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Obesity and post-prandial lipid metabolism. Feast or famine?

Ian J. Martins[a,*], Trevor G. Redgrave[b]

[a]*Centre for Human Genetics, Edith Cowan University, Joondalup Drive, Joondalup, Perth 6027, Australia*
[b]*Physiology, School of Biomedical and Chemical Sciences, The University of Western Australia, Stirling Highway, Crawley, Perth 6009, Australia*

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Abstract

Both in Western countries and in third world countries there is an increasing incidence of obesity. Obesity per se or insulin resistance associated with obesity may increase cardiovascular risk factors including dyslipidemia, hypertension and Type 2 diabetes. Over the past decade the understanding has increased of specific mediators in the hypothalamus that are involved in regulating food intake and body weight. In obese humans fasting plasma lipids can be normal but postprandial lipid metabolism is abnormal with an accumulation of triglyceride-rich remnant lipoproteins. In viscerally obese men chylomicron remnant catabolism was markedly decreased when compared with lean individuals. The decreased clearance of chylomicron remnants in viscerally obese subjects may be explained by competition between chylomicron remnants and the increased hepatic production of VLDL for clearance by low density lipoprotein receptors. Increased food intake in rodent models of obesity was shown to be associated with a delay in the catabolism of remnant lipoprotein particles. Prevention of hyperphagia was found to correct the impairment in the metabolism of remnant lipoproteins. Under fasting and food restricted conditions the improvement of remnant metabolism was associated with an increased oxidation of remnant lipids as determined by a novel stable isotope breath test. Anti-obesity and lipid lowering drugs have been used for the treatment of obesity. Inhibitors of cholesterol synthesis inhibitors (statins) have been shown to be effective in treating dyslipidemia. Inhibition of cholesterol synthesis with Atorvastatin was shown to improve chylomicron metabolism by increasing chylomicron remnant catabolism in obese subjects as assessed by the newly developed stable isotope breath test.

Keywords: Chylomicron remnant; Obesity; Post-prandial; Stable isotope; Breath test; Hyperphagia; Food restriction; Dyslipidemia

1. Introduction

In epidemiological studies, human obesity is clearly associated with the increased risk for atherosclerosis, contributing to the early onset of coronary artery disease. Obesity also has a well-documented association with Type 2 diabetes. Visceral obesity in particular increases the risk of atherosclerosis owing to both insulin resistance and dyslipoproteinemia. The metabolic basis for this association has not been established.

Risk factors for atherosclerosis that could be exacerabated by obesity include hypertension and hyperlipidemia, particularly hypertriglyceridemia. The contribution of post-prandial lipids to hypertriglyceridemia is attracting increasing attention. It is possible that the high risk of atherosclerosis is mainly due to the presence in plasma of these post-prandial lipoproteins since most individuals are in the post-prandial state for most of the day. Consistent with this view is that post-prandial hyperlipidemia is exacerbated in obesity.

Post-prandial hyperlipidemia is mostly due to increased amounts of chylomicrons (CM) and chylomicron remnants (CR), their partially lipolyzed catabolic products. Currently there are limitations in the existing methods for assessing CR metabolism, which has hindered the understanding of the contribution of cholesterol-rich remnants to the development of coronary artery disease. The capacity to metabolize CR contributes to the risk of atherosclerosis in man, as measured by the progression of coronary atherosclerosis determined angiographically [1,2].

The role of a new stable isotope breath test for CR metabolism has been evaluated in rodent models of obesity and in viscerally obese humans. The associated hyperphagia with obese mice in common with postprandial hyperlipidemia has been assessed. The effects of food restriction on postprandial hyperlipidemia in obese mice as well as other interventions in man, lipid lowering drugs and exercise will be discussed.

* Corresponding author. Tel.: +61-8-9400-5714; fax: +61-8-9400-5851.

E-mail address: imartins@cyllene.uwa.edu.au (I.J. Martins).

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Table 1
Characteristics of lean and obese men

	Lean Men (n = 11)	Obese Men (n = 12)
Age (yr)	45.7 ± 12.8	43.8 ± 8.4
BMI, kg/m2	24.6 ± 0.6	33.4 ± 0.98*
Waist, (cm)	82.6 ± 1.7	112.2 ± 3.1*
Plasma Cholesterol, (mM)	5.0 ± 0.16	5.12 ± 0.14
Plasma Triglyceride, (mM)	1.15 ± 0.07	1.36 ± 0.11
Non-HDL cholesterol, (mM)	4.09 ± 0.17	3.51 ± 0.16*
LDL cholesterol, (mM)	2.93 ± 0.16	3.45 ± 0.13
Glucose, (mM)	4.85 ± 0.22	5.01 ± 0.16
Insulin, IU/L	4.95 ± 0.63	13.0 ± 1.4*
Free fatty acids	0.64 ± 0.15	0.31 ± 0.04

* Significantly different from lean men ($P < 0.03$).
Adapted from Ref. [21] (Watts et al. Clin. Sci.)

1.1. Obesity

1.1.1. Human obesity

Many epidemiological studies have used body mass index (BMI) to assess obesity in clinical practice [3,4,5]. In centrally obese individuals with BMI greater than 30.0 Kg/m^2 lipoprotein metabolism is disturbed (**Table 1**). Plasma triglyceride- rich lipoproteins (TRL) are elevated with low concentrations of high density lipoproteins (HDL) and an increase in small dense low density lipoproteins [6,7]. Intestinal CR and hepatic derived lipoproteins account for the increased TRL.

Methods to quantitate CR content and metabolism include measurements of plasma triglycerides, apo B48 [8,9], remnant-like lipoprotein cholesterol (RLP-C) [9,10] and retinyl esters [11-17]. Plasma contents of retinyl esters after an oral fat load have been used in several studies to assess postprandial lipoprotein remnant metabolism in obese and diabetic individuals [11-17]. In obese subjects with visceral obesity the exaggerated and prolonged hyperlipidemia was associated with the accumulation of CR [18,19,20]. The defects in lipid metabolism may be related to increased output of intestinal lipoproteins or a defect in CR clearance and metabolism.

In both obese and Type 2 diabetic individuals chylomicrons appeared to be cleared at a significantly slower rate as reflected by the retinyl ester response curves indicating that CR clearance was defective [11-15]. However intrepretation is uncertain, since data are affected not only by clearance but also by kinetics of absorption of vitamin A in the intestinal tract. Furthermore retinyl esters have been shown to exchange between lipoprotein fractions and are not ideal markers for tracing CR clearance [15].

In recent studies our laboratory has developed a stable isotope breath test that has been shown to monitor CR clearance and metabolism in man [9,20-23] The stable isotope breath test is simple to perform and has been validated in individuals with familial dyslipidemias [22]. Remnant-like lipid emulsions labeled with cholesteryl [^{13}C]oleate were injected intravenously and breath samples collected. Breath tests were conducted in individuals under fasting conditions to avoid consumption of foods variable in ^{13}C and the subjects were restricted in physical activity. Potentially confounding factors such as fatty acid pool sizes and respiratory quotients have been considered and do not invalidate interpretations. Unlike rodents, HDL3 and cholesteryl ester transfer protein (CETP) are present in human plasma [24]. In man, the emulsion cholesteryl [^{13}C]oleate may be transferred to other lipoprotein fractions and breath test studies involving individuals with high and low CETP activity need to be performed to address this possibility.

The clearance and metabolism of emulsion remnants were monitored by the appearance in breath of labeled $^{13}CO_2$ and fractional clearance rates of CR were shown to be markedly decreased in obese individuals with normal lipid levels [9,20-21]. Individuals with visceral obesity and insulin resistance who did not have elevated plasma lipid levels had delayed CR clearance (Fig 1B) when compared with lean individuals (Fig 1A). In other studies viscerally obese men were shown to have increased hepatic output of VLDL [25] (Fig 1B), indicating competition between the hepatic secretion of VLDL and injected CR particles [26]. The delayed CR metabolism in viscerally obese men may not only be related to competition between hepatic VLDL and CR but related to decreased LDLr expression since LDL receptor expression is down-regulated in these individuals [27].

In obese individuals there are several abnormalities in free fatty acid metabolism [28-29]. There is an increase of FFA release from adipose tissue to the blood plasma which impairs uptake of glucose by muscle in obese individuals [28,29]. The rate of lipolysis is accelerated in visceral adipose tissue and the increase in circulating FFA results in dyslipidemia, hyperinsulinemia and hyperglycemia in obese subjects [30]. In recent studies acylation stimulating protein (ASP) an adipocyte-derived protein has been shown to be play an important role in stimulating triglyceride synthesis and fat storage [31]. In ASP knockout mice postprandial

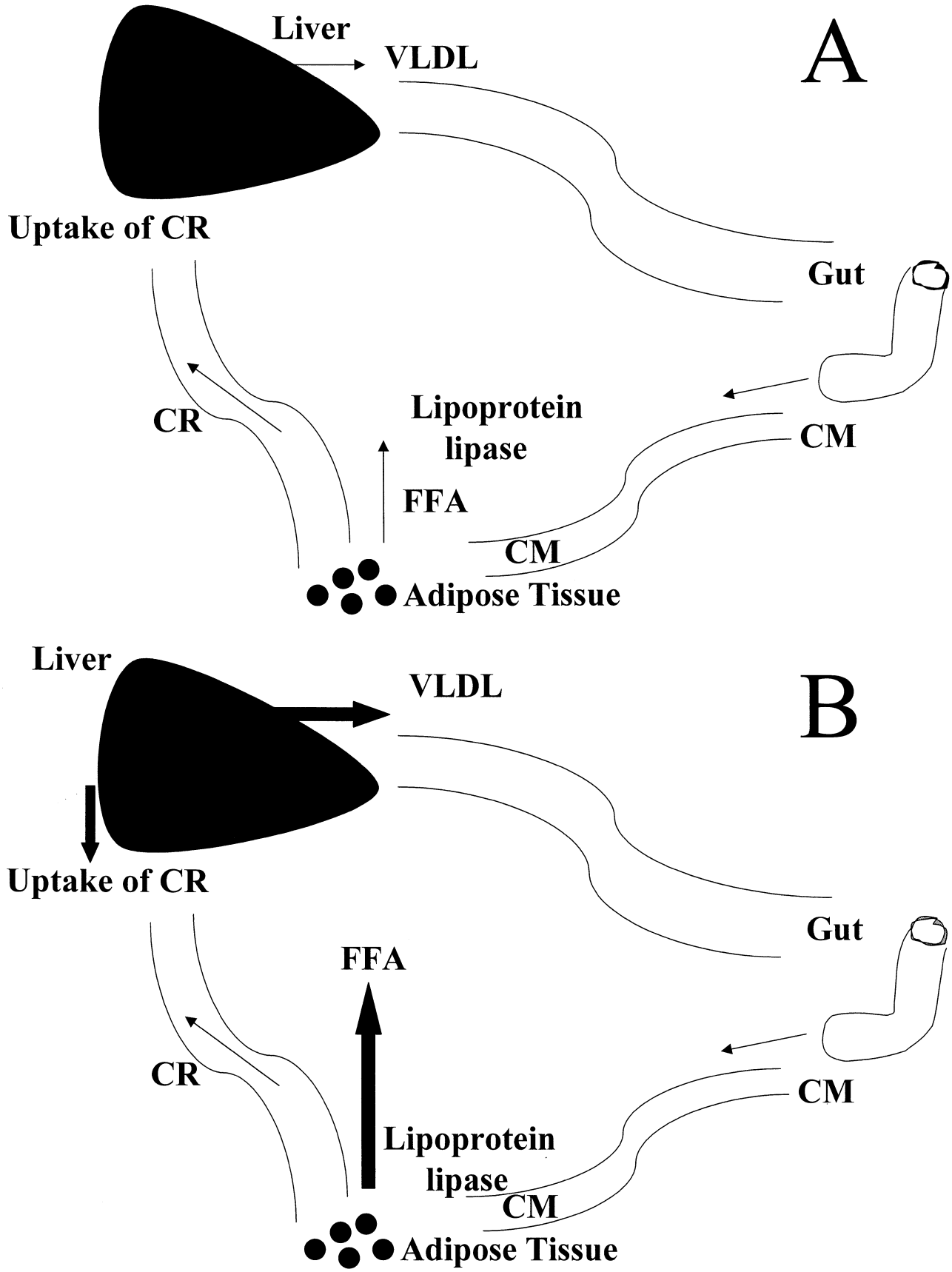

Fig. 1. CR and VLDL metabolism in A (lean subjects) and B (obese subjects).

triglyceride clearance is delayed [31]. In obese individuals plasma ASP content was markedly increased indicating a role for ASP in the pathogenesis of obesity [32].

1.2. Rodent models of obesity

The discovery of the *ob* gene and analysis of its gene product, leptin, has shown that serum leptin levels are increased in all animal models of obesity, regardless whether obesity is caused by genetic defects, hypothalamic lesions or brown adipose deficiency [33]. Resistin is a newly described protein and serum resistin levels are increased in diet-induced obesity and in genetic models of obesity and insulin resistance [34].

The availability of animal models of obesity provide an experimental tool to study the pathogenesis of obesity. The causes of obesity in different rodent models are numerous. Animal models of obesity resemble human obesity and exhibit hyperphagia, hyperinsulinemia and hyperlipidemia. Animal models of obesity provide useful tools since confounding factors such as genetic diversity, gender, diet and age can affect studies in humans. These confounding factors can be easily controlled in rodent models of obesity. There are many causes of obesity in different obese rodent models and obesity may result from excess intake of energy relative energy expenditure.

Measurements of CR clearance and metabolism have not been made previously in murine models of obesity. Recently measurements of CR clearance and metabolism have been made in *db/db*, gold thioglucose (GTG), *ob/ob*, *fat/fat*, and yellow obese (A^y), *db/db* and New Zealand Obese (NZO) mice by a newly developed stable isotope breath test [35].

1.2.1. GTG -obese mouse

Mice intraperitoneally injected with GTG become obese [36]. GTG destroys the neurons in the feeding centers of the ventromedial hypothalamus [36]. The gold component of GTG causes destruction of the neurones involved in the regulation of food intake [36]. GTG accumulation also leads to damage and lesions in other regions of the brain and in non-neural tissues such as the liver, kidneys, heart, gut and adipose tissue [37]. Mice become hypophagic within the first week after injection of GTG [38]. After 5 weeks GTG injected mice are significantly over weight when compared with lean controls [39]. GTG obese mice are hyperinsulinemic [39] and insulin resistance is associated with a reduction in the number of insulin receptors and a defect in post insulin receptor signaling pathway [40]. Hyperinsulinemia and insulin resistance may be corrected by a 40 hr fast or long term food restriction [40].

In GTG-obese mice hyperglycaemia and glucose intolerance are generally evident at about 5 to 8 weeks following GTG injection [41,42,43]. Gluconeogenesis [44] and glycogen turnover [44] are increased in GTG-obese mice and may contribute to the hyperglycemia. A reduction in insulin responsiveness in tissues may be related to a reduction in insulin receptor sites and in post insulin-receptor signaling pathways [40,45]. Long term food restriction has been shown to normalize plasma glucose, insulin and restore insulin receptor numbers [45].

Plasma cholesterol and triglycerides have been shown to be increased in GTG-obese mice [35]. Hepatic fatty acid synthesis is doubled when compared to lean mice [46,47]. Increased rates of hepatic lipogenesis in obese mice are accompanied by elevated lipogenic enzyme activities [47]. Increased rates of lipid synthesis have been shown to be accompanied by an increase in adipocyte size [48]. Elevated rates of fatty acid and cholesterol synthesis in the liver are normalized after fasting [49]. Although after an overnight fast lipogenesis in the liver and adipose tissue has been shown to be elevated even when GTG obese mice are fed the same amount of food [50].

1.2.2. Ob/ob mouse

The protein product of ob gene was identified in 1994 [33]. Leptin is a 16 kDa protein, which is synthesized exclusively by fat cells [51]. In normal mice leptin acts as a satiety factor at the level of the hypothalamus [52]. The amount of leptin secreted is proportional to the size of adipose tissue mass [53]. When adipose tissue mass increases, fat cells increase the secretion of leptin which regulates food intake.

The *ob/ob* mouse inherits obesity as an autosomal recessive mutation on chromosome 6 [54]. The gene encoding leptin was identified by positional cloning as the site of the *ob* mutation [33]. In the absence of intact leptin the food intake is not regulated and mice become grossly obese, weighing 3 times more than lean mice [51]. Obesity is recognized in *ob/ob* mice about 4 weeks of age and is accompanied by hyperphagia [55,56] and ob/ob mice rapidly gain weight during the first 3 months. *ob/ob* mice are hyperinsulinemic and hyperinsulinemia has been associated with hypertrophy and hyperplasia of the beta cells of the pancreas [54]. Fasting and food restriction markedly reduce but do not restore plasma insulin back to control values [45]. In food restricted *ob/ob* mice improvement in insulin levels is associated with an increase in insulin binding capacity of tissues and an increase in insulin stimulated glucose uptake by skeletal muscle [57]. A reduction in plasma glucose may be associated with an improvement in insulin resistance. Furthermore restricting food intake in *ob/ob* mice was associated with increased thermogenesis in brown adipose tissue [58].

In *ob/ob* mice fatty acid synthesis in the liver and adipose tissue is markedly elevated [59]. The high rates of fatty acid synthesis are associated with elevated lipogenic enzyme activities [60]. Hepatic fatty acid oxidation is diminished and esterification into lipids predominates [61]. Mobilization of free fatty acids from adipose tissue is impaired in response to starvation [61]. The increased lipid synthesis

and storage in the liver and adipose tissue of ob/ob mice are accommodated by hypertrophy and hyperplasia of the cells.

Hypercholesterolemia in ob/ob mice is mainly due to an accumulation of HDL [62]. Elevated plasma triglycerides have been reported [63]. Hepatic VLDL secretion has been reported to be elevated in some studies [64] but normal in others [61].

1.2.3. Fat/fat mouse

The fat/fat mouse was first discovered in 1973 and inherits obesity as an autosomal recessive mutation on chromosome 8 [65]. The protein product of the fat gene is an enzyme called carboxypeptidase E (CpE) [65]. CpE is widely expressed in all neuroendocrine tissues, and is involved in posttranslational processing of pro-hormone derived peptides in normal mice [66]. The fat/fat mouse does not express Cpe and obesity is believed to be related to the defective processing of neuropeptides and hormone precursors that are involved in the control of feeding and energy balance [65]. Hyperinsulinemia is present in fat/fat mice and plasma glucose is mildly elevated [67]. Plasma cholesterol and triglyceride are increased and the increased cholesterol level is related to an increase in the HDL cholesterol concentration [62].

1.2.4. Yellow-obese mouse

The yellow obese mouse (A^y) was first described in 1883. The obesity in these mice is inherited as an autosomal dominant mutation at the agouti locus of chromosome 2 [68]. The protein product of the agouti gene is a 131 amino acid peptide which is produced by hair follicles [68]. All yellow obese mice are heterozygous for the agouti mutation, littermates homozygous for the agouti mutation die during development [68].

Alpha melanocyte-stimulating hormone (MSH) is a centrally-acting appetite suppressant in mice [69]. MSH binds to MC-4 receptors in the hypothalamus to suppress appetite and also binds to MC-1 receptors on melanocytes to stimulate production of eumelanin (brown-black pigment) [69]. The agouti protein antagonises the action of MSH by competitively binding to MC-4 receptors in the hypothalamus and also inhibits melanin production by inhibiting the effects of MSH on MC-1 receptors [69]. As a result of a mutation in the agouti gene, the mice become obese and exhibit a bright yellow coat.

The A^y develop obesity after 3 months of age. A^y mice may weigh twice the body weight of control mice and maximum body weight is reached at 7 months of age [70]. Food restriction may normalize body weight but adipose tissue mass remains greater than control mice [60]. These mice are hyperinsulinemic but are not diabetic [62]. Plasma glucose may be elevated in fed yellow-obese mice but normal after fasting [70].

Hepatic lipogenesis and cholesterogenesis are markedly elevated in A^y when fed ad libitum [71]. Lipogenesis normalizes in male A^y mice but still remains elevated in female A^y after an overnight fast [71]. Fasting plasma triglyceride and cholesterol are not significantly elevated in A^y from the C57BL/6J strain [35].

1.2.5. db/db mice

In *db/db* mice the obesity is inherited as an autosomal recessive mutation at the *db* locus of chromosome 4 [54]. The *db* gene was suggested to encode the receptor for the obese (*ob*) gene product, leptin. The leptin receptor (*ob*-R) was recently cloned from the choroid plexus and mapped to the same 6-cm interval on mouse chromosome 4 [72] as *db* [72] and has six alternatively spliced forms [73]. One of the variants expressed in the hypothalamus is abnormally spliced in *db/db* mice [73]. The mutant protein lacks the cytoplasmic region resulting in defective signal transduction [74] this suggests that the effects of leptin on food intake and body weight regulation is mediated through the leptin receptor in the hypothalamus [74].

Mice homozygous mice for the *db* mutation exhibit the same obesity syndrome as found in the *ob/ob* mice [54]. As a result of a mutation in the *db* gene, the mice become obese, hyperphagic with severe diabetes and markedy hyperglycaemia [54]. Increased plasma insulin is evident within 10 days of age. Homozygous mice are sterile and heterozygotes are used to propagate mutants [54].

In *db/db* mice pair-fed normal amounts of food similar to control mice body weight markedly increases when compared with control mice [75]. Cholesterol synthesis in the liver and intestine has been shown to be increased in [76] and plasma cholesterol and triglyceride levels are elevated [77]. The dyslipidemia in *db/db* mice has been suggested to be caused by a reduced clearance of lipoprotein particles [63].

1.2.6. New Zealand obese mice

The New Zealand obese (NZO) mouse model in 1948 was developed by selective in-breeding in New Zealand and do not have true controls [78]. The NZO mouse is a polygenic model of NIDDM and is characterized by obesity [78]. In NZO mice two new major quantitative trait loci on chromosome 5 (Nob1) and chromosome 19 (Nob2) for obesity and insulin resistance have been identified [79]. The mice are hyperphagic, hyperglycemic and hyperinsulinemic [78,80] in the fed state. In overnight fasted animals plasma insulin and glucose levels are normal [81]. Food restriction of NZO mice starting at 8 weeks of age and ending at 16 weeks led to similar body weight and an improvement in metabolic abnormalities when compared with control mice [82,83]. NZO mice have an enlargement of intraabdominal fat cells [84] and fat cell size is associated with increased body weight [85]. Plasma cholesterol and triglyceride contents are increased [82].

1.3. Postprandial lipid metabolism

1.3.1. Chylomicron metabolism

On entry into the blood chylomicrons come into contact with the enzyme lipoprotein lipase located on the surface of capillary endothelial cells of adipose tissue, skeletal and cardiac muscle, and other sites. Lipoprotein lipase hydrolyzes the triacylglycerols of chylomicrons producing fatty acids and glycerol; in this process the apolipoproteins and phospholipids of chylomicrons are released back into the circulation and are taken up by the other lipoproteins, particularly HDL [86,87]. When lipolysis is almost complete, between 70 to 90% is removed, a cholesterol-rich residual lipoprotein, called the CR, is released back in the circulation [88]. CR are rapidly cleared from the circulation by the liver. This process has been demonstrated in various systems, including perfused liver, isolated liver membranes and hepatocytes [89-91]. The uptake of CR is mediated by the presence of the heparan sulfate proteoglycans [92,93], apo E [94,95], LPL [96,97], hepatic lipase [98-100], Low density lipoprotein receptor [101-103] and the Low density lipoprotein receptor related protein [104,105] by receptor mediated endocytosis.

Other receptors that may be involved in CR uptake are the VLDL receptor which binds apo E. LDLr (-/-) mice overexpressing VLDLr has been shown to have a reversal of hypercholesterolemia in these mice [106]. The existence of another remnant receptor inhibited by lactoferrin that binds apo E rich β-VLDL has been reported [107]. There is speculation that the lipolysis stimulated receptor (LSR) is involved in CR clearance and is stimulated by free fatty acids [108]. The scavenger receptor, class B, type I is a multiligand cell surface receptor and may be involved in CR metabolism [109]. Another candidate remnant receptor has been speculated to be the asialoglycoprotein receptor [110].

1.4. Chylomicron and CR-like emulsions and breath tests

Studies using artificial triacylglycerol–rich emulsions and Intralipid with lipid compositions similar to chylomicrons have been shown to be metabolized similar to chylomicrons in vivo [111-113]. Chylomicron-like emulsions rapidly incorporate the apolipoproteins A-I, A-II, A-IV, E, C-II and C-III from plasma, either by the release of apolipoproteins from plasma lipoproteins or by the association of apolipoproteins present free in plasma [114]. Results from recent studies show that remnant-like emulsion models are metabolized like CR [115-116], with remnant-like emulsions taken up by the liver, transported into endosomes and emulsion cholesteryl esters hydrolyzed in lysosomes. The fatty acids become available for oxidative metabolism, in particular metabolism to carbon dioxide [115-117].

Carbon dioxide in the expired breath can contain either ^{12}C or the ^{13}C isoform. The ^{12}C is more abundant with most CO_2 molecules containing this isoform. The content of $^{13}CO_2$ to $^{12}CO_2$ in the breath is dependent on the diet [118].

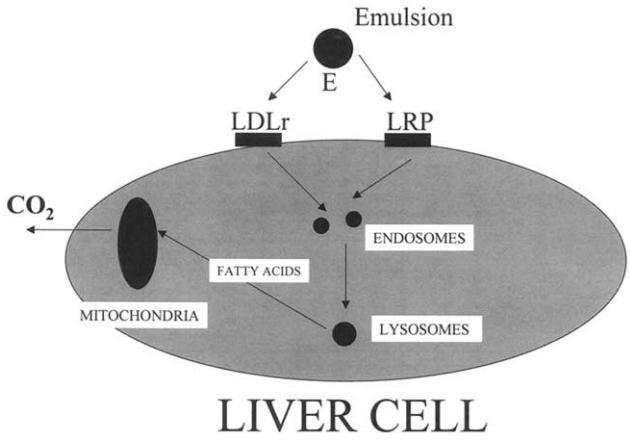

Fig. 2. Metabolism of CR emulsions in liver cells.

^{13}C is enriched in sugars derived from C4 plants and depleted in other C3 plants. The enrichment of $^{13}C/^{12}C$ of CO_2 in the breath can be measured by isotope ratio mass spectrometry [118]. Breath tests are used for various clinical applications, such as the Helicobacter pylorii test [119], assessment of gastric emptying [120] and assessment of liver enyzmes [121]. $^{13}CO_2$ and $^{14}CO_2$ breath test for CR clearance and metabolism has been developed which is useful for non-invasive measurements of CR metabolism in mice, rats and rabbits [35,115-117].

The breath test for CR metabolism involves the intravenous injection of protein-free lipid emulsion. Apo E and C from the plasma associate with emulsion particles. After hydrolysis of emulsion triglyceride by LPL, remnant-like emulsions have been shown to mimic the metabolism of CR with oxidation of CR fatty acids by liver cells [35,115-117]. Measurement by the breath test provide an assessment of the clearance and metabolism of the remnants of triglyeride-rich lipoproteins and show the importance of apo E, LDL and LRP receptors in the clearance of CR in mice with genetic defects in lipoprotein metabolism Fig 2). Further evaluation of the breath test has shown that the breath test reliably measures the metabolism of CR and that CR cholesteryl ester fatty acid is metabolized by mitochondrial pathways [116].

1.5. Hyperphagia and CR metabolism in obese rodent models

Hyperphagia leads to an increased load of transported fat from the intestine and is a common feature in obese rodent models [122]. Hyperphagia may increase the hepatic cholesterol pool by increasing the flux of dietary cholesterol to the liver and may result in the reduced expression of LDLr. The down regulation of LDLr expression may lead to a delay in CR clearance. The food intake of obese mice and diabetic rats consuming food freely (fed ad libitum) has been shown to be markedly increased [35,123]. Prevention of hyperphagia in Zucker obese rats by pair-feeding to lean

Table 2
Postprandial remnant metabolism (by $^{13}CO_2$ breath test)

	Fed ad libitum	Pair-fed	Re-fed
ob/ob	↓	↑	↓
db/db	↓	↑	↓
NZO	↓	↑	↓
fat/fat	↓	↑	↓
GTG	↓	↑	–
A^y	↓	↑	–

controls increased longevity [124]. In various studies caloric restriction and decreased adipose tissue mass has been related to increased longevity in a number of species [124-126].

The increased transport of dietary fat following a meal is thought to be accommodated by an increase in size of the chylomicron particles rather than number in rats [123] and humans [127]. In diabetic rats and mice the intestine is hypertrophic and cholesterol synthesis and transport from the intestine has been shown to be increased [76,128]. The hyperphagia in obese and diabetic rodents may be related to an increased transport of chylomicron particles by the intestine. The competition by an increase in lipid particles for clearance may delay CR removal in obese and diabetic rodents.

1.6. Effects of fasting and food restriction on CR metabolism

In Zucker obese rats and strepotozotocin induced rats the clearance of CR has been shown to be delayed [123,129]. In lymph duct cannulated streptozotocin-diabetic rats the number and size of CM produced by the intestine was not found to be different from control rats indicating that the slow clearance of CR may be related to a defect in CR removal by the liver [123]. In these diabetic rats the prevention of hyperphagia did not overcome the impairment in CR metabolism. These findings can be contrasted with CR metabolism in all murine models of obesity where the defect in CR metabolism was associated with the marked hyperphagia [35]. In all obese mice models studied CR metabolism was markedly impaired when compared with fed control non-obese mice (**Table 2**). After 24 hr food deprivation CR metabolism was still impaired in all obese mice except A^y mice [35]. When obese mice were placed on a food restricted diet for a 6 week period, CR metabolism in all obese models was similar to control mice (**Table 2**). After the 6 week diet the obese NZO, *fat/fat* and *ob/ob* mice had marked weight loss on the restricted diet, whereas A^y, GTG, and *db/db* mice did not. In all obese mice, plasma cholesterol and triglyceride levels decreased after food restriction and plasma glucose levels were significantly decreased in the obese mice except *db/db* mice [35]. While some of the obese models such as *db/db* were diabetic, our data suggest that the defect in CR clearance and metabolism was independent of diabetes, since all murine models whether or not diabetic responded similarly to food restriction [35].

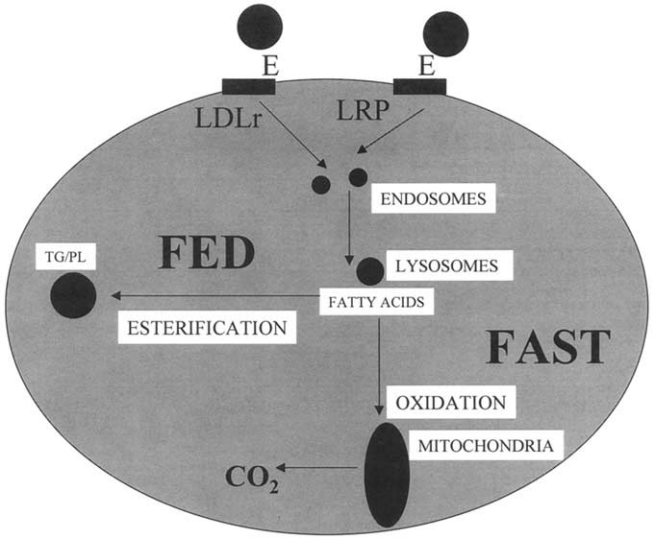

Fig. 3. Effect of fasting and feeding on CR fatty acid metabolism.

Under food restriction conditions, the decreased supply of dietary fats from the intestine may increase the clearance of VLDL produced by the liver. In man chylomicrons compete with hepatic VLDL for lipolysis by lipoprotein lipase [130,131] and removal from the circulation of CR mediated by the presence of the HSPG [92,93], apo E [94,95], LPL [96,97], hepatic lipase [98-100], LDLr [101-103] and LRP [104,105] by receptor mediated endocytosis.

In postprandial studies in mice an oral administration of intralipid delayed the clearance of injected CR lipid emulsions as assessed by the breath test [116]. In apo B100 transgenic mice the presence of human LDL delayed the clearance of injected CR particles [102]. In individuals with coronary artery disease, LDL cholesterol and apo B concentrations markedly influenced the clearance of CR [132]. These findings confirm competition between endogenous lipoprotein particles and exogenous injected remnant-like emulsions for a common removal pathway by the liver.

Under fasting and food restriction conditions in rodents hepatic fatty acid metabolism rapidly switches from oxidation in the starved state to esterification of phospholipids and triacylglycerols in the fed state [133,134]. In our studies in mice the metabolism of CR cholesteryl ester fatty acids was shown to be metabolized by mitochondrial pathways as assessed by the breath test [116]. Under normal food intake conditions in obese mice CR lipid metabolism was found to be markedly lower and was probably associated with esterification of fatty acids released from CR in the liver (Fig 3). In contrast under fasting and food restriction conditions rapid metabolism of CR was associated with increased oxidation of CR fatty acids within the livers of obese mice (Fig 3).

The peroxisome proliferator-activated receptors (PPARalpha, gamma, delta) are lipid activated transcription

factors that have important roles in the storage and catabolism of fatty acids and are members of the nuclear receptor superfamily [135]. The three isoforms have specific tissue distribution with PPAR alpha expressed in the liver, kidney and heart and is activated by hypolipidemic drugs (fibrate) and fatty acids resulting in the expression of enzymes that involve peroxisomal β oxidation [135,136]. The PPAR gamma is preferentially expressed in adipose tissue and plays an important role in adipocyte differentiation [137,138] and PPAR delta is ubiquitously expressed and is activated by fatty acids. In rodent models of obesity PPAR gamma expression is not altered but is physiologically regulated by food intake [139]. PPAR gamma activity is down regulated by fasting and insulin dependent diabetes [139]. High fat diets increased adipocyte PPAR gamma expression in adipocytes and liver in control and obese mice respectively [139]. In ob/ob mice treatment with a PPAR gamma agonist rosiglitazone (Thiazolidinedione derivative) reduced plasma triglyceride and glucose levels and changed the expression of proteins involved in peroxisomal β oxidation [140,141].

1.7. Exercise, antiobesity drugs and postprandial lipid metabolism

In healthy individuals exercise decreases the fasting hypertriglyceridemia and exaggerated postprandial lipemia [142,143]. The elevation in plasma triglycerides and high concentrations of triglyceride-rich particles after consumption of a high carbohydrate diet was markedly decreased by exercise [144]. In obese individuals increased exercise is associated with an improvement in plasma lipid profile with high levels of HDL cholesterol and low levels of triacylglycerol [145,146]. Exercise in obese individuals enhances the breakdown of triglyceride-rich lipoproteins and postprandial hyperlipidemia by stimulating lipoprotein lipase activity [147]. In obese men fat metabolism seemed to be increased during low-intensity exercise but no effect was found with high-intensity exercise training [147,148].

Antiobesity drugs such as Orlistat and Sibutramine have recently been used for the treatment of obesity [149,150]. Orlistat inhibits dietary cholesterol and intestinal fat intake by inhibiting intestinal lipases [149] resulting in weight loss in obese individuals [149,150]. Sibutramine (appetite suppressant) acts centrally on neuronal receptors as an inhibitor of noradrenalin and serotonin involved in food intake [150] and decreases caloric intake [150,151].

In the treatment of obesity Metformin has been used to improve insulin sensitivity, body weight, plasma lipids and leptin [152,153]. Thiazolidinedione derivatives have been used for the management of obese individuals [154]. These derivatives may be useful in improving multiple risk factors including fat distribution in viscerally obese individuals [150,154]. Fibrate treatment has been used to improve postprandial hypertriglyceridemia [155,156]. Obese individuals treated with gemfibrizol markedly reduced their risk of coronary artery disease [157]. Inhibitors of cholesterol synthesis, 3-Hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have been shown to be effective in treating dyslipidemia [158,159,160]. In obese individuals inhibition of cholesterol synthesis with atorvastatin was shown to improve chylomicron metabolism by increasing CR catabolism as assessed by the newly developed stable isotope breath test [20].

2. Conclusion

In Western societies obesity has become recognized as an important cause of the increased risk of coronary artery disease. Increased food consumption increases the presence in plasma of atherogenic lipoproteins since most obese individuals are in the post prandial state for most of the day. Antiobesity drugs and lifestyle changes that include food restriction and exercise should be used to improve the postprandial hypertriglyceridemia in obese individuals.

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