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Effects of Exercise on the Fatty-Acid Composition of Blood and Tissue Lipids

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Abstract

This article reviews the effects of acute and chronic exercise on the fatty-acid composition of animal and human tissues (plasma, skeletal muscle, heart, adipose tissue, liver, artery and erythrocytes), as reported in 68 studies spanning four decades. The most consistently observed effect has been an increase in the relative amount of unsaturated, especially monounsaturated, non-esterified fatty acids in plasma of both animals and humans after acute exercise. Chronic exercise seems to increase the proportion of polyunsaturated fatty acids and ω6 fatty acids, while decreasing the proportion of monounsaturated fatty acids in animal and human adipose tissue. Additionally, chronic exercise seems to decrease the relative amount of unsaturated fatty acids in liver lipids of animals and humans. There is no consensus regarding the effect of exercise on the fatty-acid composition of lipids in any other tissue. In general, the effects of exercise are independent of nutrition and, regarding skeletal muscle, muscle fibre type.

The available literature shows that, in addition to modifying the concentrations of animal and human tissue lipids, exercise also changes their fatty-acid profile. Unfortunately, the available studies are so much divided among exercise models, species and biological samples that a cohesive picture of the plasticity of the fatty-acid pattern of most tissues toward exercise has not emerged. Future studies should focus on determining the fatty-acid profile of separate lipid classes (rather than total lipids) in separate subcellular fractions (rather than whole tissues), examining tissues and organs on which no data are available and exploring the mechanisms of the exercise-induced changes in fatty-acid composition.

1. Background

1.1 The Emerging Importance of the Fatty-Acid Composition of Body Tissues

In recent years, a wealth of studies have appeared addressing the effect of exercise on the fatty-acid composition of animal and human tissues. This is probably due to the partial unravelling of the role of individual fatty acids in animal biochemistry and physiology. At the molecular level, individual fatty acids influence fundamental regulatory processes, such as ion homeostasis, gene expression, signal transduction and synthesis of lipid or lipid-derived messengers.[1] These effects can then have remarkable impact on animal and human physiology. For example, there is now considerable evidence linking insulin sensitivity to the fatty-acid composition of human skeletal muscle phospholipids (PL).[2] Variations in the distribution of one fatty acid, arachidonate, between PL and cholesteryl esters (CE) in several human tissues have been correlated with the abnormal fuel partitioning associated with some forms of genetic obesity,[3] while the proportion of polyunsaturated fatty acids in membranes has been positively correlated with cellular metabolic activity.[4] Finally, in an exercise physiology context, increased dietary intake of ω3 fatty acids has been reported to decrease (probably through alterations in the fatty-acid composition of some tissues) the endurance performance of rats[5] and salmon.[6]

The effect of exercise on the lipid content of several tissues has been studied extensively.[7-10] However, the vast majority of these types of studies appear to overlook a fundamental feature of all lipid

classes, namely, their fatty-acid composition. Compounds of a particular lipid class (e.g. triacylglycerols [TG]) are usually treated as one entity in research, although, as mentioned in the paragraph above, it is becoming increasingly apparent that their constituent individual fatty acids play distinct roles in many biological functions. Nevertheless, several researchers have tried to unveil the effects of exercise on the fatty-acid profile of lipid classes. Reports on this issue were first published in the early 1960s and their number has been rising exponentially in recent years (half of them have appeared during the last decade). Two relevant reviews have been published,[11,12] although they are short and confined to skeletal muscle lipids.

Considering all of the above, a critical review of the studies dealing with the effects of exercise on the fatty-acid composition of tissues and blood (taken as a tissue at large in the present review), along with a discussion of the physiological implications of these effects, seems indispensable.

1.2 Fatty-Acid Structure

Fatty acids consist of a long hydrocarbon chain with a carboxyl group at one end and a methyl group at the other. They are usually referred to by their trivial names but their numerical notation indicating the number of carbon atoms, number of double bonds and, occasionally, position of double bonds is more informative. For example, palmitate, one of the most abundant fatty acids, is depicted as 16:0 (figure 1). Palmitate is a saturated fatty acid (SFA), as it contains no double bonds. Oleate, another abundant fatty acid, is an unsaturated, in particular monounsaturated fatty acid (MUFA), depicted as 18:1, as it contains one double bond (figure 1).

The numerical notation of unsaturated fatty acids is often supplemented by an indication of the position of the double bond(s). The ω (or n-) numbering, showing the carbon atom after which the first double bond appears, when one counts from the methyl end (the ω carbon) onward, facilitates the identification of metabolically related fatty acids, since elongation and degradation reactions take place at the other end. Oleate is 18:1ω9 according to the ω numbering

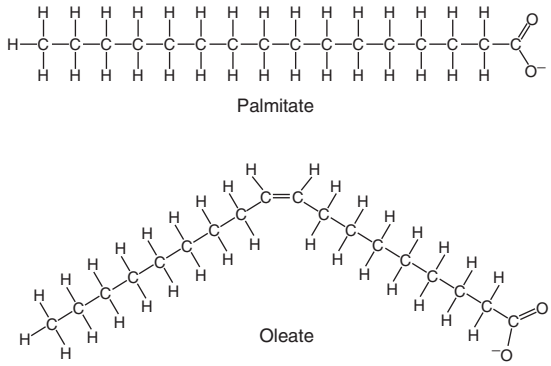

Fig. 1. Constitutional formulae of palmitate (16:0) and oleate (18:1ω9). The ionised forms predominate in biological fluids (the neutral fatty acids, with OH in place of O^-, are called palmitic acid and oleic acid). The double bond in oleate is of the *cis* configuration, as are most double bonds in naturally occurring fatty acids.

system. This system is satisfactory in describing polyunsaturated fatty acids (PUFA) as well, since their multiple double bonds are almost invariably spaced three carbons apart. Alternatively, the position of a double bond is indicated by a Δ (from the Greek *diplós*, double) followed by a superscript number referring to the carbon atom after which the double bond appears, when one counts from the carboxyl end onward. Hence, oleate carries a Δ^9 bond, which is introduced by the catalytic activity of Δ^9-desaturase.

Of the many fatty acids encountered in biological samples, eight, namely, 16:0, palmitoleate (16:1ω7), stearate (18:0), 18:1ω9, linoleate (18:2ω6), α-linolenate (18:3ω3), arachidonate (20:4ω6) and docosahexaenoate (22:6ω3), constitute approximately 90% of the amount of fatty acids in all lipid classes of the tissues that will be reviewed.

1.3 Fatty-Acid Families and Indices of the Fatty-Acid Profile

Grouping fatty acids according to chemical structure facilitates evaluating the effect of their changes on the physiology of organisms and monitoring their metabolic interconversions. Major families are the SFA, MUFA and PUFA, while PUFA are further divided into ω3 and ω6 fatty acids. Animals cannot synthesise ω3 and ω6 fatty acids *de novo* and must, therefore, receive at least one fatty acid from each

family through their diet (these are then called essential fatty acids).

A number of indices of the fatty-acid profile of a tissue or lipid class are being used in the literature. The unsaturated to saturated ratio (U/S) and the unsaturation index (UI) [the average number of double bonds per fatty acid in a fatty-acid mixture, multiplied by 100] measure the overall degree of unsaturation. Many researchers estimate the activities of enzymes involved in fatty-acid biosynthesis through appropriate product-to-precursor ratios. These include 18:0/16:0 as an index of elongase, 22:6ω3/22:5ω3 as an index of Δ^4-desaturase, 20:4ω6/20:3ω6 as an index of Δ^9-desaturase, 18:3ω6/18:2ω6 as an index of Δ^6-desaturase and 18:1ω9/18:0 as an index of Δ^9-desaturase. However, extrapolating differences in a product-to-precursor ratio to differences in enzyme activity assumes kinetic rather than thermodynamic control and no participation of the reactants in other reactions to a considerable degree. Both assumptions are rather shaky. In fact, there is usually poor correlation between the preceding indices and directly determined enzyme activities.[13-15] Therefore, these ratios should be treated as qualitative rather than quantitative indices of enzyme activity.

1.4 Lipid Classes and Their Role During Exercise

Only a small portion of the fatty acids in a tissue are present in free or non-esterified form (usually called NEFA), whereas the majority are in fact acyl groups (derived from fatty acids by removal of their O^-) within PL, TG, monoacylglycerols (MG), diacylglycerols (DG) and CE.

NEFA represent an important fuel for skeletal muscles, particularly those muscles containing a high proportion of oxidative fibres. Additionally, fatty acids such as 18:3ω3 and 20:4ω6 serve as precursors of four classes of signalling molecules, i.e. prostaglandins, prostacyclins, thromboxanes and leukotrienes, collectively known as eicosanoids. The NEFA content of a tissue emanates primarily from plasma and the hydrolysis of intracellular TG.

PL are composed of either a glycerol or sphingosine backbone, thus divided into glycerophospholipids and sphingomyelin, respectively (figure 2). Attached to the three hydroxyl groups of glycerol in a glycerophospholipid are two acyl groups and a phosphate group. Most glycerophospholipids carry an alcohol (such as choline, ethanolamine, serine and inositol) attached to the phosphate group (thus named phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol). In sphingomyelin, on the other hand, an acyl group and a phosphoryl choline moiety are attached to two positions of the sphingosine backbone. PL are major components of cell

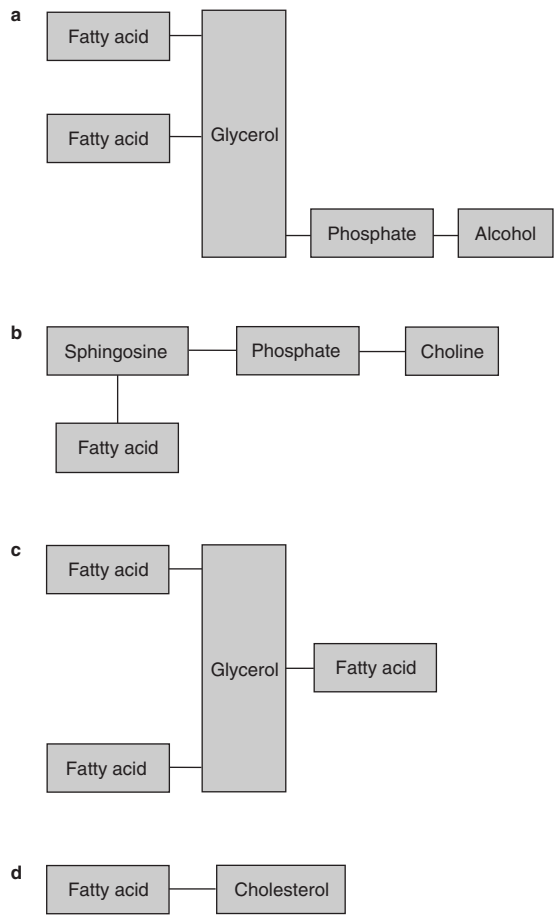

Fig. 2. Schematic representations of (**a**) glycerophospholipid (major phospholipid [PL]); (**b**) sphingomyelin (minor PL); (**c**) triacylglycerol; and (**d**) cholesteryl ester.

membranes and play a vital role in their function. Additionally, they provide second messengers (such as DG and inositol-1,4,5-trisphosphate) that are released in response to extracellular signals and convey information inside the cell. Finally, PL may provide energy in the form of fatty acids released by hydrolysis. However, this function appears to be rather unimportant, judging from the findings that acute prolonged exercise generally did not affect the amount of PL in skeletal muscle[16,17] and the liver,[8] while it reduced heart PL only slightly.[18,19]

TG are composed of three acyl groups esterified to glycerol (figure 2). They constitute 90–99% of the adipose tissue lipids of land animals[20] and represent the major storage form of fatty acids. Fatty acids released by hydrolysis of adipocyte (primarily) and myocellular TG are the main lipid fuelling muscular work at low to moderate intensities.[21] An additional minor contribution is made by fatty acids derived from lipoprotein-borne plasma TG.[21]

DG contain two acyl groups attached to glycerol and originate from three sources: they can be synthesised from MG or they can be formed from the hydrolysis of TG or PL. They represent a small portion of the lipid pool but their involvement in signal transduction renders their measurement important. DG activate protein kinase C (implicated in, among other events, the translocation of GluT4 to the plasma membrane) in skeletal muscle.[22] MG carry one acyl group esterified to glycerol and emanate from the hydrolysis of DG.

CE represent a hydrophobic storage form of cholesterol (a component of cell membranes and precursor of steroid hormones). CE are composed of one acyl group esterified to cholesterol (figure 2). We are not aware of any role of CE in exercise metabolism.

It is worth mentioning that the fatty-acid profile of the different lipid classes varies greatly. As an example, table I presents the percentage fatty-acid composition of the lipid classes in skeletal muscle. Some of the most striking differences are the 11-fold higher proportion of 16:1ω7 in NEFA compared with PL, the 9-fold higher value of 18:1ω9 in TG compared with MG and the 15-fold higher value of 20:4ω6 in PL compared with TG. Differences in individual fatty acids are then reflected to indices of the fatty-acid profile.

Table I. Molar percentage distribution of individual fatty acids and some indices of the fatty-acid profile in the lipid classes of rat soleus muscle[23]

Fatty acid or index	NEFA	PL	TG	DG	MG
16:0	35	18	30	32	23
16:1ω7	11	1	8	7	3
18:0	10	21	6	11	33
18:1ω9	24	9	36	31	4
18:2ω6	18	35	19	17	28
20:4ω6	2	15	1	3	9
MUFA	35	11	44	38	7
PUFA	20	50	20	20	37
U/S	1.2	1.6	1.8	1.3	0.8
UI	80	142	86	83	100

DG = diacylglycerols; **MG** = monoacylglycerols; **MUFA** = monounsaturated fatty acids; **NEFA** = non-esterified fatty acids; **PL** = phospholipids; **PUFA** = polyunsaturated fatty acids; **TG** = triacylglycerols; **UI** = unsaturation index; **U/S** = unsaturated/saturated.

1.5 Membrane Fatty-Acid Composition and Function

The effect of exercise on the fatty-acid pattern of membrane PL has drawn much of the researchers' attention, particularly after the association of insulin sensitivity with the PUFA content of human skeletal muscle PL.[2] Therefore, a brief description of the dependence of membrane structure and function on membrane fatty-acid composition seems warranted.

Membranes are dynamic structures in which proteins float in a sea of lipids. The lipid components (mainly PL) of a membrane form the permeability barrier, whereas proteins acting as transporters, channels or pumps endow the membrane with selective permeability. The physical properties of a membrane are greatly influenced by the fatty-acid composition of its PL. The presence of SFA favours a rigid state because their straight hydrocarbon chains are closely packed and held together by many hydrophobic attractions. As *cis* double bonds are introduced, the hydrocarbon chains bend (see figure 1) and packing becomes less dense. As a result, hydrophobic attractions decrease with increasing unsatu-

ration and membranes assume a less ordered, fluid state. Membrane fluidity also depends on hydrocarbon chain length (the shorter the chain the higher the fluidity). Finally, membrane fluidity in eukaryotes is modulated by cholesterol[24] but the description of its role lies outside the scope of this review.

The fatty-acid profile of membrane PL is likely to determine several features of membrane and cellular function, including the amount and activity of membrane proteins controlling many aspects of cellular energetics.[11] For example, two ion pumps involved in muscle contraction, the Na^+-K^+ adenosine triphosphatase (ATPase) of the sarcolemma and the Ca^{2+} ATPase of the sarcoplasmic reticulum, are known to be influenced by the fatty-acid composition of the surrounding PL.[25] At an organismal level, the fatty-acid composition of membranes is associated with metabolic activity in a predictable manner. This has resulted in the proposal of the 'membrane pacemaker theory',[4] which asserts that the balance between MUFA and PUFA in membranes is a fundamental determinant of the metabolic rates of species.

1.6 Scope and Aim of the Review

The available data regarding the effects of exercise on the fatty-acid profile of tissue lipids are somewhat fragmented, i.e. they involve various fatty acids, lipid classes, tissues and species. Additionally, they are derived from experiments of different designs and research goals. Therefore, the main aim of the present review is to present the effects of both acute and chronic exercise on the fatty-acid composition of the lipid classes of animal and human tissues in a coherent and meaningful manner. We believe that this integrative approach will produce a complete picture of what is known on this subject. Additionally, the comparison of different lipid classes and tissues will provide interesting information on the specificity of the effects of exercise.

An additional aim of the review is to bring out studies from disciplines outside exercise science, such as animal sciences, biochemistry and nutrition, whose main purpose might not have been to examine the effect of exercise on the fatty-acid composition of tissues and which might go unnoticed by exercise physiologists. This aim has been achieved by thorough literature search and cross-referencing. Let us point out that a search in PubMed using 'fatty acid composition' and 'exercise' as key words produced only 16 of the 68 studies that will be reviewed.

2. Methodological Issues

2.1 Animal versus Human Studies

The literature to be reviewed refers to both animals and humans. Reliable data on the latter are less easy to obtain, as diet (probably the physiological factor mostly affecting fatty-acid composition[26]) cannot be controlled completely in free-living individuals. Furthermore, animal experiments offer the opportunity to study tissues that are very hard or impossible to sample from living humans (e.g. the liver and heart). However, caution must be taken when extrapolating results from exercising animals to humans.

2.2 Type of Exercise

In the present review, we separate exercise into acute, if it has been performed only once, and chronic, if it has been performed repeatedly. Most of the studies that are presented have used running, cycling or swimming of moderate intensity for 0.5–2 hours per bout and the studies with chronic exercise have applied 40–60 bouts. The vast majority of the animal studies have employed exercise models that closely mimic human physical activity (according to the classification by Booth and Thomason[27]). For the sake of thoroughness, studies that employed electrical stimulation of animals, a model of increased contractile activity that does not mimic human physical activity, are also presented.

2.3 Fatty-Acid Analysis

The fatty-acid composition of a tissue can be determined at several levels (figure 3). The most rudimentary one is analysing total lipids of the whole tissue. Obviously, data from this type of

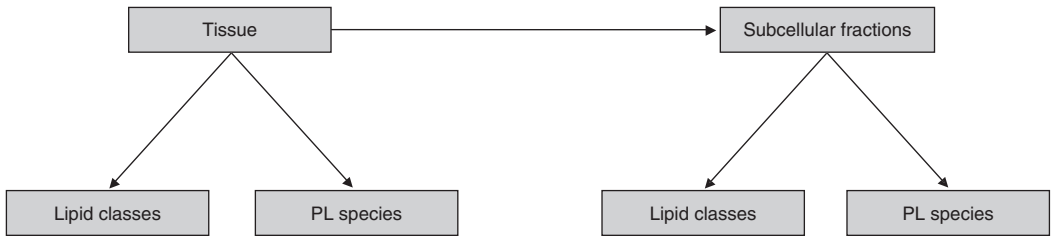

Fig. 3. Levels at which fatty-acid composition in a tissue can be determined. **PL** = phospholipid.

analysis are of limited value, since it is impossible to assign any changes in the fatty-acid pattern to specific cellular components or lipid classes. A more elaborate approach would be to fractionate the tissue and analyse the fatty-acid composition of its subcellular fractions (e.g. plasma membrane, mitochondria). Alternatively, one could separate the lipid classes of a tissue (e.g. PL, TG) and determine the fatty-acid composition of each. An integration of the latter two approaches (i.e. tissue fractionation followed by separation of lipid classes in each subcellular fraction) would yield the most detailed information possible. Most of the studies to be reviewed have adopted either of the two intermediate approaches. It is worth noting that, if PL analysis is intended, one can go even further by separating PL into their constituent species (e.g. phosphatidylcholine, phosphatidylethanolamine). The importance of separating subcellular fractions and lipid classes is discussed in more detail in sections 4.1 to 4.3.

In most studies, lipids have been extracted from tissues or subcellular fractions using chloroform-methanol 2:1 (per volume), while lipid classes or PL species have been separated by thin-layer chromatography of the lipid extract. Fatty-acid analysis has been carried out by gas chromatography after preparation of fatty-acid methyl esters from either total or separated lipids using a variety of reagents.

2.4 Presentation of Data

Most of the relevant studies have reported data on individual fatty acids as percentages (either by weight or molar) of the sum of fatty acids rather than concentrations in a tissue. Percentage distribution is easier to determine (since measurement of concentrations requires the addition of appropriate internal standards) and allows comparison of the amount of individual fatty acids relative to the sum among tissues, subcellular fractions and lipid classes of quite different total fatty-acid content. However, by comparing percentages of individual fatty acids, one may miss significant changes in concentrations, if most or all are in the same direction. Additionally, a spectacular change in the concentration of just one fatty acid may cause significant perturbations in the percentages of fatty acids whose concentrations have not changed, thus confounding interpretation of the results. Luckily, indices calculated as ratios of fatty acids (such as U/S and enzyme activities) are the same whether based on percentages or concentrations.

Given the form of the available data, the presentation in this review will be based on percentages of fatty acids only. In the few cases where mere concentrations have been reported in the original papers, we have converted them into molar percentages. Additionally, for the sake of accuracy, we have converted percentages by weight to molar percentages. Based on the latter, we have calculated the following indices of the fatty-acid profile (if they are not reported in the original papers): MUFA, PUFA, ω6 fatty acids, ω3 fatty acids, ω6/ω3, U/S, UI, Δ^4-, Δ^5-, Δ^6- and Δ^9-desaturase activities, as well as elongase activity. Indices of enzyme activity were calculated only in tissues where such activity has been directly demonstrated and only when the available fatty-acid data corresponded to total lipids or the majority of tissue lipids. We make only limited reference to individual fatty acids because their large number (frequently exceeding ten in a single

article) makes comparisons among studies unattainable.

Since most of the preceding indices have been calculated by us based on mean values reported in the original papers, there was no way of evaluating differences statistically. Therefore, only numerical comparisons are made in these cases. Whenever we use the term 'significant', this reflects the outcome of statistical comparisons reported in the original paper.

The results of the studies are classified first by tissue, then by form of exercise (acute, chronic) and then by lipid class. Differences described throughout the review as a result of exercise are in reference to the resting condition (when dealing with acute exercise) or the untrained condition (when dealing with chronic exercise). To avoid repetition, we do not mention this unless it is necessary for clarity.

3. Effects of Exercise on the Fatty-Acid Composition of Tissue Lipids

A concise listing of the studies that measured the effects of acute and chronic exercise on the fatty-acid composition of tissue lipids is presented in table II and table III, respectively.

3.1 Plasma

Blood plasma carries a multitude of substances including NEFA and lipoproteins that contain PL, cholesterol, TG and CE. NEFA are the most labile lipid class of plasma during exercise, since they receive a generous input from TG hydrolysed in adipose tissue, whereas lipoproteins and their constituents are not affected considerably. Therefore, NEFA seem to be the most worthwhile lipid class, in terms of addressing the effect of exercise on its fatty-acid profile, from both a physiological point of view (changing the composition of the mixture delivered to tissues) and a utilitarian point of view (increasing the possibilities to find significant differences). Indeed, the studies examining the effect of acute exercise on the profile of plasma NEFA greatly outnumber those examining all other plasma lipid classes together (for the sake of simplicity, we use the term 'plasma' even for studies in which serum was actually analysed).

3.1.1 Acute Exercise

Exercise increased monounsaturated plasma NEFA (on average, by 16%) in both animals and humans according to all the studies that have reported this index or have provided sufficient data for us to calculate it.[19,28-31,33,35,40,42,43,45,47,48,50-52,59-61] In addition to an increase after low-intensity exercise, Horstman et al.[42] reported a slight decrease after high-intensity exercise.

Regarding U/S, all studies showed increased values (on average, by 22%) in the plasma NEFA of acutely exercised animals and humans,[19,28-31,33,35,40,42,43,45,47,48,50-52,59-61] while, regarding UI, most of the studies also reported increased values (on average, by 7%).[19,28,30,31,35,40,42,43,47,48,50-52,59-61] These changes are apparently due to stimulation of lipolysis in adipose tissue, since U/S and UI of adipose tissue TG are markedly higher than those of plasma NEFA in both rats (unpublished data from our laboratory) and humans[50] (figure 4). It is noteworthy that the observation that acute exercise shifts the composition of plasma NEFA toward the fatty-acid composition of adipose tissue was made originally in humans over 30 years ago.[42]

In contrast to the consensus regarding MUFA, U/S and UI, there is no agreement among studies as to the effect of exercise on polyunsaturated, ω6 and ω3 NEFA, as well as ω6/ω3.

How long after exercise do the reported changes in the profile of plasma NEFA last? This seems to be a question worth asking, since it is reasonable to think that the magnitude of the effect(s) of the changes in fatty-acid composition will depend on their duration; that is, the longer the changes in fatty-acid composition remain, the higher their impact on metabolism will probably be. Mougios et al.[52] reported significant increases in U/S and 18:1ω9, as well as significant decreases in 16:0 and 18:0 (be reminded that we refer to percentages throughout the review) in humans at the end of acute exercise but not 2, 6, 10 or 22 hours post-exercise, compared with the respective values of the same

Table II. Studies that measured the fatty-acid composition of tissues after acute exercise

Study	Species	Exercise	Tissue (subcellular fraction)[a]	Lipid class
Bernard et al.[28]	Trout	Swimming	Plasma	NEFA
Børsheim et al.[29]	Human	Cycling	Plasma	NEFA
Carlsten et al.[30]	Human	Cycling	Plasma	NEFA
Ceder et al.[31]	Human	Running	Plasma	NEFA, total lipids
			Erythrocytes	Total lipids
Cleland et al.[32]	Rat	Electrical stimulation	Skeletal muscle	DG, PL
Conquer et al.[33]	Human	Cycling	Plasma	NEFA, PL
Dobrzyń and Górski[34]	Rat	Running	Skeletal muscle	PL
Donike et al.[35]	Human	Cycling	Plasma	NEFA
Dvořáková and Bass[36]	Rat	Swimming	Adipose tissue, heart, skeletal muscle	Total lipids
Gold et al.[37]	Dog	Running	Plasma	NEFA
Hall et al.[38]	Human	Running	Plasma	NEFA
Hambleton et al.[39]	Horse	Running	Plasma	Total lipids
Havel et al.[40]	Human	Cycling	Plasma	NEFA
Helge et al.[41]	Rat	Electrical stimulation	Skeletal muscle	PL, TG
Horstman et al.[42]	Human	Running	Plasma	NEFA
Hurter et al.[43]	Human	Running	Plasma	CE, NEFA, PL, TG
Jones et al.[44]	Human	Cycling	Plasma	NEFA
Kirkeby et al.[45]	Human	Skiing	Plasma	CE, NEFA, PL, TG
Mataix et al.[46]	Rat	Running	Heart, liver, skeletal muscle (mitochondria)	Total lipids
McClelland et al.[47]	Dog, goat	Running	Plasma	NEFA
McClelland et al.[48]	Rat	Running	Plasma	NEFA
Meydani et al.[49]	Human	Running	Skeletal muscle	Total lipids
Mougios et al.[50]	Human	Handball	Plasma	NEFA, TG
Mougios et al.[51]	Human	Cycling	Plasma	NEFA, TG
Mougios et al.[52]	Human	Cycling	Plasma	NEFA, TG
Petridou and Mougios[53]	Human	Cycling	Adipose tissue	TG
Quiles et al.[54]	Rat	Running	Plasma	Total lipids
Rose and Sampson[55]	Horse	Running	Plasma	NEFA
Sen et al.[56]	Rat	Running	Heart, liver, skeletal muscle	Total lipids
Sumikawa et al.[57]	Human	Sailing	Erythrocytes (membrane)	PL
Vapaatalo et al.[58]	Human	Cycling	Plasma	NEFA
Vihko et al.[59]	Human	Cycling	Plasma	NEFA
Vihko et al.[60]	Human	Cycling	Plasma	NEFA
Vincent and Brackenbury[61]	Fowl	Running	Plasma	NEFA
Wirth et al.[62]	Human	Cycling	Plasma	Total lipids
Wójcik et al.[19]	Rat	Running	Heart	DG, NEFA, PL, TG
			Plasma	NEFA
Wood et al.[63]	Human	Cycling, running	Plasma	NEFA

a Where no subcellular fraction is indicated, lipids were isolated from the whole tissue.

CE = cholesteryl esters; **DG** = diacylglycerols; **NEFA** = non-esterified fatty acids; **PL** = phospholipids; **TG** = triacylglycerols.

individuals while resting. Ceder et al.[31] found several changes in the profile of plasma NEFA immediately after marathon running but not 21 hours post-exercise. From these two studies, it seems that the effect of exercise on the profile of human plasma NEFA is short-lived. Other studies that provide late post-exercise data[38,45,55] are not described because methodological constraints limit their value.

McClelland et al.[47] were the only researchers who studied the responses of the profile of plasma

Table III. Studies that measured the fatty-acid composition of tissues after chronic exercise

Study	Species	Exercise	Tissue (subcellular fraction)[a]	Lipid class
Ågren et al.[64]	Human	Not specified	Erythrocytes, platelets	Total lipids
Allard et al.[65]	Human	Cycling	Adipose tissue	Total lipids
			Plasma	CE, PL, TG
Andersson et al.[66]	Human	Cycling, running	Plasma	PL, CE
			Skeletal muscle	PL, TG
Andersson et al.[67]	Human	Cycling, skiing, orienteering	Plasma	PL, CE
			Skeletal muscle	PL, TG
Ayre et al.[68]	Rat	Running	Heart, skeletal muscle	PL
Bailey et al.[69]	Rat	Swimming	Adipose tissue	Total lipids
Danner et al.[70]	Human	Rowing	Adipose tissue	Total lipids
Demaison et al.[71]	Rat	Running	Heart	PL
Fiebig et al.[72]	Rat	Running	Liver	Total lipids
Fiebig et al.[73]	Rat	Running	Liver	Total lipids
Hambleton et al.[39]	Horse	Running	Plasma	Total lipids
Hashimoto et al.[74]	Rat	Running	Artery, plasma	Total lipids
Helge et al.[75]	Rat	Running	Skeletal muscle	PL
Helge et al.[76]	Human	Leg extension	Skeletal muscle	PL, TG
Hurter et al.[43]	Human	Running	Plasma	CE
Kamada et al.[77]	Human	Running	Erythrocytes	PL
Kriketos et al.[78]	Rat	Running	Skeletal muscle	PL
Masumura et al.[79]	Rat	Running	Plasma	Total lipids
Mataix et al.[46]	Rat	Running	Heart, liver, skeletal muscle (mitochondria)	Total lipids
Nakano et al.[80]	Human	Running	Erythrocytes (membrane)	PL
Ohkubo et al.[81]	Rat	Swimming	Artery	Total lipids
Quiles et al.[82]	Rat	Running	Liver, skeletal muscle (mitochondria)	Total lipids
Quiles et al.[83]	Rat	Running	Heart, liver, skeletal muscle (mitochondria)	Total lipids
Quiles et al.[54]	Rat	Running	Plasma	Total lipids
Rocquelin and Juaneda[84]	Rat	Running	Adipose tissue	Total lipids
Rocquelin et al.[85]	Rat	Running	Heart	PL
Šimko et al.[86]	Rat	Swimming	Adipose tissue	TG
			Liver	CE, TG
Sumikawa et al.[57]	Human	Sailing	Erythrocytes (membrane)	PL
Sutherland et al.[87]	Human	Running	Adipose tissue	Total lipids
Szabó et al.[88]	Rabbit	Running	Skeletal muscle	Total lipids
Thomas et al.[89]	Human	Running	Skeletal muscle (membranes)	Total lipids
Thorling and Overvad[90]	Rat	Running	Adipose tissue	Total lipids
Tibbits et al.[91]	Rat	Running	Heart (plasma membrane)	PL
Venkatraman et al.[92]	Rat	Running	Liver (microsomes)	Total lipids
Venkatraman et al.[93]	Rat	Running	Liver (microsomes)	Total lipids
Vihko et al.[59]	Human	Cycling	Plasma	NEFA
Wirth et al.[62]	Human	Basketball training	Plasma	Total lipids
Wirth et al.[94]	Rat	Running	Adipose tissue, heart, liver, plasma, skeletal muscle	Total lipids

a Where no subcellular fraction is indicated, lipids were isolated from the whole tissue.

CE = cholesteryl esters; **NEFA** = non-esterified fatty acids; **PL** = phospholipids; **TG** = triacylglycerols.

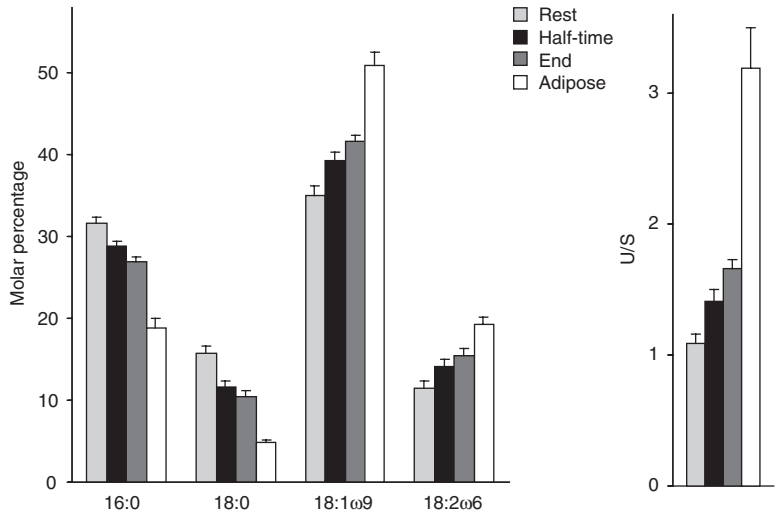

Fig. 4. Mean and standard error of the mean molar percentages of the four major fatty acids and unsaturated to saturated ratio (U/S) in plasma non-esterified fatty acids (NEFA) of 19 players at rest, at half-time and at the end of a handball game, as well as in their adipose tissue triacylglycerols (TG). Note the size of the difference between the profiles of adipose tissue TG and plasma NEFA at rest; only part of this difference is bridged after 60 minutes of exercise (reproduced from Mougios et al.,[50] with permission).

NEFA to acute exercise in two species, goats and dogs, concurrently (in fact, this is the only comparative study reviewed in the present article). Comparative exercise studies are indispensable in providing a criterion as to how safe it is to extrapolate findings from one species to another, which is frequently done by researchers in an effort to compare their findings with those of other researchers because of the lack of studies that used the same species. However, the comparison between goats and dogs in the aforementioned study is confounded by the large differences in the fatty-acid composition of their diets (for example, 18:1ω9 constituted 14% of the fatty acids in the diet of goats and 42% in the diet of dogs). These differences are likely to have evoked quite different fatty-acid profiles in the animals' adipose tissue TG, which, as presented above, exert a major influence on the changes in the fatty-acid profile of plasma NEFA with exercise. Determination of the fatty-acid composition of adipose tissue TG would have been very helpful in this respect. This limitation aside, McClelland et al.[47] found that exercise caused similar changes in the plasma NEFA composition of both species (findings are included in the preceding cumulative presentation). The investigators used two exercise intensities (40% and 60% of the animals' maximal oxygen uptake) but the overall pattern of changes was similar. Moreover, they measured the NEFA composition not only immediately but also 1 hour after the end of exercise and generally found that the percentages of the major fatty acids moved toward baseline values, suggesting that changes in the profile of plasma NEFA with exercise are temporary in animals too.

Wójcik et al.[19] studied the effects of acute treadmill running either for 30 minutes or until exhaustion (on average, 3.5 hours) on the profile of plasma NEFA of rats. The results were similar in both cases indicating that 30 minutes of exercise might be an adequate stimulus for inducing changes in the composition of rat plasma NEFA. However, the effects of both exercise regimens were very slight.

For the sake of thoroughness, we have to mention that we have not presented some studies dealing with the effect of acute exercise on individual plasma NEFA[37,38,44,55,58,63] because they have reported inadequate data (they present the percentages of one or two fatty acids only,[58,63] they report only changes in concentrations, not percentages, of individual fatty acids[37,38] or their data are flawed[44,55]).

Additionally, we have not presented data on plasma lipid classes other than NEFA (i.e. TG, PL and CE) because they vary widely among the relevant studies;[31,33,39,43,45,50-52,54,62] besides, the changes detected were small. Overall, the influence of acute exercise on the fatty-acid composition of plasma lipids appears to be confined to NEFA.

Given the strong evidence that acute exercise markedly increases the relative amount of unsaturated, especially monounsaturated NEFA in plasma, the question arises: what is the physiological importance of this effect? We are far from an answer but we hypothesised that, as with increased dietary intake of unsaturated fatty acids, the effect, if any, of exercise-induced changes in the profile of plasma NEFA on physiological or health parameters will have to be mediated by changes in the composition of the fatty-acid mixture taken up by tissues from plasma. Could then the relative increase in unsaturated plasma NEFA cause proportionally more fatty acids of this family to enter tissues? The entrance of fatty acids into tissues is a complicated multifactorial process, which has been only partially elucidated and is apparently a combination of passive and active transport.[95] If the rate of uptake of each fatty acid by a tissue is positively related to its plasma concentration, then, indeed, relatively more unsaturated fatty acids will enter tissues during exercise.

The consequences of this higher rate of uptake of unsaturated relative to saturated fatty acids by tissues on the fatty-acid composition of their lipids are almost impossible to predict at the time. If, for example, unsaturated fatty acids are preferentially oxidised over saturated ones, then the fatty-acid composition of tissues may not change. If, on the other hand, the rate of fatty-acid oxidation is independent of unsaturation, then more unsaturated fatty acids will be available for esterification and the fatty-acid profile of PL, TG etc. may change. Of course, many other possibilities exist (e.g. enzymes involved in the synthesis of one lipid class being selective to particular fatty acids and hence indifferent to changes in the composition of the NEFA pool). This shows how difficult it is to predict the effects of any change in the fatty-acid composition of plasma on the fatty-acid composition of tissue lipids.

3.1.2 Chronic Exercise

Changes in the profile of plasma NEFA in response to chronic exercise are less apparent than those in response to acute exercise. Changes in the fatty-acid profile of the other lipid classes are also small. The probable reason is the much smaller magnitude of the chronic changes in the concentration of plasma lipids compared with the acute changes in the concentration of plasma NEFA. Moreover, obtaining a clear picture is confounded by the insufficient number of relevant studies on each lipid class. Specifically, only one study examined NEFA,[59] three examined TG and PL,[65-67] four examined CE[43,65-67] and six examined total lipids.[39,54,62,74,79,94] Given the situation, the studies will be described individually.

Quiles et al.[54] investigated whether feeding rats diets rich in olive oil (high in 18:1ω9) or sunflower oil (high in 18:1ω9 and 18:2ω6), in conjunction with chronic exercise, affected the fatty-acid profile of total plasma lipids. They found that trained rats, practically irrespective of the diet consumed, exhibited significantly lower MUFA and higher PUFA (both ω6 and ω3 fatty acids). The data also showed lower ω6/ω3 and U/S, as well as higher UI in the trained animals.

The data reported by Hashimoto et al.[74] generally show no changes in the fatty-acid profile of total plasma lipids after treadmill training in aged hypercholesterolaemic rats. However, the profiles presented in the study need to be treated with some caution, since the authors report no data on 18:0, a fatty acid constituting 8–20% of total plasma lipids in rats, according to Quiles et al.[54] and Wirth et al.[94]

Masumura et al.[79] measured three highly unsaturated fatty acids (20:4ω6, 20:5ω3 and 22:6ω3) in total plasma lipids of sedentary and treadmill-trained rats. To examine whether the response to training was affected by the season of the year, the experiment was conducted during the winter and then again during the summer (with different animals). Chronic exercise, regardless of season, did

not affect the preceding PUFA, except for a near halving of 20:4ω6 in rats trained during the summer. However, it is not evident how the animals sensed the season, considering that they lived in a temperature- and photoperiod-controlled environment.

A possible threat to studies examining the effect of chronic exercise on the physiology of male rats is the lower bodyweight attained by the trained animals. To address this issue, Wirth et al.,[94] in addition to trained and untrained male rats feeding *ad libitum*, introduced a group of untrained animals whose food intake was restricted in order to match the bodyweight of the trained group (this is usually called pair-feeding). There were no differences between the two untrained groups in the fatty-acid composition of total plasma lipids, while the trained group had lower MUFA and higher PUFA (both ω6 and ω3 fatty acids), as well as UI.

Hambleton et al.[39] found no significant changes in 16:0, 18:0, 18:1ω9 or 18:2ω6 (the only fatty acids mentioned in the study) of total plasma lipids in four chronically exercised horses.

According to the data reported by Wirth et al.,[62] training slightly decreased MUFA, U/S and UI in total lipids of human plasma; however, these changes were small (5–12%).

The only study that investigated the influence of training on the profile of plasma NEFA[59] showed lower MUFA and U/S, as opposed to higher PUFA and ω6 fatty acids in humans after training; however, the changes were small (4–7%). The lack of a quantitatively major effect of chronic exercise on the profile of plasma NEFA is in accordance with its rapid return to baseline after acute exercise, as discussed in section 3.1.1.

The studies of Allard et al.[65] and Hurter et al.[43] have reported opposite results concerning the effect of chronic exercise on the fatty-acid profile of plasma CE. This is probably due to the fact that the former study employed patients with coronary heart disease, whereas the latter employed healthy men. Allard et al.[65] have also reported the effect of chronic exercise on the fatty-acid profile of plasma TG and PL, and found increased PUFA, ω6 fatty acids, U/S and UI in both lipid classes. MUFA increased in TG and decreased in PL. Finally, two studies from the same laboratory reported no significant effect of chronic exercise on the fatty-acid composition of human plasma PL and CE in general.[66,67]

In summary, the studies reviewed in this section have found either generally stable or decreased MUFA and either generally stable or increased PUFA in the plasma lipid classes of trained animals and humans.

3.2 Skeletal Muscle

Excluding plasma, skeletal muscle has been by far the most frequently studied tissue in terms of the effect of exercise on fatty-acid composition. This preference seems justifiable because of the well described extensive plasticity of muscle toward exercise. Besides, muscle metabolism accounts for at least 20% of daily resting energy expenditure,[96] rendering it one of the most important tissues for glucose and fatty-acid homeostasis. Finally, its accessibility to biopsy makes it the tissue of choice for studying metabolic adaptations in humans.

When examining the effect of exercise on the fatty-acid profile of skeletal muscle, an additional variable, muscle fibre type, has to be taken into consideration, as it is known that different types often respond and adapt differently to an exercise stimulus.[97] Therefore, one of the aims of this section is to detect possible muscle-type-specific responses to acute or chronic exercise. This examination will be based only on work that studied different skeletal muscles under the same experimental setting, since the diversity of designs makes it unsafe to compare the responses of different muscle fibre types among studies.

3.2.1 Acute Exercise

It is difficult to group the available studies on the effects of acute exercise on the fatty-acid composition of skeletal muscle,[32,34,36,41,46,49,56] since they have presented divergent results, probably mainly as a result of dissimilarities in methodology. Therefore, they will be presented separately.

Cleland et al.[32] stimulated the calf muscles of rats electrically for 2 or 30 minutes and examined

the fatty-acid composition of DG and phosphatidate (i.e. glycerol with two acyl groups and a phosphate group at one end; a common intermediate in the synthesis of PL and TG). In both cases, there was almost no change in the fatty-acid profile of DG. In contrast, 16:0 and 20:4ω6 increased, whereas 18:0 and 18:2ω6 decreased in phosphatidate. The changes after just 2 minutes of stimulation are the highest reported in this review (ranging from −82% to 456%) and are difficult to interpret.

Helge et al.[41] showed that electrically induced eccentric contractions caused significant, although small (4–13%), increases in 20:4ω6, 22:5ω3, long PUFA (20–22 carbons) and UI in the PL of rat white gastrocnemius but did not change the fatty-acid profile of TG 2 days after the stimulation. These effects were similar in rats fed normal rodent chow or chow enriched with either fish oil (high in 20:5ω3 and 22:6ω3) or ascorbic acid (vitamin C).

Mataix et al.[46] reported significantly more PUFA in mitochondrial total lipids of rat vastus lateralis immediately and 30 minutes after the end of treadmill running. This effect was independent of diet (enriched with either olive oil or sunflower oil).

Sen et al.[56] found no effect of exhaustive treadmill running on the fatty-acid composition of total lipids in red gastrocnemius (intermediate type) and superficial vastus lateralis (type II) muscles of rats fed a diet rich in either soybean oil (high in 18:1ω9 and 18:2ω6) or fish oil. However, the data reported include only four fatty acids (i.e. 18:2ω6, 20:4ω6, 20:5ω3 and 22:6ω3) comprising only half of the fatty acids in white quadriceps PL (the major lipid class in skeletal muscle) of the rat, according to Helge et al.[75]

Dvořáková and Bass[36] reported a significant increase in U/S of total lipids in soleus, tibialis anterior (type II) and extensor digitorum longus (EDL; type II) muscles of rats after swimming. In general, the effects of exercise on fatty-acid composition were not dependent on muscle fibre type.

Dobrzyń and Górski[34] studied the effects of treadmill running on the fatty-acid pattern of sphingomyelin and ceramide (i.e. sphingosine with one acyl group; precursor of sphingomyelin) in soleus, white gastrocnemius (predominantly type II) and red gastrocnemius muscles of rat. These compounds belong to a recently characterised transmembrane signalling pathway. Sphingomyelin, which is located mostly in the extracellular layer of the plasma membrane, is hydrolysed to phosphorylcholine and ceramide, which has been implicated in apoptosis, cell differentiation, cell damage and inflammation.[98] Dobrzyń and Górski[34] found generally increased MUFA and decreased PUFA in sphingomyelin and ceramide of all three muscles in exercised animals. Moreover, there were large decreases in ω6/ω3 in sphingomyelin of soleus and ceramide of all muscles (on average, by 66%). In contrast, there were large increases in ω6/ω3 in sphingomyelin of white and red gastrocnemius (on average, by 44%). In addition, the investigators found increased U/S in sphingomyelin of soleus and ceramide of all muscles, as well as decreased UI in sphingomyelin of all three muscles and ceramide of white gastrocnemius. Notably, this study is one of the very few that provide fatty-acid composition data for individual PL species using an animal model that closely mimics human physical activity (treadmill running[27]).

Meydani et al.[49] were the only investigators who used humans to study the effects of acute exercise on the fatty-acid profile of skeletal muscle. Subjects were divided into a tocopherol (vitamin E)-supplemented group and a placebo group, and ran downhill on a treadmill. Needle biopsies were taken from vastus lateralis before exercise, immediately post-exercise and 5 days post-exercise for analysis of total lipids. The exercise-induced changes were independent of supplementation. MUFA, ω6/ω3, U/S and Δ^9-desaturase activity decreased, whereas PUFA, UI and elongase activity increased immediately post-exercise. The fatty-acid profile 5 days post-exercise was similar to baseline.

A lack of consensus among studies regarding the effects of acute exercise on any index of the fatty-acid composition of skeletal muscle is obvious. However, an interesting conclusion can be drawn from the studies of Dvořáková and Bass,[36] Sen et al.[56] and, partly, Dobrzyń and Górski,[34] who

analysed concurrently more than one muscle, as well as from the studies of Helge et al.,[41] Mataix et al.,[46] Meydani et al.[49] and Sen et al.,[56] who administered more than one diet. That is, the response of the fatty-acid profile of skeletal muscle to acute exercise seems to be largely independent of muscle fibre type and diet.

3.2.2 Chronic Exercise

There is great diversity among the studies that investigated the effect of chronic exercise on the fatty-acid composition of animal skeletal muscle,[46,68,75,78,82,83,88,94] which necessitates presentation of each separately. On the contrary, the few studies on humans[66,67,76,89] allow some consensus to be reached.

Helge et al.[75] investigated the effect of training on the PL fatty-acid profile of rat red quadriceps (mainly type II), white quadriceps (type II) and soleus muscles. UI, long PUFA and Δ^5-desaturase activity were generally lower in the trained muscles. These effects were, in essence, independent of diet (carbohydrate-rich, SFA-rich or MUFA-rich).

Ayre et al.[68] examined the effect of chronic exercise on the PL fatty-acid pattern of soleus, EDL and white gastrocnemius muscles of obese Zucker rats (an animal model of insulin resistance) and lean (virtually healthy) counterparts. MUFA and PUFA decreased in all three muscles of trained lean rats compared with untrained lean rats except for an increase in PUFA of soleus. ω6/ω3 was practically unaltered in all three muscles. U/S, UI and elongase activity were lower in EDL and white gastrocnemius but higher in soleus of trained lean animals. Δ^5- and Δ^6-desaturase activities were higher in all three muscles of trained lean animals, while Δ^9-desaturase activity was lower in all three muscles. Differences between trained and untrained obese animals were less consistent in the three muscles and, in most cases, opposite to the corresponding differences in the lean animals, leading to several significant interactions of exercise and genotype. Probably the most interesting of these appeared in 20:4ω6, which increased in all three muscles of the obese trained (compared with untrained) animals, whereas it decreased in all three muscles of the trained lean animals. The only uniform differences in the three muscles between trained and untrained obese animals were a higher Δ^5-desaturase activity and a lower UI as well as Δ^6-desaturase activity in the former.

Quiles et al.[82] and, duplicating the data, Quiles et al.[83] studied the effects of chronic exercise on the fatty-acid profile of vastus lateralis mitochondria of rats fed a diet rich in either olive oil or sunflower oil. The results showed a decrease in PUFA, U/S and UI independent of diet. On the contrary, changes in MUFA and ω6/ω3 were opposite under the two diets. Oddly, an identically designed study from the same laboratory[46] reported significantly higher PUFA in vastus lateralis mitochondria of trained rats fed the olive oil diet. Comparison of other fatty-acid-related parameters between the two experiments is not feasible due to the lack of data in the latter.

Kriketos et al.[78] determined how a stress-free exercise model (wheel running) influenced the PL fatty-acid pattern of rat EDL and soleus. Investigators reported no significant differences between trained and untrained animals in individual fatty acids except for a significant decrease of 22:6ω3 in soleus after training. Interestingly, all numerical differences between trained and untrained animals were in opposite directions in the two muscles, implying that the responses to wheel running depended on muscle fibre type.

Wirth et al.[94] reported practically no differences in the fatty-acid profile of red quadriceps total lipids between trained and untrained rats pair-fed for weight, except for 16:1ω7 being significantly lower in the trained animals.

Szabó et al.[88] studied the effects of chronic treadmill running on the fatty-acid composition of total lipids in longissimus dorsi and vastus lateralis (both intermediate-type muscles) of rabbits. Trained rabbits exhibited higher MUFA, U/S and Δ^9-desaturase activity, as well as lower PUFA, ω6/ω3, UI and elongase activity in both muscles.

Regarding the human studies already mentioned,[66,67,76,89] all examined the effects of chronic exercise on the fatty-acid profile of vastus lateralis

PL. To be exact, Thomas et al.[89] analysed total muscle membranes but almost all PL are located in membranes and PL are practically the only fatty-acid-containing compounds in membranes. These studies found borderline changes in MUFA, PUFA and U/S. ω6/ω3 decreased, whereas UI exhibited small increases (by 4.4, 4.5 and 4.4% in the studies by Andersson et al.,[67] Helge et al.[76] and Thomas et al., [89] respectively) or no change.[66] Elongase activity increased in all studies, whereas Δ^5- and Δ^9-desaturase activities showed no consistent changes. Concerning the fatty-acid profile of TG, the three relevant studies[66,67,76] found increased U/S (by 0.5, 3 and 26%, respectively) and no consistent changes in MUFA, PUFA, ω6/ω3 and UI.

3.2.3 Integration

Most of the animal studies reviewed in the previous two sections[34,36,56,68,75,78,88] have determined the fatty-acid composition of more than one skeletal muscle, probably because the investigators expected different muscles to respond differently to acute or chronic exercise. This supposition is justified by numerous studies that have shown the effects of exercise on many aspects of muscle plasticity to be modulated by muscle fibre type.[99] Does this apply to the fatty-acid pattern of muscle lipids? The answer (based on the rather limited data available) is, generally no. This may relate to the fact that differences in fatty-acid pattern among muscles are rather small, smaller than, say, differences in the proteome. Suffice it to say that one of the most striking and consistently observed differences in the fatty-acid profile of muscle PL (PL account for about two-thirds of total muscle fatty acids[100]) is the higher content of type I compared with type II muscles in unsaturated fatty acids by a mere four percentage units (on average, 62% in soleus and 58% in EDL[5,68,78,101]).

Due to the connection of the fatty-acid profile of skeletal muscle PL with insulin sensitivity, most of the studies that investigated the effect of exercise on the fatty-acid profile of muscle have separated and analysed PL. Unfortunately, there is an obvious lack of consensus among these studies, even when they refer to the same muscle of the same animal species. In fact, a longitudinal and a cross-sectional study from the same laboratory (Andersson et al.[66] and Andersson et al.,[67] respectively), reported several divergent results. Therefore, the well documented augmentative effect of exercise on insulin sensitivity[66] cannot be ascribed to changes in the fatty-acid composition of muscle PL.

3.3 Heart

Unlike skeletal muscle, the effects of exercise on the energy metabolism of cardiac muscle appear to be rather subtle.[102] For example, in rat models, training does not elicit striking changes in enzyme markers of oxidative or glycolytic capacity.[102] This is consistent with the observation that rat myocardium has an intrinsically high oxidative metabolic capacity.[102] One would then expect even smaller changes in fatty-acid composition than the ones described in the previous sections for skeletal muscle. On the other hand, the high rate of fatty-acid oxidation in the myocardium[103] renders its fatty-acid profile largely dependent on that of the plasma lipids (mainly NEFA) entering it. Since the profile of plasma NEFA changes considerably in response to acute exercise, single or repeated exercise bouts have the potential of altering the fatty-acid composition of heart lipids.

3.3.1 Acute Exercise

Wójcik et al.[19] studied the effects of treadmill running, either for 30 minutes or until exhaustion, on the fatty-acid composition of most lipid classes (NEFA, DG, TG and PL) in rat heart. Regarding the profile of NEFA, exercise decreased PUFA, ω6 fatty acids, U/S and UI in both cases. On the other hand, MUFA increased after 30 minutes of exercise and decreased after exhaustion. Changes in the fatty-acid profile of DG were variable and less pronounced. Regarding the fatty-acid pattern of TG, exercise decreased PUFA, ω6 fatty acids and U/S in both cases. Finally, the fatty-acid pattern of PL remained generally unaffected by exercise. As with plasma NEFA (section 3.1.1), this study showed that the effects of exercise on the fatty-acid composition of most heart lipids were similar after 30 minutes of exercise and after exhaustion. It is notable that the

changes in fatty-acid composition differed among lipid classes. The profile of NEFA was the most labile, probably due to the fact that their concentration increased appreciably after exercise, in contrast to the concentration of the other lipid classes, which remained practically unaltered.

Mataix et al.[46] studied the effect of treadmill running on the fatty-acid profile of heart mitochondria either immediately or 30 minutes after the end of treadmill running in rats fed diets rich in olive oil or sunflower oil. The study reported no significant changes in PUFA regardless of diet and sampling time. Besides this index, data on only two individual fatty acids were reported, therefore other indices cannot be calculated.

Sen et al.[56] reported no effects of exhaustive treadmill running on the fatty-acid profile of heart total lipids in rats fed a diet rich in either soybean oil or fish oil. On the other hand, Dvořáková and Bass[36] reported that one hour of swimming induced significant increases in 16:1ω7 and 18:1ω9, as well as a significant decrease in 18:2ω6 in total lipids of rat heart.

3.3.2 Chronic Exercise

Rats fed a diet supplemented with sunflower oil, erucate (22:1ω9)-rich rapeseed oil or erucate-poor rapeseed oil (rich in 18:1ω9) were subjected to treadmill training and the fatty-acid pattern of PL species of the heart was compared with that of untrained animals fed the same diets.[85] The main finding of the study was that diet and exercise interacted significantly but, in general, changes in individual fatty acids of all PL species in animals fed the same diet moved in the same direction. Exercise generally increased MUFA, ω6/ω3, U/S and Δ^9-desaturase activity, while decreasing PUFA and UI in the rats fed the sunflower oil diet. In the rats fed the erucate-rich rapeseed oil diet, exercise generally decreased PUFA, ω6/ω3, U/S, UI and Δ^9-desaturase activity, while MUFA moved upward or downward depending on the PL species. Finally, in rats fed the erucate-poor rapeseed oil diet, exercise generally increased PUFA, U/S, UI and elongase activity, while MUFA, ω6/ω3 and Δ^9-desaturase activity decreased.

Rats were fed ordinary rodent chow or chow enriched with either sunflower oil or fish oil in a study by Demaison et al.[71] Half of the animals receiving each diet were subjected to treadmill training, whereas the other half served as controls. Chronic exercise did not alter the fatty-acid profile of heart PL significantly. However, this may stem in part from the low power of the study (there were only three rats per group) and/or the short training period (3 weeks).

Two studies from the same laboratory[46,83] examined the effects of chronic exercise on the fatty-acid profile of heart mitochondria of rats fed diets rich in olive oil or sunflower oil. The researchers reported no significant effects of chronic exercise on PUFA, ω6 fatty acids or U/S. On the other hand, MUFA increased in the trained rats fed the olive oil diet but did not change in the rats fed the sunflower oil diet.

Ayre et al.[68] examined whether chronic exercise affected the fatty-acid profile of heart PL in lean and obese Zucker rats. The effects of exercise were relatively small, particularly in the lean animals, and the only significant changes were a marked increase of 18:2ω6 (by 37%) in the trained obese animals and a decrease of 20:3ω6 in the trained animals of both genotypes. As with skeletal muscle, 20:4ω6 increased in the heart of the trained (compared with the untrained) obese animals and decreased in the heart of the trained lean animals.

Wirth et al.[94] assigned a group of untrained rats to pair-feed with trained animals in order to control for bodyweight. Results showed higher percentages of fatty acids having 18 or 20 carbons in heart total lipids of the trained animals.

Finally, Tibbits et al.[91] investigated the effects of chronic treadmill exercise on the fatty-acid composition of plasma membrane PL in a large number of rats (30 sedentary and 30 trained). The investigators found lower MUFA, PUFA, U/S, UI and Δ^9-desaturase activity, as well as higher ω6 fatty acids in the trained animals.

3.3.3 Summary

The effect of exercise (either acute or chronic) on the fatty-acid pattern of heart lipids has been studied

only in rats. In most of the relevant studies, exercise proved able to change this pattern without, on the other hand, a clear picture emerging from these changes. It is worth noting that, of the five studies that employed more than one diet,[46,56,71,83,85] four (excluding Rocquelin et al.[85]) reported that the effects of exercise on the fatty-acid composition of heart lipids were practically independent of nutrition.

3.4 Adipose Tissue

The major metabolic role of adipose tissue is the regulated storage (in the form of TG) and release (in the form of NEFA) of fat. Today it is clear that adipose tissue is a rather dynamic tissue and there is evidence that its morphology and metabolism adapt to endurance exercise in humans.[104] Due to its role as the main supplier of fatty acids to tissues in the postabsorptive state, changes in its fatty-acid composition can, in theory, modify the fatty-acid composition of other tissues. Therefore, determining the effects of exercise on the fatty-acid profile of adipose tissue seems to be crucial for understanding the plasticity of other tissues in terms of their fatty-acid repertoire. Moreover, now that adipose tissue, through its endocrine and paracrine function, is recognised as playing a more active role in the regulation of whole body metabolism than it was previously thought,[105] the possibility arises that the fatty-acid pattern of adipose tissue may affect its regulatory functions.

With two exceptions,[53,86] studies addressing the effect of exercise on the fatty-acid composition of adipose tissue have not separated its lipid classes but have instead used total lipids. Although it is improbable that any change in total lipids will emanate from any lipid class other than TG (since, as mentioned already, they represent 90–99% of adipose tissue lipids), analysing total lipids may mask changes in a minor lipid class, such as PL.

3.4.1 Acute Exercise

We found only two studies examining the effects of acute exercise on the fatty-acid pattern of adipose tissue lipids.[36,53] In the first study, swimming induced significant increases in 16:1ω7, 18:2ω6 and U/S, as well as significant decreases in 16:0, 18:1ω9 and 20:4ω6 of rat subcutaneous adipose tissue. On the contrary, the fatty-acid composition of human subcutaneous adipose tissue TG did not change significantly during 30 minutes of cycling and at 15 minutes of recovery.[53]

3.4.2 Chronic Exercise

Studies addressing the effect of chronic exercise on the fatty-acid profile of human subcutaneous adipose tissue[65,70,87] have reported decreased levels of MUFA in trained individuals. The effect on rat adipose tissue MUFA is less clear, with some investigators reporting generally lower levels in trained animals[69,86,94] and others reporting miniscule differences from untrained animals.[84,90] Bailey et al.[69] reported that the effect of exercise on MUFA was relatively independent of adipose tissue site (they compared epididymal, perirenal and inguinal fat) and age (they compared rats aged 12, 16, 20, 24 and 28 months). Additionally, Rocquelin and Juaneda[84] generally found no differences in the effect of chronic exercise on adipose tissue MUFA among rats fed the three diets mentioned at the beginning of section 3.3.2.

Regarding adipose tissue PUFA and ω6 fatty acids, most of the studies reported generally higher levels in trained animals and humans.[65,69,70,84,87,90,94] On the other hand, results regarding the effect of exercise on adipose tissue U/S are conflicting, with some studies showing increased values in trained subjects,[84,90,94] other studies showing decreased values[65,86,87] and one study showing practically no difference.[70] Bailey et al.[69] reported different effects according to age and adipose tissue site, with no clear pattern emerging from the data.

UI was generally either slightly higher in adipose tissue of trained animals and humans[69,70,84,90,94] or virtually not different between trained and untrained humans.[65,87] However, Bailey et al.[69] reported lower UI in inguinal adipose tissue of young rats (aged 12–16 months) and perirenal adipose tissue of old rats (aged 28 months). Likewise, Šimko et al.[86] reported lower UI in adipose tissue of trained rats.

Most of the studies indicate increased elongase activity in adipose tissue of trained animals and humans.[65,70,87,90,94] Additionally, Rocquelin and Juaneda[84] reported opposite changes depending on diet, while Bailey et al.[69] reported opposite changes depending on age and adipose tissue site, although, again, a clear pattern of the interaction among exercise, age and adipose tissue site cannot be drawn.

Regarding Δ^9-desaturase activity in adipose tissue, most of the studies have found a reduction in trained animals and humans.[65,70,86,87,90,94] As with the preceding enzyme, Rocquelin and Juaneda[84] reported diet-dependent effects, while Bailey et al.[69] reported site- and age-dependent effects of exercise.

Two of the previous studies merit special mention because of their design. First, the fact that Wirth et al.[94] found several differences between trained rats and pair-fed untrained rats suggests that the differences were not due to the reduction in bodyweight gain. Secondly, the fact that Thorling and Overvad[90] used rats of both sexes and found similar (although more pronounced in the male) effects of training on the fatty-acid profile of adipose tissue suggests that sex does not affect these responses appreciably. It is worth considering that female rats are sometimes preferred over male ones in exercise studies because the former compensate for the increased energy expenditure of training by overeating so that they lose little or no weight compared with sedentary counterparts.[72,74]

In summary, most of the relevant studies indicate that chronic exercise generally increases PUFA, ω6 fatty acids and elongase activity, while decreasing MUFA and Δ^9-desaturase activity in animal and human adipose tissue.

3.5 Liver

Although the role of the liver in exercise metabolism involves primarily the increase in the production and mobilisation of glucose, it also includes biochemical pathways for amino acid and lipid metabolism that are accelerated during muscular work.[106] NEFA taken up from the plasma have two major fates inside hepatocytes: oxidation or esterification to produce TG mainly.[107] TG are then used to form the bulk of very-low-density lipoproteins, which are secreted into the bloodstream and form the main source of plasma TG. One may then assume that the composition of NEFA entering the liver can affect the composition of liver TG, which may, in turn, reflect on the composition of plasma TG.

3.5.1 Acute Exercise

We found two studies addressing the effects of acute exercise on the fatty-acid composition of liver lipids.[46,56] In the first study, PUFA increased significantly 30 minutes after the end of acute treadmill running in liver mitochondrial total lipids of trained rats fed a diet rich in olive oil but decreased significantly in rats fed a diet rich in sunflower oil. However, these changes were not seen immediately after exercise. Sen et al.[56] found no effect of acute exhaustive treadmill running on the fatty-acid pattern of total liver lipids of rats fed a diet rich in either soybean oil or fish oil.

3.5.2 Chronic Exercise

Three studies have reported nutrition-dependent effects of chronic exercise on MUFA of liver lipids. Venkatraman et al.[92,93] found higher MUFA in liver microsomal lipids of trained rats fed ordinary rodent chow, lower MUFA in trained rats fed chow enriched with corn oil and practically no differences between trained and untrained rats fed chow enriched with fish oil. Likewise, Fiebig et al.[72] reported higher MUFA in total liver lipids of trained rats fed a high cornstarch diet, while trained rats fed a high fructose diet had lower MUFA than untrained controls. On the other hand, Quiles et al.[82] and, duplicating the data, Quiles et al.[83] reported significantly decreased MUFA in liver mitochondria of chronically exercised rats fed diets rich in either olive oil or sunflower oil. Šimko et al.[86] reported lipid class-dependent effects of chronic exercise on MUFA in liver. Specifically, MUFA decreased significantly in CE and increased significantly in TG. Finally, lower MUFA have been reported in total liver lipids of trained rats compared with pair-fed untrained controls[94] and in trained lean as well as obese Zucker rats.[73]

Studies addressing the effect of chronic exercise on liver PUFA have also reported divergent results. One study found opposite effects depending on diet[72] and some studies found diet-independent effects.[82,92,93] Specifically, Fiebig et al.[72] reported lower PUFA in total liver lipids of trained rats fed the high-cornstarch diet, while trained rats fed the high-fructose diet had higher PUFA than untrained controls. On the other hand, Quiles et al.[82] reported higher PUFA in liver mitochondria of chronically exercised rats fed diets rich in either olive oil or sunflower oil, whereas Venkatraman et al.[92,93] reported lower PUFA in liver microsomes of trained rats fed ordinary rodent chow or diets rich in either corn oil or fish oil. Finally, Fiebig et al.,[73] Wirth et al.[94] and Šimko et al.[86] found increased PUFA in liver total lipids (the former two studies) or TG (the latter study) of trained animals.

Concerning U/S in liver lipids, most of the studies reported lower values in trained rats compared with untrained ones,[72,73,82,92,93] this being the only relative consensus as to the effect of chronic exercise on the fatty-acid profile of liver lipids. Finally, there is no consensus regarding the effects of chronic exercise on ω6/ω3, UI, elongase activity and Δ^9-desaturase activity in liver.

3.6 Artery

Dietary fish oils rich in 20:5ω3 and 22:6ω3 may protect against cardiovascular disease.[108] Evidence suggests that these oils, among other effects, lower blood pressure in hypertensive animals and humans.[109] This action may be mediated by the vasorelaxant effect of 20:5ω3 and 22:6ω3, as has been demonstrated in several rat models.[109] Similarly, exercise has long been known to offer protection against cardiovascular disease.[110] The mechanisms of the beneficial effects of highly unsaturated fatty acids and exercise are not known but alterations in the fatty-acid composition of vessels may be involved. A reduction in unsaturated fatty acids and membrane fluidity has been reported in vascular smooth muscle cells from hypertensive animals,[109] while abnormal fatty-acid profiles have been observed in a variety of tissues from spontaneously hypertensive rats.[109] Therefore, it is possible that the effects of exercise on the fatty-acid composition of vascular tissue have clinical implications.

The two available studies addressing the effects of exercise on the fatty-acid composition of arteries have employed chronic exercise protocols.[74,81] Hashimoto et al.[74] trained aged hypercholesterolaemic rats on a treadmill and determined the fatty-acid profile of total caudal artery lipids, while Ohkubo et al.[81] trained male and female rats by swimming and determined the fatty-acid profile of total aorta lipids. Their results are in agreement regarding MUFA, ω6/ω3 and U/S, which were found lower in the trained rats, but diverge regarding PUFA and UI, which were found higher by Hashimoto et al.[74] and lower by Ohkubo et al.[81] in the trained animals. Swimming induced similar changes in male and female rats.[81] It is noteworthy that the sedentary male rats were pair-fed to their trained counterparts (there was no need to pair-feed the female rats since, as mentioned in section 3.4.2, trained female rats do not exhibit reduced food intake).

3.7 Erythrocytes

Erythrocytes have been used often to study changes induced by various factors (such as oxidative stress) on the composition of cell membranes because they are easier to obtain compared with cells from tissues. As erythrocytes are unable to carry out *de novo* synthesis of PL, they maintain their membrane composition by obtaining PL from plasma lipids.[111] Therefore, exercise-induced changes in the fatty-acid composition of plasma PL may affect the fatty-acid composition of erythrocytes. Alternatively, exercise may alter the rate of exchange of PL between erythrocyte membranes and plasma, provided that the two pools differ in fatty-acid composition.

3.7.1 Acute Exercise

Sumikawa et al.[57] investigated the effects of maximal cycling on the fatty-acid composition of two major PL species of human erythrocyte membranes, i.e. phosphatidylcholine and phosphatidylserine. They found decreased PUFA, ω6 fatty acids,

ω3 fatty acids, U/S and UI in both PL species after exercise. Contrary to these findings, Ceder et al.[31] reported slightly increased PUFA, ω6 fatty acids, ω3 fatty acids, U/S and UI in total erythrocyte lipids immediately after a marathon race. By 21 hours after the race, the fatty-acid composition of erythrocytes had returned to baseline.

3.7.2 Chronic Exercise

The fatty-acid profile of erythrocyte lipids seems to remain largely unaffected by chronic exercise in humans.[57,64,77,80] A cross-sectional study reported similar fatty-acid profiles of erythrocyte membrane PL in long-distance runners and sedentary individuals.[80] Likewise, a longitudinal study reported that the fatty-acid composition of erythrocytes (and platelets) remained unchanged after a 14-week training protocol.[64] However, the training stimulus was apparently insufficient judging from the small increase in the training frequency of the already exercising subjects at the time of recruitment (from 2.2 to 3.5 sessions per week) and the decrease in maximal oxygen uptake at the end of the programme.

Sumikawa et al.[57] compared the fatty-acid pattern of erythrocyte membrane phosphatidylcholine and phosphatidylserine in sailors and sedentary individuals. The two groups had similar patterns except for the higher MUFA and ω6/ω3 in both PL species in the sailors. Finally, the fatty-acid composition of erythrocytes was measured in male sprinters, long-distance runners and sedentary individuals.[77] Both trained groups had slightly lower MUFA and slightly higher PUFA than controls. In addition, long-distance runners had higher U/S and UI than controls and sprinters. Generally, long-distance runners differed from untrained subjects more than sprinters did.

The main reason for examining the fatty-acid profile of erythrocyte membranes is probably the influence that it exerts on membrane fluidity (see section 1.5). Several studies have reported increased erythrocyte membrane fluidity or erythrocyte deformability (a parameter strongly and positively related to membrane fluidity) after chronic exercise.[77,80,112,113] However, given the paucity of remarkable effects of exercise on the fatty-acid composition of erythrocyte membranes, changes in fatty-acid composition cannot be proposed as the link between exercise and the alteration of erythrocyte membrane properties.

4. How Results on Fatty-Acid Composition May Be Inadequate or Misleading

4.1 The Importance of Separating Subcellular Fractions

The vast majority of the studies presented in this review have not separated tissues into subcellular fractions. Since cells are made of compartments with different lipid and fatty-acid composition, examining the whole tissue may mask changes in a compartment, if they are cancelled out by opposite changes in another compartment or 'diluted' to the effect that they are not detected. Alternatively, the fatty-acid profile of the tissue may change by a mere change in the mass of a compartment. Consider, for example, skeletal muscle PL. PL are almost exclusively associated with membranes but most of the relevant studies have not differentiated among sarcolemma, sarcoplasmic reticulum membranes, mitochondrial membranes, etc. With endurance training, muscle mitochondria increase[99] and so does their contribution to tissue PL. While mitochondrial membranes differ from the other cellular membranes in fatty-acid composition,[114] endurance training can alter the fatty-acid composition of total muscle PL without any change in the fatty-acid composition of any cellular membrane. In this case, failing to fractionate the tissue may create a fictitious image of alteration in its fatty-acid composition.

4.2 The Importance of Separating Lipid Classes

Analysing total lipids in a tissue is of limited value due to differences in fatty-acid pattern among lipid classes (table I). By analogy to the preceding discussion, analysis of total lipids may mask changes in one class or may lead to erroneous con-

clusions, if a mere change in the amount of one class occurs. A case in point is skeletal muscle TG, which have quite different proportions of MUFA and PUFA from PL in both rats[23] and humans:[66,76] MUFA are much more than PUFA in TG, whereas PUFA are much more than MUFA in PL. Chronic exercise has been repeatedly shown to reduce the TG content of rat skeletal muscle.[9] This will increase MUFA and decrease PUFA in total muscle lipids with no change occurring in these indices in either PL or TG. The reverse may occur in humans, where muscle TG are reportedly elevated in trained individuals.[115,116] Here, it is failing to separate lipid classes that may create a fictitious image of alteration in the fatty-acid composition of a tissue.

4.3 The Importance of Separating Phospholipid Species

If PL is the desired lipid class for fatty-acid analysis, then an additional level of resolution, separation of PL species, is needed for a detailed description of the effects of exercise on the fatty-acid composition of a tissue. Different PL species play distinct biological roles. For instance, phosphatidylinositol bisphosphate can be hydrolysed by phospholipase C to yield inositol trisphosphate and DG, two key intermediates in the mobilisation of intracellular Ca^{2+} and activation of protein kinase C.[117] Sphingomyelin, as already mentioned in section 3.2.1, is involved in signalling a multitude of cellular events. Finally, in an example suggesting possible clinical implications of particular PL species, the fatty-acid composition of skeletal muscle phosphatidylcholine, but not phosphatidylethanolamine, has been found to correlate with insulin sensitivity in humans.[118]

In summary, subcellular fractionation, separation of lipid classes and separation of PL species in a tissue prevent the data on the effect of exercise on the fatty-acid composition of tissue lipids from becoming misleading and permit differences to emerge in more realistic dimensions.

5. Conclusions

It has long been known that exercise can modulate the lipid make up of many tissues.[104,116,119,120] It is now clear that this ability comprises alterations in not only the quantity of lipid classes but also their fatty-acid composition.

From the analysis of the relevant literature in the preceding sections, the following effects of exercise have emerged:

- acute exercise increases unsaturated, especially monounsaturated, NEFA in plasma immediately after activity;
- chronic exercise seems to increase PUFA, ω6 fatty acids and elongase activity, while decreasing MUFA and Δ^9-desaturase activity in adipose tissue;
- chronic exercise seems to decrease U/S in liver lipids.

In general, the effects of exercise on the fatty-acid composition of tissue lipids are independent of nutrition and, regarding skeletal muscle, muscle fibre type.

Unfortunately, there is no consensus among studies regarding the effect of acute or chronic exercise on the fatty-acid profile of lipids in any other tissue. Therefore, it would be probably incongruous to try to explore the physiological significance of the changes in the fatty-acid profile of tissues with exercise any more than we have already done in the introduction and in sections 1 and 3.

It is even more difficult to propose mechanisms for the changes in the fatty-acid composition of tissue lipids with exercise (except for the acute changes in plasma NEFA discussed in section 3.1.1). Potential control points of the fatty-acid composition include lipid biosynthesis, degradation, transport and permeation through cellular membranes. We know very little about whether and how exercise affects these processes.

Why is there so much divergence among studies addressing the effect of exercise on the fatty-acid profile of tissue lipids? We believe that the main reason is the near uniqueness of each study in terms of type of exercise (acute or chronic), species, tissue, subcellular fraction and lipid class examined. In

fact, with the exception of the 18 papers that described the effect of acute exercise on the profile of human plasma NEFA (and produced a remarkable consensus), the number of papers that are uniform in terms of all the criteria listed above does not exceed four and averages only two. Other factors that could explain some of the diversity of results include nutrition, subject characteristics, exercise characteristics and experimental error arising from the complexity of the techniques employed in tissue fractionation, lipid separation and fatty-acid analysis. Finally, the lack of consensus may be partially explained by the biological variability of lipid metabolism.

In summary, it is clear that exercise, both acute and chronic, can change the fatty-acid composition of tissue lipids. However, the available studies are so much divided among exercise models, species and biological samples that a cohesive picture of the plasticity of the fatty-acid composition of most tissues toward exercise has not emerged. Thus, in most cases, studies emit divergent messages as to the effects of exercise.

Future studies on the effect of exercise on the fatty-acid composition of tissue lipids could:

- determine the fatty-acid profile of separate lipid classes (including individual PL species) in separate subcellular fractions, aiming at obtaining the most detailed information possible;
- examine tissues and organs on which no data are available at all (e.g. the brain);
- explore mechanisms by comparing changes among tissues, subcellular fractions or lipid classes (e.g. adipose tissue TG with plasma NEFA and plasma NEFA with heart NEFA) or measuring the activity of key proteins implicated in the modulation of the fatty-acid profile (e.g. enzymes and carriers).

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