptin levels in the circulation. Lower serum leptin levels (measured 3–6 h after initiation of the dark phase) were found in 8-week-old lean male Wistar rats fed a diet rich in long-chain SFA (cocoa butter at 60 % of energy) than in animals fed a diet rich in long-chain PUFA (safflower-seed oil at the same percentage) or chow for 8 weeks[61]. Although total body fat was similar across dietary groups, SFA-fed rats had less abdominal and epididymal fat, and more intrathoracic fat compared with the other groups. Another study found that adult male Sprague–Dawley rats fed a beef tallow-based diet for 10 weeks had lower leptin levels than animals fed safflower-seed or fish oil, while fish oil-fed animals had the lowest amount of perirenal fat[62]. These studies suggest that the site of fat accumulation depends on the fatty acid profile of the diet, and various adipose tissue depots can differently contribute to circulating leptin. However, no differences were found between moderate-SFA and -MUFA beef tallow, high-PUFA safflower-seed oil and high-n-3 PUFA fish oil in the increased fasting leptin levels in adult male Sprague–Dawley rats fed these diets for 10 weeks[187]. Greater leptin levels were found in weanling C57BL/J6 male mice fed high-fat diets (at 58 % of energy) based on beef tallow for 7 weeks than mice fed high-fat diets based on fish oil, safflower-seed oil or animals fed low-fat diets (at 10 % of energy); leptin levels were correlated with body fat as well[60]. Similar results were found in other studies[102,188].

Ghrelin. Ghrelin is a peptide released by cells in the fundus of the stomach that stimulates the release of growth hormone from the pituitary and was identified by Kojima *et al.* in 1999[189]. Ghrelin rises before and falls after each *ad libitum* meal and increases food intake[190,191]. In humans ghrelin levels peak in the morning (08.00 hours), at noon (12.00 to 13.00 hours) and in the evening (17.00 to 19.00 hours) and fall after each peak[192]. Obese individuals have lower fasting ghrelin levels than lean individuals and reduced suppression of ghrelin secretion after a meal[193–196]. A fat-rich meal has a smaller suppressive effect on plasma ghrelin concentration than a carbohydrate-rich meal regardless of obesity status[197]. So far, no effect of dietary fatty acid profile on total ghrelin levels has been reported[177,198].

In rats there is a peak of plasma levels of ghrelin 5 h after light onset (resting phase) which remains relatively high for 9 h[178]. There is also a second rise just before the beginning of the dark phase, followed by a sharp drop and then a gradual rise during the remainder of the dark phase[199]. Ghrelin gene expression and plasma ghrelin concentrations have been found to be lower in mice with dietary obesity than in their lean counterparts, coupled with a decrease in sensitivity to the orexigenic effects of ghrelin as well as

impairment in suppression of ghrelin in response to a meal[200,201]. A study was conducted by Liu *et al.*[202] in two strains of rats with different susceptibilities to develop obesity (Osborne–Mendel prone and S5B/P1 resistant) fed a diet high in fat (56 % of energy) for 2 weeks. Ghrelin gene expression was increased in the stomach of fasted susceptible rats but plasma ghrelin concentrations remained unchanged, while in resistant rats both expression and plasma levels of ghrelin remained unchanged. This indicated that ghrelin may play a role in susceptibility to dietary obesity. In adult Long–Evans rats, 2 weeks of high-fat feeding (70 % of energy) was associated with lower levels of ghrelin than was feeding on a high-carbohydrate diet[203]. In an attempt to distinguish between the effects of a high-fat diet and of dietary obesity on ghrelin concentrations, Greeley *et al.*[204] fed adult male Sprague–Dawley rats high- (45 % of energy) or low (12 % of energy)-fat diets for 3 weeks. Both groups were tested with triiodothyronine (T$_3$) to prevent accumulation of fat. Decreased ghrelin levels in high-fat-fed animals were not restored by T$_3$ treatment, despite the fact that the groups had comparable weights. Moreover, duodenal and jejunal infusion of fat suppressed plasma ghrelin less than glucose and amino acids in adult male Sprague–Dawley rats[205].

The mechanisms suggested for ghrelin's actions are twofold. It stimulates hypothalamic secretion of neuropeptide Y that increases food intake, decreases fat oxidation and utilisation of fat and plays a role in meal initiation[190,203]. Ghrelin also decreases the utilisation of fat[191]. High-fat diets are known to down-regulate ghrelin secretion[200,203] and an inverse relationship between leptin and ghrelin has been reported[203]. On the other hand, hypothalamic expression of ghrelin receptors was enhanced and ghrelin levels were greater in adult male Wistar rats fed a fat-rich meal[206]. Thus, regulation of ghrelin concentration through fat intake remains inconclusive.

Since suppression of ghrelin levels after a meal is associated with postprandial satiety, the lower suppression of ghrelin secretion following high-fat diets might be an explanation for hyperphagia on high-fat diets. Thus, in an environment with abundant high-fat foods, impairment of ghrelin suppression after a meal leads to overconsumption of energy and induces obesity. Furthermore, the obesity itself impairs the suppression of ghrelin secretion after a meal which further exacerbates the development of obesity.

Insulin. Obesity is associated with elevated basal plasma insulin levels and resistance to the metabolic effects of insulin[77,207]. Independent of obesity, high-fat feeding itself contributes to impaired glucose tolerance and insensitivity to the blood glucose-lowering effect of insulin[207,208]. The fatty acid profile of the diet plays a crucial role in insulin resistance dependent on a high-fat diet[207–209]. In a human study, intake of SFA and MUFA was positively correlated with plasma levels of glucose and insulin[210]. Replacing SFA with MUFA had no beneficial effect on blood glucose and insulin levels during 4 weeks of high-fat feeding in adult overweight and obese men[119]. On the other hand, some studies have shown beneficial effects of MUFA intake on glucose homeostasis and insulin sensitivity[211].

Animal studies have also shown that hyperinsulinaemia and insulin resistance are induced by high-fat feeding[42,166,212]. In female C57BL/6J mice fed high-fat diets (at 10, 20, 30, 40, 50 and 60 % of total energy) for 15 weeks, a linear relationship between the percentage of dietary fat and glucose intolerance was found[26]. This dose-dependent effect was also seen in weanling male Sprague–Dawley rats fed diets with different percentages of energy as fat (10, 32, 45 %)[24].

Mechanisms of the hyperinsulinaemia and insulin resistance with high-fat diets and obesity are discussed in reviews by Lichtenstein & Schwab[207], and Riccardi et al.[208]. These authors suggest that decreases in insulin receptors, glucose transport and metabolism are involved, plus reduction in liver and muscle glycogen synthase activity and storage of glucose as glycogen[207,208]. These abnormalities thus develop when the intake of fat is more that 40 % of total energy. Excessive amounts of adipose tissue (hypertrophy and hyperplasia) stress the endoplasmic reticulum, resulting in secretion of cytokines and decrease in the responsiveness of the cells to insulin[77].

Differences among dietary fatty acids affect the composition of the cell membranes and this in turn influences the affinity of receptors for insulin and so its action on the cell[207,208,213]. Some studies have found that insulin secretion and sensitivity are enhanced as the degree of unsaturation of fatty acids increases, especially with n-3 feeding, and thus feeding diets rich in SFA results in more insulin resistance than MUFA and PUFA[116,207,208,213]. In a study in 7-week-old female C57BL/6J mice fed high-fat diets (60 % of energy) composed of palm oil, lard, fish oil, perilla oil or rapeseed oil for 18 weeks, blood glucose levels were higher in all the high-fat-fed animals 30, 60 and 120 min after an oral glucose challenge than in the group fed a high-carbohydrate–low-fat diet (fat: 11 % of energy), but the increase in fasting blood insulin levels was only reliable in the group fed palm oil[52]. In weanling female Wistar rats, no difference in insulin levels was found between soyabean oil and palm oil groups[102], whereas lower plasma insulin levels were found in adult male Wistar rats fed a high-fat diet (60 % of energy) rich in SFA (cocoa butter) than in the control animals (10 % of energy)[61]. These disparities might be related to different fats used in these studies: palm oil and cocoa butter differ in SFA content and so diets will vary in SFA at the different percentages of total energy used in the studies. The same can be said for lard, soyabean oil and safflower-seed oil. Beneficial effects of n-3 PUFA on action of insulin are reported in many studies[52,62,214,215].

Since human and animal studies have shown comparable relationships of hormones to obesity, these models can be used to clarify the uncertain areas such as effects of fatty acid profile of the diet on these hormones. However, relating hormone action to obesity itself requires demonstration of its effect on energy intake and/or expenditure.

Behavioural mechanisms of high-fat diet-induced obesity

As discussed in the previous sections, one explanation why high-fat diets induce obesity is hyperphagia[24,38,39,41,42], i.e. increased weight or volume of daily dietary intake.

Effects of energy density were reviewed earlier. A possible lack of inhibitory effects of fats on intake ('satiety') was discussed above. Here the intake-facilitatory effects of sensory characteristics (or palatability) of high-fat diets will be considered[13,22,69,70]. Feeding rhythmicity[216,217], social environment[5,218–228] and stress[229–231] may also promote obesity. Each of these will be reviewed below. Because social environment is not documented in relation to high fat intake, only feeding rhythmicity and stress will be reviewed below.

Sensory facilitation of intake

Facilitation of intake by the sensory characteristics of high-fat foods is an important influence on ingestion. Sensory stimulation from food consumption can influence energy intake directly[232], by promoting selection, consumption, digestion and absorption of a food[233]. It also increases diet-induced thermogenesis[234,235]. Foods high in fat are usually preferred by rats to those that are low in fat and are consumed in greater amounts as a result[13,70,156,236]. A variety of sensory properties contribute to this high palatability of fat-rich diets, mainly texture and odour[69,160,237,238].

In a study on adult male Long–Evans rats, Warwick & Weingarten[160] compared the sensory effects of a high-fat (59·9 % of energy) and a high-carbohydrate diet (fat at 16·7 % of energy). In order to minimise the post-ingestive effect of diets on intake, they used a preparation in which most of the ingested liquid food drained out of the stomach via a fistula. When both diets were offered simultaneously, rats consumed more of the high-fat diet than the high-carbohydrate diet, demonstrating a sensory preference. Warwick et al.[238] concluded from a study in weanling female Sprague–Dawley rats that consuming high-fat diets early in life can lead to a sensory preference for this fat product which is relatively stable.

Evidence for sensory preferences for fats in rat and mouse animal models is likely to be based on NEFA released from the TAG in food[239,240]. Lingual lipase has such activity in rodents; taste receptor cells in the oral cavity of rats can easily detect these NEFA; these gustatory signals are transmitted to the brain where they cause release of neurotransmitters such as dopamine and endorphin[239–241]. Long-chain PUFA stimulate T-cell receptors more efficiently and thus are more strongly preferred than other types of fatty acid[241]. Preference for fat is also found in humans, with textural, olfactory and gustatory cues being involved[242].

Rhythmicity of feeding

Rhythmicity in feeding (variation over time in total amount ingested, size and frequency of meals) may play a role in the development of obesity. In human subjects, a lower risk of obesity was reported in both adults and children with a high frequency of eating episodes[216,217,243]. A greater number of meals each day was consumed by obese women than healthy-weight women in Sweden in a cross-sectional survey[244]. However, similar meal patterns were found in

obese and healthy-weight Swedish men in a dietary survey[245].

Time of eating also may play a role in the development of obesity. In humans, meals eaten late in the evening have been suggested to be one of the risk factors of obesity[217,246]. In free-living individuals food intake in the morning was more satiating and associated with less overall intake throughout the day than evening food[5]. However, in another study, percentage energy from evening food intake and weight changes were unrelated[247]. Taylor *et al.*[248] and Bellisle[249] suggested that the effects of meal patterns on human obesity have yet to be clarified.

Unlike humans, rats are nocturnal animals that ingest 70–80 % of their food during the dark phase[250]. There are two peaks in meal frequency and rate of intakes: at the beginning of the night and towards the end, i.e. dusk and dawn feeding[251,252]. In adult male Wistar rats fed a stock diet containing 10 % energy as fat, the greater intake during the dark phase resulted in positive energy balance and fat deposition, with negative energy balance along with the oxidation of fat in the light phase over fourteen 24 h cycles[250,253]. Altered circadian rhythmicity of intake characterised by larger meal size and decreased meal frequency has been found in genetically obese animals fed non-purified diets[252,254–257].

Some animal studies have found a relationship between sizes of meals and susceptibility to obesity. Adult male Sprague–Dawley rats that ingested chow in larger meals had a higher rate of weight gain when fed high-fat diets than rats that were fed on chow in smaller meals[258]. When weanling male obesity-prone Sprague–Dawley rats were fed high-fat diets (45 % of energy) for 19 weeks, they ate larger meals than resistant animals[259]. In adult inbred obesity-prone and -resistant rats fed chow, on the other hand, the obesity-prone rats ingested smaller meals more frequently[260]. These results suggest that an irregular meal pattern is not a cause of developing obesity in obesity-prone animals. A 6 h meal pattern analysis during the dark phase in adult male Sprague–Dawley rats exposed to isoenergetic high- and low-fat diets (soya oil at 38 and 10 % of total energy) for 2 weeks revealed comparable amounts of food ingested in the first meal, but less food ingested in the second and third meal of high-fat-fed rats, as well as greater meal frequency, shorter inter-meal interval (IMI) and lower rate of weight gain than animals fed the low-fat diet[261]. However, when feeding period was prolonged to 8 weeks, the size of the second meal and IMI increased. Increased meal size and decreased meal frequency have also been found in rats acclimatised to a mixture of high-fat and high-carbohydrate diets (providing 38·5 % energy as fat) for 14 d and then fed a fat-rich diets (at 60 % of total energy) for an additional 8 d[262].

There is a shift of food intake from the dark phase to the light phase in genetically obese rats and mice[254–256]. Mistlberger *et al.*[263] reported higher weight gain in genetically obese Zucker rats when fed *ad libitum* than in those fed only during the 14 h dark phase, while both groups had similar food intakes. In addition, rats differ in their macronutrient selection during the light–dark cycle. It has been reported that when rats are offered a two- or three-way selection between macronutrients, they eat more carbohydrate at the beginning of the dark phase, and more protein and fat at the end of the dark phase and during the light period[264]. Thus it is probable that, with high-fat feeding, more food will be ingested in the light period that may further facilitate the development of obesity.

Obesity-prone rats respond more than resistant animals with an increase in meal size. This might account for the hyperphagia with high-fat feeding in dietary obesity. Further research is needed to find out the cause–effect relationship between eating patterns and obesity.

Stress

Many studies have shown that long-term stress increases food intake and promotes weight and fat gain in human subjects[265,266]. In addition, obesity was found to be associated with depression[267]. Higher levels of obesity in depressed individuals as well as higher prevalence of depression in overweight and obese women and extremely obese men (BMI $\geq 40 \, \text{kg/m}^2$) were found[268,269]. Depressed individuals with eating disorders often describe themselves as chronically stressed and usually are obese, suggesting that they eat more when stressed in an attempt to cope with the situation and feel better[230]. Energy-dense foods with high fat and sugar are known as 'comfort food' and are more often eaten during stress[229,266,270]. On the other hand, some individuals show loss of appetite during stress[271]. It has been suggested that this difference is based on the dieting history of the individual: usually dieters increase and non-dieters decrease their intake while in a stressful situation[271].

A different pattern of responsiveness to stress has been shown in a variety of rodent models[99,272–274]. Rowland & Antelman[274] discovered that in adult female Sprague–Dawley rats mild stress induced by six daily sessions (10–15 min) of pinching of the tail for 5 d at equal intervals while they had free access to sweetened milk and tap water resulted in greater food intake and body-weight gain than in the control animals. However, chronic exposure of adult male Sprague–Dawley rats to an immobilisation stressor led to a decrease in food intake, independent of the duration of the stress, while handling stress did not result in change in food intake[273].

Obesity-prone and -resistant animals are also different in their responsiveness to stress. A study was conducted by Levin *et al.*[272] in 2·5-month-old selectively bred male obesity-prone and -resistant Sprague–Dawley rats fed a high-fat diet (31 % of energy) for 1 week. They were then randomly assigned to a stress group or control group while fed the high-fat diet for 3 weeks and then the high-fat diet plus Ensure® (Ross Products Division, Medical Supplies Depot, AL, USA) for another 2 weeks. Rats in the stress group had daily exposure to different stressors for 5 weeks, which were restraint for 15 min, moving the animal to the cage of another, exposure to another male rat for 10 min, 2 min swimming or saline injection. Results showed that stressed obesity-resistant rats gained less weight without any decrease in energy intake with little effect of the stressors on body-weight gain and energy intake of obesity-prone animals. Adding Ensure® to the high-fat diet increased energy intake and rate of weight gain in resistant

animals, but cumulative weight gain over 5 weeks was still lower in stressed rats than in control animals. Weight gain and intake of the obesity-prone rats were unaffected by the addition of Ensure®. It was suggested that resistant rats had a lowered sympathetic activity compared with their unstressed controls, which was shown by lower noradrenaline levels in their urine.

The effect of a high-fat diet on weight gain after stress was investigated in a study in 3- to 4-month-old male obesity-prone and -resistant Sprague–Dawley rats that were restrained once for 20 min, and after release were presented either a high-fat diet (at 31 % of energy) or chow for 9 d[99]. Stressed prone rats fed the high-fat diet gained more weight than unstressed prone rats fed the same diet while having similar food intakes. However, when stressed prone rats were fed chow, they gained less weight than unstressed prone rats fed the same diet. These results showed that prone rats were less responsive to the weight-reducing effect of immobilisation stress when fed a high-fat diet; at the same time they were more responsive to this effect when fed chow. Immobilisation stress had no effect on body-weight gain in resistant rats fed either diet[99]. In another study, adult male Sprague–Dawley rats fed high-fat (at 40 % of total energy) or low-fat diets (at 12 % of total energy) for 4 d were divided into two groups of stressed (restraint tubes with no food and water access followed by tail blood sampling, 3 h daily for three consecutive days) and mildly stressed rats (moved to new cages, food and water deprived for the same period and blood sampled)[275]. On the days of restraint, stressed rats lost weight regardless of the diet. High-fat-fed mildly stressed animals stopped gaining weight; however, low-fat-fed mildly stressed rats gained weight throughout the experiment[275]. Results showed that low- and high-fat diets resulted in similar body-weight changes under a severe stress, whereas with a mild stress high-fat-fed animals were more responsive to the weight-lowering effect of stress. In adult male Long–Evans rats, the weight loss resulting from chronic stress was regained after recovery from stress and body-weight and fat gain were greater in high-fat-fed rats than in chow-fed control animals[276]. Higher preference for high-fat feeding during chronic stress was reported in mice[277].

Mechanisms that influence food intake during acute and chronic stress are different. Physiologically, the initial response of the body to an acute stress is secretion of corticotrophin-releasing factor from the paraventricular nucleus of the hypothalamus that stimulates the secretion of adrenocorticotropin hormone from the anterior pituitary which in turn leads to the release of cortisol from the adrenal cortex to provide energy for the brain and/or muscles. Then cortisol itself makes a negative feedback for its further secretion. However, with a chronic exposure to stressor, the negative feedback does not work efficiently and thus induces an increase in food intake and body-weight gain through increased secretion of glucocorticoids which elevate appetite, food intake and fat storage especially in the abdomen[230,231,278]. In adult male Wistar rats, a chronic stress of keeping rats in cages filled with water to a height of 2 cm for 5 d led to delayed gastric emptying during the first 24 h of exposure, but after that it was accelerated and exceeded that of the control group by day 5. In addition,

catecholamines were increased during the first 24 h and then decreased while active ghrelin levels were high on day 3 and remained elevated until day 5[279]. It was suggested that the increased sympathetic activity after 24 h stimulated ghrelin secretion, and therefore the increased food intake found during chronic stress might be a result of enhanced plasma ghrelin. Plasma ghrelin levels were also found to be increased with acute stress[280].

Susceptibility to obesity

There is a genetic background for susceptibility to obesity with interacting environmental factors; the environment alone has an impact on the inherent risk of obesity in individuals[5,6,281−283]. This has been shown in many studies in human subjects[2].

An underlying genetic predisposition to be obesity prone or resistant is also shown in animal models[46,184]. Rats and mice known as the standard models for studying dietary obesity are different in their susceptibility to obesity: outbred Sprague–Dawley rats, Wistar rats and C57BL/6C mice can be easily categorised to prone and resistant phenotypes with *ad libitum* access to high-fat diets[7,8,21]. There are also strains known as genetically obese, such as Zucker *fa/fa* rats and *ob/ob* mice[8,35].

When exposed to high-fat diets, some animals are sensitive to high-fat diet-induced obesity and become obese (obesity-prone animals), while others resist to this obesogenic effect and grow normally (resistant animals)[82,284]. Some researchers have attributed this difference to higher energy intakes in obesity-prone animals[51,60,97,259,285,286], while others have found similar intakes in prone and resistant animals, and suggested that susceptible animals were capable of storing energy with greater efficiency[95,287,288].

Suggested mechanisms for the difference between prone and resistant animals in responding to high-fat diets are that prone animals have lower fat oxidation[40,98,288,289], increased lipoprotein lipase activity in their adipose tissue and no change in lipoprotein lipase activity of their muscles which favours fat storage in these animals[97,289,290]. However, Commerford et al.[286] fed 7-week-old male Wistar rats high-fat diets (45 % of energy) for 1 or 5 weeks and found comparable fat accumulation and lipogenesis in prone and resistant rats after provided with an isoenergetic ^{14}C-labelled high-fat meal, suggesting that the increased energy intake is the main reason for accelerated weight gain in prone animals.

Dietary obese-prone animals also had increased arcuate neuropeptide Y mRNA expression (an orexigenic neuro-peptide)[291], decreased noradrenaline turnover and α_2-adrenoceptor binding in some parts of the hypothalamus (ventromedial, dorsomedial and lateral) compared with resistant animals, as well as in the pancreas and heart, which shows a reduced sympathetic activity in these organs[292]. The reduction in noradrenaline turnover in the pancreas leads to an increase in insulin release and development of obesity.

Sex differences

In humans, there are differences between the two sexes in energy expenditure and requirements as well as in fat

metabolism and fat distribution[293–295]. Greater storage of fat in the lower body in females (gynoid) due to lower basal fat oxidation and greater number of α_2-adrenoceptors, as well as decreased α_2-adrenergic sensitivity in the abdominal region, all lead to more fat storage in the thigh region and less in the abdomen compared with men who have greater storage of fat in the upper body (android)[293–295]. Moreover women have more subcutaneous fat than men[296]. Despite all these differences, in a recent review of the genetic studies of obesity in different countries it was shown that overall obesity rates of males and females as determined by BMI were small and inconsistently different, with no indication of obesity in either sex being more prevalent[295].

These differences can also been found in animal models of obesity[35]. In laboratory rats, males gain weight steadily throughout their lives while the body weight of female rats becomes stable in early adulthood[297]. As a result, female rats are better models for studying obesity during adulthood since they are more like humans in their growth patterns. Besides, more subcutaneous fat is found in females due to higher concentrations of oestrogen and progesterone receptors in these depots while males have more visceral fat related to high concentrations of androgen receptors in this area[298].

The sex of the animals may also affect the cellular response of the adipose tissue to high-fat feeding. This was shown in adult rats fed cafeteria diets for 9 weeks which led to a more rapid development of obesity in female rats, and their difference in weight compared with control animals became obvious after 5 d while in males this became significant after 40 d[44]. The same report showed that weight gain of male and female rats fed a supermarket diet is more similar to each other than that of rats fed chow. Therefore, the sex difference in weight gain normally seen in rats is reduced when animals are developing dietary obesity. Female golden hamsters, aged 10 weeks, fed a fat-rich diet (52 % of energy) ate significantly more energy and gained more weight than males[106]. Likewise, 10 d old female Wistar rats fed a cafeteria diet for 14 weeks gained more weight than their male counterparts fed the same diet, suggesting less thermogenic capacity in females when fed the cafeteria diet[299]. A study in 3-month-old Sprague–Dawley rats showed that female rats fed chow had higher food intake and greater increase in ghrelin and decrease in leptin levels than males following a 12 h fast[300]. Moreover, an interaction between sex and site of fat accumulation was found in 6-week-old NMRI mice given different amounts of fat (17, 27, 43·5, 60 % of energy) for 14 weeks, with more fat accumulation in retroperitoneal and parametrial sites in females, and in subcutaneous depot in males[25].

All together, similar to humans, male and female rats have different body fat distribution which makes them appropriate models for studying adipose tissue. Besides, female animal models are better responders to high-fat feeding, mimicking susceptibility to obesity in humans. However, in a recent review, male mice and rats are introduced as 'gold standards' for studying dietary obesity[7]. This might be because of the oestrous cycle of the female animals which is repeated every 4–6 d and can affect the food intake of the animal during this period[301].

Reversibility

Animal studies have shown that low-fat diets can induce weight loss in dietary obese rats. A reduction in energy intake and obesity reversal was found when adult male Wistar rats fed a high-fat diet at 60 % of total energy for 17 weeks were switched to chow for 13 weeks[302]. Decreased energy intake and obesity reversal with significant weight and fat loss were found in weanling male C57BL/6 mice switched from 17 weeks of high-fat feeding (at 58 % of energy) to low-fat feeding (at 11 % of energy) for 17 weeks[303] or after 13 weeks of high-fat feeding (at 59 % of energy) to low-fat feeding (10 % of energy) for 6 weeks[51]. Likewise, a reduction in energy intake and a complete reversal of diet-induced obesity were found when 13-week-old female Wistar rats originally fed high-fat diets (at 30 or 60 % of energy provided by Crisco®; Proctor & Gamble, Cincinnati, OH, USA) for 8 or 14 weeks were switched to chow[101].

In other studies, however, *ad libitum* low-fat feeding was not an efficient method to completely reverse dietary obesity. For example, an initial decline in body weight followed by a plateau have been found in adult male obesity-prone and -resistant Sprague–Dawley rats after switching from 10 weeks of a high-fat diet (at 31 % of energy) to chow feeding for 2 weeks[288]; however, when animals were restricted on chow to 50 % of their energy intake for 3 weeks, their body weights reached the level of chow-fed control animals. Decline in body weight and a plateau were also found in adult male obesity-prone Sprague–Dawley rats switched from 10 weeks of being fed a high-fat diet (at 31 % of energy) to 7 weeks of chow feeding, although their energy intake was decreased while on chow[82]. Wade[304] reported that young male and female golden hamsters fed a high-fat diet (at 52 % of energy) for 4 weeks and then switched to chow for 4 weeks (fat at 4·5 % energy) decreased their energy intake and lost 80 % of their weight gain from feeding on the fat-rich diet. Adult male obesity-prone Sprague–Dawley rats fed a high-fat diet (at 31 % of energy) for 12 weeks and then switched to chow for 1 week decreased their energy intake (by 10–20 %) but failed to lose weight[305].

Both hyperplasia and hypertrophy of fat cells are involved in developing obesity[77,78,81]. A total of 8 weeks of energy restriction in normal-weight adult male Sprague–Dawley rats did not result in hypoplasia despite the significant decrease in body weight and body fat[306]. When weanling male Sprague–Dawley rats made obese by feeding a diet containing chow, Crisco®, sweetened condensed milk and sucrose solution for 19 weeks were then food deprived for 8, 15 or 25 d, body weight and fat cell size decreased, but fat cell number was comparable with that of the chow-fed control animals[307]. Another study in adult male C57BL/6J mice fed a high-fat diet (45 % of energy, Research Diets, New Brunswick, NJ, USA) for 10 weeks and then switched to chow for 2 weeks had similar results[308]. Centrally administered leptin (10 μg, ICV) for 4 d in normal-weight adult male Sprague–Dawley rats caused a decrease in the number of inguinal fat cells[309]. Leptin injections (5 μg; ICV) over 5 d decreased the number of fat cells in young (aged 3 months) male Sprague–Dawley rats, but not in mature (aged 8 months) animals[310]. This was also found in

a study in mice[308]. However, a decrease in fat cell number was not found following dietary reversal of obesity in rats and mice[306–308]. These findings contrast with human studies that showed hypoplasia of adipocytes following reversal of obesity[78,81].

Conclusions

The physiological mechanisms involved in high-fat diet-induced obesity are overconsumption of high-fat diets due to their low satiating effects, the high efficiency of dietary fat in being stored in the body as well as the alterations in the hormones involved in energy balance, such as high-fat diet-induced hyperleptinaemia and hyperinsulinaemia accompanied by leptin and insulin resistance, and lowered suppression of ghrelin secretion following high-fat diets. Among the behavioural mechanisms, the sensory facilitation of intake with high-fat diets is well understood. Meal pattern analysis of high-fat-fed animals in a pre-obese v. obese state could be useful to understand the development of obesity. An area for future research is to investigate whether different patterns of eating in animal models before obesity development can be a predictor of prone and resistant phenotypes, and to assess their feeding circadian rhythms. There has been extensive research on the obesogenic effects of fatty acids with different degrees of saturation but no constant pattern of outcome under different conditions has been found. More work is needed to prove that body weight can be regulated by the fatty acid profile in high-fat diets. An important key point in designing animal studies is that high-fat diets meet animals' minimal nutrient requirements, especially for protein, vitamins and minerals, to eliminate the possibility of overconsumption of the diet to fulfill these nutrient needs. The ineffectiveness of low-fat diets fed *ad libitum* to reverse dietary obesity induced by long-term high-fat feeding stresses the use of restricted regimens. This could help to investigate whether a significant and sustainable weight loss accompanied by decrease in fat cell number can be achieved.

Acknowledgements

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