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Effect of Exercise on Carbohydrate and Lipid Metabolism in the Liver

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Abstract

The liver is a key metabolic organ and governs body energy metabolism. It acts as a hub to metabolically connect various tissues, including skeletal muscle and adipose tissue. The liver stores, releases, and recycles potential energy. Strong response from the liver comply the accelerated metabolic demands of the working muscle. Prolonged acute exercise reduces hepatic blood flow, stimulating hepatic glycogenolysis and gluconeogenesis; but, lipid metabolism shows little change. The main triggers are humoral, but hepatic afferent nerves, cytokines, reactive oxygen species, and changes in hepatic blood flow may all play some role. Regular aerobic exercise training improves blood glucose control during exercise by increasing glycogen stores and up-regulating enzymes involved in gluconeogenesis and carbohydrate metabolism. Lipogenic enzymes are down-regulated, and lipid metabolism is augmented.

1. Introduction

Liver is vital to the health of the human organism. This essentially depends upon constant maintenance of the numerous biochemical functions of the liver and the diverse metabolic processes occurring in the hepatocytes and sinusoidal cells. About 500 separate biochemical processes occur in one single liver cell. The most important of these include: Carbohydrate metabolism, Lipid and lipoprotein metabolism, Bile acid metabolism, Bilirubin metabolism, Amino acid and protein metabolism, Hormone metabolism, Biotransformation and detoxification, Porphyrin metabolism, Vitamin metabolism, Acid-base balance, and Alcohol degradation (1). Physical exercise poses a unique challenge to the liver as metabolic demands of working muscles require the liver to mobilize energy stores, recycle metabolites, and convert compounds that are toxic in excess to innocuous forms. The focus of this review will be effects of exercise on carbohydrate and lipid metabolism in the liver.

2. Liver structure and metabolic functions of zones

The major cell type of the liver is the hepatocyte, a parenchymal cell, which makes up to 80 % of the entire liver mass and performs the majority of the liver functions (2). The other 20 % of the liver mass are comprised of nonparenchymal cells (NPCs) such as biliary epithelial cells, and sinusoidal-lining cells (Kupffer cells and endothelial cells), stellate cells (formerly known as Ito cells), and cells involved in the immune response (3). Hepatocytes specialized cells that perform a wide range of metabolic activities. Hepatocytes are responsible for the synthesis of glucose (gluconeogenesis), albumin, and other plasma proteins, cholesterol and bile acids, the metabolism of drugs and toxins, and the oxidation of fatty acids (4). A widely accepted concept for the microscopic architecture of the liver is the "lobule" model. In this model, a hepatic lobule is centered with the hepatic vein in the center and the portal areas are organized at the periphery in the shape of a hexagon. The hepatic lobule has been divided into three zones based on the difference in oxygen tension within the hepatic lobule. The oxygen tension of the blood entering the sinusoid is highest around the portal area (zone 1: periportal), lowest in the region surrounding the central vein (zone 3: intermediate), and intermediate between zone 1 and zone 3 (zone 2: pericentral or perivenous) (5). Hepatocytes from different zones of the liver show phenotypical heterogeneity in metabolic features, leading to zonation of metabolic processes across the acinus (Fig 1). Regarding glucose and fatty acid metabolism, periportal hepatocytes are more involved in gluconeogenesis and β-oxidation, while perivenous hepatocytes are more engaged in glycolysis and lipogenesis (6). Zonation of glucose and fatty acid metabolism shows flexibility in different conditions in such a manner that dynamic adaptation of gene and protein expression can be observed in different nutritional states. Interdependent metabolic pathways (e.g. lipogenesis and glycolysis) are colocalized to allow for synergistic action, whereas opposing pathways are segregated in different zones, likely to avoid interference and thereby waste of energy. Altogether, the heterogeneity of the liver enables the simultaneous performance of different and even opposing metabolic pathways (7).

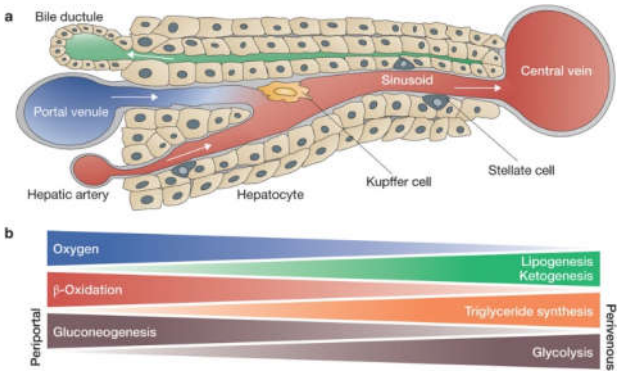

Figure 1. (a) Liver functions are arranged across a unique architectural unit: the lobule. Venous blood from the intestines mixes with arterial blood near the periportal zone, where the bile ductules are also located (left). Blood then travels through the liver sinuses and collects in the central veins (8). (b) The liver architecture contains distinct metabolic zones that separate various functions, such as β-oxidation and gluconeogenesis (increased on the portal side), lipogenesis, ketogenesis and glycolysis (increased on the central side) (9).

Desy and colleagues found that hepatic zonation should be considered when analyzing the

contribution of the liver to energy metabolism during exercise (10). They demonstrated that exercise differentially stimulates the gluconeogenic activity of perivenous hepatocytes to a larger extent than periportal hepatocytes, indicative of a heterogeneous metabolic response of hepatocytes to exercise.

3. Carbohydrate Metabolism in the Liver

The liver plays a unique role in controlling carbohydrate metabolism by maintaining glucose concentrations in a normal range. In hepatocytes, glycolysis only consumes about 20–30% glucose taken up by the liver for energy metabolism; the remaining glucose is utilized for synthesis of glycogen, fatty acids, and ketone bodies. Glucose, fatty acids, and ketone bodies are stored in the hepatocytes and transported to other tissues for energy metabolism. In the liver, blood glucose enters hepatocytes via GLUT2, a plasma membrane glucose transporter. The liver GLUT2 has a very high Km (10 mM) for glucose. After a meal when blood glucose concentrations in portal circulation increase to above 10 mM, glucose enters hepatocytes via GLUT2 (11). Glucose is phosphorylated by glucokinase (GCK) in hepatocytes to generate glucose 6-phosphate (G6P), which lowers intracellular glucose concentrations and further increases glucose uptake. Moreover, G6P is unable to be transported by glucose transporters, so it is retained within hepatocytes. In the fed state, G6P acts as a precursor for glycogen synthesis. It is also metabolized to generate pyruvate through glycolysis. Pyruvate is channeled into the mitochondria and completely oxidized to generate adenosine triphosphate (ATP) through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. Alternatively, pyruvate is used to synthesize fatty acids through lipogenesis. G6P is also metabolized to generate NADPH via the pentose phosphate pathway. NADPH is required for lipogenesis as well as for the biosynthesis of other bioactive molecules. In the fasted state, G6P is transported into the endoplasmic reticulum and dephosphorylated by glucose-6-phosphatase (G6Pase) to release glucose (12).

Glycolysis is dominant in the fed state in which glucose is abundant. Glycolytic intermediates are used to synthesize lipids, amino acids, and other important molecules in addition to be completely oxidized to generate ATP. In the fasted state with low levels of glucose, hepatocytes switch to fatty acid β oxidation for energy supply. The glycolytic flux is controlled largely by four kinases: GCK, 6-phosphofructo-1 kinase, liver pyruvate kinase, and pyruvate dehydrogenase kinases (PDKs) (12). The levels and activity of these glycolytic enzymes are lower in the fasted state and increase in the postprandial period (13). The liver produces glucose mainly through glycogenolysis in short-term fasting. During prolonged fasting, hepatic glycogen is depleted, and hepatocytes synthesize glucose through gluconeogenesis using lactate, pyruvate, glycerol, and amino acids as precursors. Gluconeogenic substrates are either generated

within the liver or delivered to the liver from extrahepatic tissues through the circulation. The rate of gluconeogenesis is determined by both the availability of gluconeogenic substrates and the expression/ activation of gluconeogenic enzymes (e.g., cytosolic phosphoenolpyruvate carboxykinase (PEPCK-C) and G6Pase). During exercise or fasting, skeletal muscles produce pyruvate through glycogenolysis and glycolysis. Pyruvate has two fates. It can be catabolized to produce acetyl-CoA by mitochondrial pyruvate dehydrogenase complex, and acetyl-CoA is then completely oxidized through the TCA cycle. Alternatively, pyruvate is converted into lactate which is released into the circulation and utilized by hepatocytes to produce glucose through gluconeogenesis (14). Glycerol, which is released from adipose tissue through lipolysis, is also a gluconeogenic substrate. Fatty acid β- oxidation is unable to produce gluconeogenic substrates, but it does generate ATP which is required for gluconeogenesis. Prolonged starvation leads to protein degradation and release of amino acids, which are important gluconeogenic substrates (12). Gluconeogenic enzyme activity is regulated by posttranslational modifications and/or allosteric regulation. Most liver enzymes, which regulate glycolysis, gluconeogenesis, the TCA cycle, the urea cycle, and fatty acid and glycogen metabolism, are acetylated, and acetylation levels are regulated by nutrient availability (15).

3.1 Acute Exercise and Carbohydrate Metabolism

It is essential to maintain blood glucose levels during exercise, due to the increased glucose uptake into the skeletal muscle. The requirement of glucose uptake for the working muscle is transferred in part to the liver, which must release glucose at a rate that matches the accelerated rate of glucose uptake to maintain glucose homeostasis (16). This is achieved by increasing hepatic glucose production through glycogenolysis and gluconeogenesis (17). Previous studies have shown that hepatic glucose production during the initial part of exercise is mainly derived from glycogenolysis and as exercise duration increases a shift toward gluconeogenesis is observed (18). Indeed, accelerated muscle glucose uptake during exercise is matched by the sum of increased mobilization of hepatic glycogen and gluconeogenesis (19). With the onset of exercise, liver glycogen store is hydrolyzed by activation of glycogen phosphorylase that contributing to the release of glucose from the liver (18). Exercise causes hydrolysis of ATP in the liver and resulting in accumulation of Adenosine monophosphate (20) and adenosine diphosphate. Liver AMP concentrations evident during exercise creates a potent breakdown of liver glycogen, due maybe to increased allosteric activation of glycogen phosphorylase. Thus, the AMP produced with chemical energy discharge may combine with or mediate endocrine stimuli to enhance the release of potential energy by mobilization of hepatic glycogen (19). The increased liver glucose output is partly a result of glycogenolysis, particularly during the first hour or more of sustained exercise

(21). However, the relative contribution of hepatic gluconeogenesis to total glucose output increases progressively as work duration is increased, and it accounts for some 50 % of glucose production during physical activity that is prolonged for more than one hour (22).

Gluconeogenic activity depends on gluconeogenic enzyme activity, adequate substrate, and availability of energy in the form of ATP (23). It has been shown that liver PEPCK mRNA content increase immediately after acute exercise in rodents (24, 25) but it must be noted that not all studies observe an increase in PEPCK mRNA in response to acute exercise (26-29). Additionally, it has previously been observed that acute exercise increases the G6Pase mRNA content in mouse liver (25-28) without an exercise training-induced increase in G6Pase protein content (26). Furthermore, it has been shown that hepatic PEPCK and G6Pase activities increase immediately after exercise in rats (30, 31), and it remains to be elucidated whether this increase is a result of acute changes in PEPCK and G6Pase protein contents concomitant with the changes observed in mRNA content with acute exercise (24-26, 28). In addition, another study found that changes in PEPCK or G6Pase protein content do not underlie the exercise-induced increases in PEPCK or G6Pase activity during 60 min of moderate intensity exercise. However, the observed increase in PEPCK protein late in recovery may result in adaptations in gluconeogenic capacity with exercise training (23).

The increase in gluconeogenic activity during prolonged exercise requires an increase in energy production, which may be suggested to be accomplished through β-oxidation. In accordance, 5'AMP-activated protein kinase (AMPK) phosphorylation and concomitantly acetyl-CoA carboxylase (32) phosphorylation have been reported to increase in mouse and rat liver during acute exercise (28, 33-35). As ACC converts acetyl-CoA to malonyl-CoA, which inhibits carnitine palmitoyltransferase 1 and hence mitochondrial acyl-CoA uptake, increased phosphorylation of ACC may be expected to reflect an increased β-oxidation. On the contrary, another study has reported no changes in hepatic ACC and AMPK activities in rats in response to moderate intensity exercise (36). In addition, another study found that PDK4 protein did not increase during 60 min of moderate intensity exercise and that AMPK, ACC, and pyruvate dehydrogenase (PDH) phosphorylations were reduced in the liver immediately after exercise suggest that FA oxidation is decreased, and carbohydrate oxidation is increased in the liver during moderate intensity exercise (23). Thus, the roles of AMPK and ACC in the regulation of substrate choice in the liver during exercise are still unclear.

Lactate (37), amino acids (released from skeletal muscle through the action of cortisol), and glycerol all contribute to gluconeogenesis during

exercise (38). In agreement, liver lactate content has been shown to decrease with prolonged exercise (30). However, pyruvate can also be converted to acetyl-CoA by PDH and further oxidized. In order to conserve pyruvate for gluconeogenesis during exercise, it must therefore be important that PDH is inactivated. The activity of PDH is determined by the phosphorylation level of the catalytic PDH-E1a subunit, which is controlled by PDKs and PDH phosphatases (39). PDK4 knockout in mice has been shown to reduce blood glucose and increase plasma 3-hydroxybutyrate levels during fasting (40), suggesting a decreased gluconeogenic activity in the absence of PDK4. In addition, the recent finding that liver PDK4 mRNA content increased immediately after exercise in mice (28) that may suggest that PDK4-mediated inhibition of PDH activity reduces the conversion of pyruvate to acetyl-CoA during exercise. This would result in an increased availability of pyruvate for gluconeogenesis during exercise. However, whether hepatic PDK4 protein content and hepatic PDH phosphorylation are regulated during exercise is unknown. In addition, it's showed that lactate-derived gluconeogenesis plays an essential role in hepatic and renal glucose production during exercise in the fasted state, regardless of training history (41). Additionally, gluconeogenesis can be augmented during exercise when blood lactate is increased by endogenous or exogenous supply, suggesting that the contribution of gluconeogenesis to total glucose production may be limited by delivery of gluconeogenic precursors (41).

As hepatic glycogen reserves become depleted, the rate of gluconeogenesis is usually insufficient to sustain vigorous exercise, and a decline in the blood glucose concentration can therefore occur unless the work rate is reduced (17). Depending upon an individual's training status and diet, both liver and muscle glycogen reserves can be almost completely exhausted over 90– 180 min of vigorous aerobic exercise (42). Indeed, exercise significantly increases liver glucose output by way of hepatic glycolysis and gluconeogenesis, making an important contribution to blood glucose control and oxidation during sustained endurance activity. These mechanisms can become exhausted during exercise such as a marathon run that continues for more than 90 min (43).

3.2 Exercise Training and Carbohydrate Metabolism

Exercise training induces metabolic adaptations in both humans and laboratory animals that help to conserve glucose homeostasis during prolonged exercise, including greater glycogen storage in both liver and muscle, and the sparing of carbohydrate through greater fat metabolism (43). It is well known that regular exercise training increases a person's ability to sustain a higher work-rate during prolonged activity, and to exercise for longer before the onset of fatigue. One component of this change is

an enhanced resistance to hypoglycemia during exercise. This is partly a consequence of an increased capacity for skeletal muscle to store glycogen and to oxidize fat at the expense of glucose. Although there is relatively little human data, further 'glucose sparing' adaptations likely include an increased resting liver glycogen concentration and a reduced rate of both glycogenolysis and gluconeogenesis at any given intensity of exercise (44, 45). Other changes associated with exercise training include a reduced availability of gluconeogenic precursors (lactate and glycerol) at a given volume of exercise, and altered hormonal responses (a higher insulin, and lower glucagon and catecholamine concentrations) (43). Rodent investigations generally agree with human observations in showing that the gluconeogenic and the gluconeogenic responses to glucagon are enhanced with training (46, 47). However, there are some differences in the responses of rats, probably related to the fact that gluconeogenesis accounts for some 20 % of glucose production when humans undertake moderate exercise, whereas in rats the figure ranges from 40 to 70 % (43). In particular, training increases exercise hepatic glucose clearance in humans, but not in rats (44). Underlying mechanisms apparently include a normalizing of the ratio of inhibitory to stimulatory guanine nucleotide binding protein (G protein), and a resultant increase in activity of the "second messenger" adenyl cyclase (46). The increased capacity for glucose output contributes to the ability of trained individuals to sustain higher work-rates and to maintain euglycemia during exercise (48). Moreover, the liver of a trained person has an increased absolute capacity for lactate (48, 49) and alanine (50) clearance, and associated gluconeogenesis (51).

4. Lipid Metabolism in the Liver

When carbohydrates are abundant, the liver not only utilizes glucose as the main metabolic fuel but also converts glucose into fatty acids (*de novo* lipogenesis). Hepatocytes also obtain fatty acids from the bloodstream, which are released from adipose tissue or absorbed from digested food in the gastrointestinal. Fatty acids are esterified with glycerol 3-phosphate to generate triglyceride (TG), or with cholesterol to produce cholesterol esters. TAG and cholesterol esters are either stored in lipid droplets (LDs) within hepatocytes or secreted into the circulation as very low-density lipoprotein (VLDL) particles. Fatty acids are also incorporated into phospholipids, which are essential components of cell membranes and the surface layer of LDs, VLDL, and bile particles. In the fasted state, fatty acids are oxidized mainly in the mitochondria to generate ATP as well as ketone bodies (12). Non-esterified fatty acids can arise from the hydrolysis of complex lipids by lipases, or the hydrolysis of fatty acid-CoA by thioesterases. The liver takes up nonesterified fatty acids (NEFA) from the blood in proportion to their concentration. Non-esterified fatty acids enter cells via transporters (fatty acid transport protein (FATP2,4,5) or fatty acid translocase (FAT), CD36) or diffusion.

Pregnane X receptor and aryl hydrocarbon receptor activates the expression of CD36 in hepatocytes, increasing hepatocyte fatty acid uptake and TG levels (52, 53). Within the hepatocytes, long-chain fatty acids of 14 carbons or more are covalently bound and activated by fatty acid binding protein (FABP) or acyl-CoA synthetases (ACS) found in the microsomes and outer mitochondrial membrane. Several isoforms of ACS have been identified (ACS1, 3-6) (54) and the further fate of a particular acyl-CoA (especially channeling towards complex lipid synthesis and storage, or toward oxidation) depends on which of the isoforms catalyzes its synthesis (55). Nonesterified fatty acids and fatty acyl-CoA are bound to FABP and acyl CoA binding protein which transport them to intracellular compartments (for metabolism) or the nucleus (to interact with transcription factors). Cells challenged with exogenous fatty acids rapidly assimilate the fatty acids into neutral and polar lipids, and some are oxidized. The result of these metabolic pathways is to keep intracellular NEFA and fatty acyl-CoA very low (56).

4.1 Acute Exercise and Lipid Metabolism

The liver's dominant role in disposing of circulating fatty acids is suspended during exercise. Hormonal responses to exercise increase the net availability of circulating free fatty acids (FFAs) during physical activity (57), but with the ensuing changes in blood flow distribution, the majority of these FFAs are directed to the contracting muscle; their oxidation accounts for most of the whole-body fat that is metabolized during exercise, although there is also a small contribution from intramyocellular triglyceride-derived fatty acids (58). Helge et al. are believed that VLDL makes a trivial contribution to whole-body fat metabolism during exercise (59). While the hepatic VLDL derived fatty acids can be oxidized by skeletal muscle (60). Borsheim et al. reported that the hepatic release of triglyceride in the form of VLDL remains unchanged during exercise (90 min at 58 ± 5% (mean ± SD) of maximal O2 uptake on a cycle ergometer followed by 4.5 h bed rest) (61).

Even a sustained bout of physical activity appears to have little immediate effect upon hepatic lipid metabolism. For instance, endurance-trained men showed no change in proton magnetic resonance spectroscopy estimates of hepatic triglycerides following 90 min of cycle ergometry at 65 % of VO 2peak (62). Likewise, a 60-min bout of cycle ergometry at 60 % of VO2max had no influence upon hepatic lipid metabolism in sedentary women (63). One review also concluded that exercise had no effect upon the hepatic concentrations of total lipids, phospholipids and cholesterol in normally fed rats (64). However, the high levels of circulating fatty acids induced by 60–90 min bouts of exercise led to an increase of hepatic triglycerides 3–4 h post-exercise in both mice (65) and human (62) studies. Two studies using VLDL–TG and palmitate tracers measured VLDL secretion directly during, and after 90 min of, aerobic exercise at 50% of the VO2max (66,

67). These studies showed that in both healthy lean individuals and in overweight untrained men hepatic VLDL–TG secretion and clearance were reduced during exercise and in the early recovery phase. Furthermore, because VLDL–TG secretion and clearance were both reduced to a similar extent, plasma VLDL–TG concentrations were not changed. Therefore it can be suggested that, in the early recovery phase, changes in VLDL–TG secretion and/or clearance do not contribute to decreases in plasma TG levels. However, Magkos and colleagues demonstrated that VLDL-TG secretion rate was not reduced by a recent bout of continuous exercise in men compared with a sedentary trial (8), for a study conducted in women performing an exercise session of similar duration and relative intensity vs. a sedentary trial, a significant reduction in VLDL-TG secretion was reported (68), revealing this aspect of lipid metabolism can be altered by acute exercise with possible sex differences in this response. Additionally, it has been demonstrated that women exhibit a higher VLDL-TG secretion rate under basal sedentary conditions (69). Tuazon et al. examined the impact of single bouts of moderate-intensity continuous exercise vs. High-intensity interval exercise on hepatic TG metabolism and secretion in female and male mice. They have discovered a novel metabolic impact of exercise in which transient alterations in hepatic TG metabolism are exhibited after exercise. The changes in hepatic lipid trafficking appear to be modulated by exercise-induced alterations in Perilipin-2 expression, and this response may be important for achieving health benefits of exercise or for adaptation to the stresses of exercise participation. Second, they have discovered potential mechanisms for sex differences in VLDL-TG secretion in the basal state and in response to a recent bout of intense exercise, and these results shed light upon sex-specific regulation of energy metabolism and the integration of metabolism between the liver and other tissues (70).

Using stable isotope techniques it was calculated that approximately 50% of whole-body re-esterification immediately after physical exercise (1 h at 60% VO2peak) occurs in the splanchnic area (32). This data indicates that splanchnic (i.e. hepatic) NEFA re-esterification might be an important factor immediately after exercise. So, while long-term exercise training results in lower NEFA levels and decreased intrahepatic lipid content, NEFA are increased after acute exercise and hepatic TG content tends to increase after acute exercise in the fasted state (71). On the other hand, plasma TAG levels remain relatively low for 24 h after an acute exercise bout (8), after which they return to baseline values. Although changes in VLDL–TG metabolism do not contribute to the decrease in plasma TG in the early recovery phase, it might be that they contribute to the sustained lower plasma TG the day after a single exercise bout (8). It has been shown that moderate-intensity exercise bouts lasting at least 2 h reduce plasma TG concentrations by approximately 30% (72-74),

whereas shorter bouts of similar exercise have no effect on plasma TG concentrations (75, 76). Consistently, it was found that 2 h of evening exercise (60% of the VO2peak) did increase fasted VLDL-TG clearance rate by approximately 40% on the following day, without affecting VLDL–TG secretion in healthy, lean, young men (8). In women, a comparable exercise protocol decreased VLDL–TG secretion rate on the following day by approximately 22%, concomitant with increased VLDL–TG clearance (68). Thus, performing acute exercise for 2 h in the evening induces changes in VLDL–TG metabolism on the following day and these changes positively affect TG concentrations, mainly by causing increased clearance of VLDL–TG from the plasma and only marginally involving changes in hepatic VLDL–TG secretion (71). In addition, Al-Shayji et al. suggested that exercise (120 min walk on a treadmill at an intensity of 50% VO2max) increased the affinity of VLDL for clearance from the circulation, an effect that was related to the exercise-induced increase in VLDL particle size and TG enrichment. Exercise-induced reduction in circulating VLDL could reflect reduced hepatic VLDL production, increased lipoprotein lipase-mediated VLDL clearance, or a combination of the two (77). Gill and colleagues showed that 90 minutes of exercise at 50% of VO 2peak performed on the day before a high-fat meal significantly reduces postprandial VLDL by 34% when compared to non-exercise control in middle-aged overweight men (78). Together, this results indicate that the reduction in triglycerides in the hours following exercise is due to decreases in VLDL production and increases in VLDL clearance.

A single 4-h bout of swimming also up-regulated hepatic stearyl CoA desaturase in rats and increased hepatic triglyceride content (79). Further, exercise to exhaustion increased the hepatic content of the bound form of alpha-lipoic acid (lipoyl–lysine), an important co-factor for many mitochondrial proteins that are active in metabolism (80). Ruderman et al. observed that AMPK and malonyl CoA decarboxylase activities are increased and ACC activity diminished in with 30 min treadmill running in normal rats. In liver, these changes were associated with a decrease in the activity of glycerol-3-phosphate acyltransferase, which catalyzes the first committed reaction in glycerolipid synthesis and, which like ACC, is phosphorylated and inhibited by AMPK. AMPK plays a major role in regulating lipid metabolism in multiple tissues following exercise. The net effect of its activation is to increase fatty acid oxidation and diminish glycerolipid synthesis (81). In addition, it's demonstrated that phosphorylations of ACC and AMPK decreased immediately after exercise relative to rest suggests that β-oxidation was not a major contributor to energy production in the liver with the exercise intensity and duration used in this study (1 h of treadmill running, 15.5 m/min, 10 incline) (23). Together, these observations may suggest that pyruvate rather than fatty acids is the

substrate utilized by the liver for oxidation, and that this pyruvate may be derived from lactate.

4.2 Exercise Training and Lipid Metabolism

Endurance-trained individuals are characterized by low fasting plasma NEFA concentrations (82), suggesting that regular exercise may have an effect on adipose tissue lipid NEFA uptake and lipolysis. The enhanced ability to utilize fat during exercise following regular training is largely a function of adaptations in skeletal muscle (and associated hormonal changes); there is little evidence that the liver contributes to this response (43). This is perhaps understandable, given the apparently trivial role of the liver in contributing to fat oxidation (via VLDLs) (59). Moreover, exercise training blunts the lipolytic hormone response to exercise, so that after training circulating concentrations of insulin and insulin-like growth factor binding protein-1 tend to be higher, and blood glycerol and NEFA concentrations are lower at a given absolute exercise intensity (83). Exercise training-induced decreases in intrahepatic lipid content do not necessarily occur in parallel with decreased plasma NEFA concentrations in the fasted state (71). Several studies report a decrease in intrahepatic lipid content even though fasted plasma NEFA concentrations remained unchanged (84, 85). In this respect, it is well established that endurance training improves whole-body fat oxidation (20, 86) and that this is accompanied by higher plasma NEFA uptake in skeletal muscle. With exercise training, this increased capacity for plasma NEFA uptake into the myocyte has been associated with an upregulation of membrane-associated plasma NEFA transport proteins (87). It was found that, compared with healthy sedentary individuals, athletes possessed a higher plasma NEFA uptake in skeletal muscle, while hepatic retention of plasma NEFA was 20% lower (88). Taken together, exercise training may lower intrahepatic lipid content via effects on plasma NEFA. Whereas the effects on adipose tissue lipolysis are less clear, exercise training does seem to improve plasma NEFA uptake in skeletal muscle. This might lower the plasma NEFA availability for the liver, lowering hepatic plasma NEFA uptake and changing fatty acid partitioning from liver to skeletal muscle (71).

In addition, exercise training could influence intrahepatic lipid content by modifying VLDL metabolism. As yet, no study has investigated the effect of exercise training-induced changes in VLDL metabolism on intrahepatic lipid content in humans, but some studies have investigated how exercise training influences VLDL secretion and clearance. For example, 6 months of supervised exercise training resulted in a significant decrease in VLDL–ApoB-100 secretion rate in obese individuals with type 2 diabetes (89). The VLDL–ApoB-100 catabolic rate, representing removal of VLDL particles from the vascular compartment by complete hydrolysis to Intermediate-density lipoproteins or by direct removal via the hepatic VLDL receptor (89), did not change. Moreover,

the VLDL–TG/ApoB-100 ratio was not altered, suggesting there was no change in TG content per VLDL particle secreted. Since VLDL–ApoB-100 secretion rate decreased, plasma VLDL–TG concentrations decreased. These findings were confirmed in a 2-month exercise training experiment with sedentary, non-obese young men (90). Stable isotope-labeled 1,1,2,3,3-[$^2H_5$] glycerol tracer infusion in the post-absorptive phase revealed VLDL–TG concentrations to be reduced by 28%, due to a 35% reduction in the hepatic VLDL–TG secretion rate, whereas no differences in VLDL–TG clearance could be observed. Thus, with exercise training, there seems to be a decrease in hepatic VLDL–TG secretion (71). It's showed that regular exercise also down-regulated the hepatic gene and protein content of stearoyl-CoA desaturase-1, the rate-limiting enzyme in the biosynthesis of saturated-derived monounsaturated fats that are a major constituent of VLDLs. Further, there was a down-regulation of the microsomal triglyceride transfer protein that plays a key role in the assembly and secretion of VLDL lipoprotein (91). Although this indicates beneficial adaptation in liver metabolism, it cannot explain why exercise training lowers intrahepatic lipid content, since a lower VLDL–TG secretion would theoretically lead to greater intrahepatic fat storage. Therefore, the reduced VLDL–TG secretion rate is most likely a consequence of the reduced intrahepatic lipid content upon exercise training (71).

Moreover, cross-sectional research shows that high-density lipoprotein cholesterol (HDL-c) levels are higher in regular exercisers versus their inactive counterparts (92), and HDL-c increases with exercise training interventions (93). These benefits are associated with a decreased activity of hepatic lipase (94) and alterations in the levels of other hepatic enzymes involved in HDL-c remodeling (including cholesteryl ester transfer protein and lecithin cholesteryl acyl transferase) (95). In addition, it's showed that exercise training increased levels of hepatic mRNA for the ATP-binding cassette transporter A-1 that plays a vital role in membrane transport and plasma HDL cholesterol remodeling (96).

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