Organ-Specific Physiological Responses to Acute Physical Exercise and Long-Term Training in Humans

Virtually all tissues in the human body rely on aerobic metabolism for energy production and are therefore critically dependent on continuous supply of oxygen. Oxygen is provided by blood flow, and, in essence, changes in organ perfusion are also closely associated with alterations in tissue metabolism. In response to acute exercise, blood flow is markedly increased in contracting skeletal muscles and myocardium, but perfusion in other organs (brain and bone) is only slightly enhanced or is even reduced (visceral organs). Despite largely unchanged metabolism and perfusion, repeated exposures to altered hemodynamics and hormonal milieu produced by acute exercise, long-term exercise training appears to be capable of inducing effects also in tissues other than muscles that may yield health benefits. However, the physiological adaptations and driving-force mechanisms in organs such as brain, liver, pancreas, gut, bone, and adipose tissue, remain largely obscure in humans. Along these lines, this review integrates current information on physiological responses to acute exercise and to long-term physical training in major metabolically active human organs. Knowledge is mostly provided based on the state-of-the-art, noninvasive human imaging studies, and directions for future novel research are proposed throughout the review.

The decision to commence physical movements is made in the motor cortex in the brain (74). Simultaneously with voluntary activation of skeletal muscle movement, central command activates sympathetic nervous system and depresses the parasympathetic branch to coordinate the associated cardiovascular and ventilatory responses resulting in increased cardiac output and thus oxygen supply via blood flow to contracting myocardium and skeletal muscles, but also to skin, to dissipate excess heat, whereas vasoconstriction occurs in other organs, especially in splanchnic vascular beds (91). A decrease in peripheral resistance is the result of an increase in diameter of small arteries (100–300 μm) and especially arterioles (<100 μm), whereas the increase in diameter of conduit arteries does not contribute significantly. Immediately after initiation of exercise, afferent inputs from contracting skeletal muscles, but also from other organs, fine tune the hemodynamic responses to meet the increased metabolic requirements produced by exercise. To facilitate oxygen supply, a small increase in arterial hemoglobin occurs. In most animal species, splenic contraction-induced release of erythrocyte-rich blood contributes to the increase in hemoglobin (91). In contrast, in humans, the increase in hemoglobin is negligible and is principally the result of hemoconcentration due to an extravasation of fluids (120). Arterial supply of energy substrates remains relatively constant and close to resting levels as exercise initiates. This response is triggered and maintained by lowered circulating insulin and elevated glucagon and epinephrine levels, with simultaneous elevation in hepatic glucose production that corresponds to the utilization of glucose in actively exercising tissues (18, 44, 78, 79). However, muscle glycogen and fatty acid storages are also being used, and as exercise intensity increases, there is an elevation in circulating lactate levels and an increased contribution of lactate to energy metabolism. With increasing exercise duration, the utilization of free fatty acids released from adipose tissue also increases substantially. After the cessation of exercise, limb blood flow remains elevated above resting levels 1) to restore metabolic debts and wash out accumulated metabolic by-products, and 2) to
also likely dissipate exercise-induced excess heat production (46). These general physiological responses to acute exercise, which are illustrated in FIGURE 1, can be uniquely studied with the positron emission tomography (PET) method even at the whole-body level (FIGURE 2), will be discussed at the organ level in detail. Furthermore, due to repeated exposures to altered hemodynamics and hormonal milieu produced by acute exercise, long-term exercise training is capable of inducing physiological effects in many organs. Thus consistent long-term physical exercise training of a sufficient intensity, frequency, and duration produces numerous adaptations in the human body, which are generally beneficial for health and well being (28). Particularly relevant in today’s aging society is that the resultant improved functional capacity and fitness will enhance the independency of people, especially when at a higher age, and markedly reduce the likelihood of premature death (88, 114). These adaptations, in response to mainly endurance-type exercise training, are summarized in FIGURE 3 and are discussed organ by organ after discussion of acute responses.

The focus of this review will be mostly on adaptations in healthy humans. However, in view of the high prevalence of obesity in modern society, stemming from an imbalance of physical activity and energy consumption (49, 174, 176, 178), which causes predisposition to increased risk of cardiovascular disease, we will occasionally also discuss the impact of obesity on exercise (training) responses when appropriate. For review of epidemiological evidence of physical activity against that of drug therapies and associated molecular mediators, readers are referred to a recent comprehensive review article in this journal (28). Furthermore, knowledge in this review is mostly provided based on the state-of-the-art, noninvasive human imaging studies, mostly PET imaging. PET is a molecular imaging method based on radioactive isotopes, of which general and exercise-related principles have been described in excellent reviews (6, 45, 98, 173, 189), and the feasibility is also compared with other techniques in human exercise investigations ranging from whole-body to tissue levels (80). For methodological details, readers are referred to these previous reviews.

FIGURE 1. Physiological responses to acute endurance exercise
In response to acute endurance-type exercise, triggered from brain, the main physiological adjustments include increased ventilation and pumping function of the heart associated with substantially decreased peripheral vascular resistance in the muscles but largely unchanged or even increased resistance in many other tissues. This facilitates the delivery of oxygen and nutrients to working muscles, which consume high amounts of oxygen and nutrients, especially when exercise intensity increases. These organ-specific responses are discussed in detail in the text. ↑, Increases; ↔, no change in response; ↓, decreases; †, may increase or decrease.
Brain Studies in humans and animals have shown that brain blood flow remains largely unchanged in response to acute exercise (8, 65, 91). Brain blood flow may marginally increase from rest to mild exercise but does not increase with increasing exercise intensity. This means that increased metabolic demands of active brain parts are mostly met by redistributing oxygen supply from the areas that were active at rest but are not necessary during exercise, although changes in oxygen extraction may also contribute. During exercise, blood flow is directed to the areas controlling locomotor, vestibular, cardiorespiratory, and visual functions (8, 91), facilitated by direct communication of neurons and vascular cells (94, 134). The blood flow redistribution follows the changes in metabolic activity. With respect to utilization of energy substrates, the brain is a highly omnivorous organ capable of glucose, fatty acid, and lactate utilization. In general, an increased fatty acid oxidation is characteristic of the fasted state, whereas the uptake of glucose is the preferred substrate that predominates particularly during mild- to moderate-intensity exercise. However, with increasing exercise intensity, brain glucose uptake decreases (75) as the uptake and utilization of lactate is enhanced (65, 139, 182). Regional differences in brain glucose uptake are also evident, which is furthermore influenced by the level of physical fitness. Thus the decrease in glucose uptake in the dorsal part of the anterior cingulate cortex during exercise is significantly more pronounced in subjects with higher exercise capacity (75), which is illustrated in FIGURE 4. Importantly, however, even with current imaging techniques, it is not always possible to differentiate whether observed changes in brain metabolism or perfusion are due to regional descending feed-forward activation associated with voluntary activation of muscles or rather sensory feedback from afferent nerves (158). To be able to differentiate between these responses would certainly deepen our understanding in brain physiology.

Although basic circulatory and metabolic physiological adjustments to acute physical exercise in brain appear to be fairly well characterized to date, several important research areas warrant further investigation. Acute exercise is, for instance, known to increase endocannabinoids in peripheral blood (62, 162) in an exercise-intensity-dependent manner (141). Endocannabinoids, acting through CB$_1$ and CB$_2$ receptors, reduce pain sensation among their other functions. Quantification of cannabinoid receptors and their functional investigation in humans is currently possible with PET (119, 194), and to further understand exercise brain physiology (140) it should be explored whether acute exercise triggers similar kinds of alterations in endocannabinoid receptor functions as noted in certain cannabinoid-dependence disorders (118). It would also be important to investigate whether acute exercise blunts the reward circuit activation known to be altered in obesity (122). This could provide mechanistic physiological human information to explain why especially acute high-intensity (152, 159), or aerobic rather than strength-training, exercise (34) suppresses energy intake after a single bout of exercise. Non-invasive imaging approaches for the mapping of

**FIGURE 2. Effect of cross-country skiing on glucose uptake in all human organs**

Three-dimensional, whole body illustration of the effect of cross-country skiing on glucose uptake in all human organs, as investigated by Bojsen-Møller et al. (7) by positron emission tomography. Double-poling was used as a skiing technique, which resulted in high glucose uptake, particularly in triceps brachii and abdominal muscles as expected. Note also, however, a high brain activation and a resultant glucose uptake, as well as fairly high uptake of glucose in heart.
protein synthesis, shown to be enhanced by exercise (115), would also be important to better understand neuronal adaptations to exercise. Finally, recent advances in imaging methods and tracer development have made it possible that opioid receptors also can be investigated in the human brain (61), but the understanding of acute exercise on opioid receptor expression and function warrants further exploration (6).

The Effects of Long-Term Exercise Training

In contrast to acute exercise, long-term physiological adaptations to exercise training in the human brain have been fairly poorly characterized to date. Hence, research in this area could yield a wealth of physiologically novel and medically relevant information. Although human brain studies have not yet been performed to repeat training-induced increased capillarity, neurogenesis, and mitochondrial biogenesis reported in animal studies (3, 87, 168, 183), a physically active lifestyle has been shown to lead to higher cognitive performance and delayed or prevented neurological conditions in humans (71, 101, 143, 191). This is likely important for mental functional capacity complementing improved physical functional capacity. There is also

![FIGURE 3. Long-term adaptations of human organs to repeated exposures of mainly endurance exercise](http://physiologyonline.physiology.org/)

Illustrated are the long-term adaptations of human organs to repeated exposures to mainly endurance-type physical exercise, which are discussed in the text in detail organ-specifically in terms of most metabolically active organs. The main physiological and structural adaptations involve increased capacities for blood flow and oxygen consumption basically in every organ in the human body, especially heart and skeletal muscles. Directly contributing to better aerobic fitness are also larger lung volumes and higher ventilatory capacity of highly endurance-trained subjects, which might be the result of remodeling of the lungs (17) and its vasculature (59), although it remains unclear whether larger lungs are largely genetically determined or a result of training, since evidence stems mostly from cross-sectional investigations. A higher fitness level is also facilitated by training-induced increased oxygen-carrying capacity in the form of an increase in red blood cell mass, although hematocrit decreases slightly due to an even greater increase in plasma volume (129), hence the term pseudoanemia. In addition, favorable changes in circulating serum lipid and amino acid profiles have been documented in physically active adults (84). Blood vessels also adapt structurally by increasing their diameter to make it possible to accommodate increased total blood delivery capacity (91). However, although flow-mediated dilatation is generally improved by exercise training in patient populations with endothelial dysfunction, it is usually not enhanced in healthy subjects and may even be slightly impaired in highly endurance-trained athletes (32, 33). Similarly, resting blood pressure can be lowered by exercise training in hypertensive subjects but remains normal in normotensive subjects (22) as factors regulating the tonus of the blood vessels are adjusted to limit a decrease in peripheral resistance. Largely uncharacterized are the effects on bone, inner organs and brain, which should thus be the focus of the future studies. ↑, Increases; ↔, no change in response; ↓, decreases; ↕, may increase or decrease.
evidence that brain size, one determinant of cognitive performance, is larger in individuals with higher exercise capacity (101, 142), suggesting that training-induced increases in fitness levels may also enhance brain size. This may also explain why brain blood flow is well maintained in aerobically fit but old subjects (2), as brain hypoperfusion is associated with cognitive performance in elderly subjects and explained by brain atrophy (136). In addition to an improved cognitive performance, exercise training may also produce re-organization at the synaptic and receptor-level in several areas of the brain, including those areas controlling satiety and anxiety, which would explain the beneficial effects of regular physical activity on body weight control and prevention of depression (25), respectively. Research in this area is mandatory to advance our understanding of the mechanisms underlying the beneficial effects of low-intensity exercise on anxiety relief and of high-intensity exercise on appetite control. The results from such studies will provide the scientific evidence to further support implementation of exercise as a therapeutic tool for these neurological conditions.

For example, it would be interesting to study whether exercise training, similar to bariatric surgery (180), can correct abnormal (increased) insulin-stimulated brain glucose metabolism in obesity. This is likely in view of experimental data showing that prolonged exercise decreases brain glycogen content in rats (105), a phenomenon classically also observed in skeletal muscles and liver. Moreover, the same group of investigators also showed that subsequent glycogen supercompensation can occur in the brain (104), possibly as an adaptation to cope with the increased metabolic demands and glycogen depletion during prolonged exercise. Since brain glycogen content can be measured in humans (130, 131), it would be of great interest to study whether these observations in animals can be confirmed in humans. This could, for example, aid in examining the relation between local depletion of brain glycogen due to high local neural activity and central fatigue during prolonged exercise (20).

The production of brain-derived neurotrophic factor (BDNF), a key protein regulating maintenance and growth of neurons, is known to be stimulated by acute exercise (145), which may contribute to learning and memory. BDNF is released from brain already at rest but increases two- to threefold during exercise, which contributes 70–80% of circulating BDNF (145). It has recently been shown in mice that exercise-induced irisin release contributes to the increase in BDNF levels (195). Although irisin may not exert the exact same effects in humans as in mice (132, 144, 177), it would be worthwhile to explore, using noninvasive imaging methods with novel tracers, whether BDNF is also increased in the human brain, and if so in what brain regions, following several bouts of exercise. A study in mice suggests that the formation of BDNF is increased in hippocampus and cortex (145), and it has been shown in humans that endurance training enhances BDNF release from the brain (157), which is likely to promote not only brain health but also general whole body metabolism (81).

Finally, it is presently unknown whether endurance training leads to reductions in resting brain blood flow and higher oxygen extraction similar to what has been observed in many other organs. This question could be addressed using noninvasive imaging techniques such as PET and MRI (99), which would have the additional advantage over arterial-venous determinations of allowing assessment of the regional differences in alterations in perfusion and oxygen extraction in the brain.
Cardiac and Skeletal Muscles

The Effects of Acute Exercise

Cardiac and especially skeletal muscles play a central role in determining the level of whole body metabolism not only at rest but particularly during exercise. This is best illustrated by the fact that these tissues receive almost all (85–95%) of the cardiac output and thus oxygen delivery during maximal exercise (91). Due to their central role in body movement and in pumping oxygen and energy substrates to all tissues of the body, skeletal and cardiac muscle have also been the most intensively investigated organs in exercise physiology. Here, we will highlight only the main adjustments to acute exercise.

Although there is some animal and indirect human evidence that sympathetic nervous system plays an important role in distributing blood flow, not only to different organs but also between active and inactive skeletal muscle (48), it was not until recently that direct human evidence was provided (60). Using PET, which is capable of measuring organ perfusion and metabolism noninvasively (FIGURE 5), it was shown that blood flow is markedly increased in nonactive but not in active muscles during α-adrenergic receptor inhibition in healthy volunteers (60). These findings indicate functional sympatholysis in contracting muscles but not in any other tissue such as adipose tissue or bone (60), highlighting the importance of sympathetic nervous control in controlling organ perfusion during exercise. Distribution of blood flow within and between active skeletal muscles not only is of substantial importance for matching of oxygen delivery and consumption locally in skeletal muscle (80), but it also plays an important role in matching energy substrate delivery with local metabolic needs (43, 54, 86). Thus, although glucose uptake is increased in response to exercise and further enhanced by hypoxia (53), its regional uptake does not correlate with local muscle perfusion (86). This is particularly true with low-intensity exercise, where regional uptake of free fatty acids correlates tightly with local muscle perfusion (43, 86). It is presently unclear whether matching between glucose uptake and local muscle perfusion improves when exercise intensity increases. Nonetheless, the uptake of glucose is controlled among others by nitric oxide during heavy- (12) but not low-intensity exercise (57), whereas nitric oxide, on the other hand, regulates muscle oxygen uptake more robustly in a quiescent rather than an exercising skeletal muscle (58).

Although glucose uptake increases with increasing exercise intensity in working skeletal muscle (76) and reaches higher uptake levels in endurance-trained men as the absolute workloads they can perform are higher (29), glucose uptake in myocardium increases only up to moderate-intensity

FIGURE 5. Fusion image of structural MRI and functional PET
A typical fusion image of structural MRI and functional PET blood flow image from the middle thigh region at rest. Outer layer white areas and in the middle of the legs are subcutaneous adipose tissue and bone marrow, respectively, and darker areas are muscle tissue. Red spots (highest activity and thus highest blood flow) show the blood flow in larger artery, and yellow and green colors illustrate moderate to high blood flow within the leg. Blue color depicts lower blood flow areas relative to the areas with the highest blood flows. MRI and PET fusion images are oftentimes needed to combine high anatomical and functional imaging insights, respectively. Fusion images enable precise localization and investigations of different limb tissues, such as different muscles, adipose tissue, and bone, which cannot be differentiated by methods that measure bulk blood flow of the limb. However, in contrast to Doppler ultrasound, for instance, PET can be mostly applied only to steady-state conditions due to its fairly low temporal resolution, which limits its use when it is of interest to investigate rapid transitions from rest to exercise and rapid changes with increasing exercise intensities.
whole body exercise (76). Strikingly, with higher exercise intensities, when circulating lactate increases, myocardial glucose uptake returns back to the level observed at rest (76). This highlights the role of other energy substrates, mainly or solely lactate (100, 166, 167), increasing their contribution serving as energy substrates for heavily working myocardium, whereas uptake of glucose correlates inversely with circulating free fatty acids at the low exercise intensities (76). In contrasts to glucose uptake, cardiac blood flow, however, increases with increasing exercise intensity and is lower in endurance-trained subjects at the same absolute, but not with the same relative, exercise intensity compared with untrained subjects (85). The aforementioned is known regarding the left ventricle, but there is a lack of very basic physiological knowledge from healthy human volunteers as to what happens in the right ventricle in response to acute exercise. Also unknown is whether regional ventricular blood flow or energy substrate uptake changes from rest to exercise. Novel imaging data software now allow fairly detailed physiological investigations also at the regional level (from base to apex and different walls of the left ventricle) (117), making it possible to elucidate whether blood flow or glucose uptake heterogeneity decreases with increasing exercise intensity also in myocardium as it does in skeletal muscle (54, 55). In addition, this approach would allow determination of whether endurance training alters the distribution of blood flow and its changes from rest to exercise, as one might expect if blood flow were to follow the changes in mechanical contraction found to be altered especially in apex in fit subjects (170).

The Effects of Long-Term Exercise Training

Investigations made possible by the needle biopsy muscle sampling technique several decades ago have demonstrated that endurance exercise training substantially increases the aerobic respiratory capacity of the skeletal muscle. This is mainly due to an increase in mitochondrial mass but also due to an increase in mitochondrial enzyme concentrations and activities. In addition, endurance training can stimulate angiogenesis, leading to higher muscle capillary densities, which act to facilitate oxygen transport to the mitochondria (24). The higher capillary density increases mean blood transit time (154), which facilitates an increase in oxygen extraction (70), thereby allowing a lower blood flow at rest and at each level of submaximal exercise. The enlarged capillary surface area and longer blood transit time similarly facilitate the uptake of substrates, with the relative contribution of glucose, free fatty acids, and lactate remaining constant at corresponding relative exercise intensities in trained vs. untrained subjects (4, 19). However, it remains to be demonstrated whether blood transit time and hence oxygen extraction is enhanced in the endurance-trained human heart.

At the organ level, substantial structural, functional, and electrical cardiac remodeling occurs in response to exercise training, as recently reviewed by Prior and La Gerche (137). However, many of these differences between elite athletes might be due to genetic differences and self-selection, since many conclusions are based on cross-sectional investigations. Furthermore, heavy exercise training, in terms of durations and intensities, appears to be required to produce structural cardiac adaptations. Thus differences in (non-athlete level) physical activity had no influence on cardiac structure in genetically identical twins despite clear effect on fitness (41). When structural adaptations do occur, they consist of symmetrical enlargement of all chambers of the heart (163), with eccentric remodeling (due to lengthening of cardiomyocytes) occurring in response to endurance-type training and concentric remodeling (due to cross-sectional cardiomyocyte hypertrophy) when a static muscle loading component is present (137). However, a recent study, in fact the first prospective long-term training investigation, failed to observe cardiac structural adaptations in response to resistance training in healthy volunteers (164). Major alterations in the cardiac function due to training are not evident either (137), but conclusions may be hampered by the fact that most of the comparative studies were performed at rest, and adaptations could perhaps have been observed during heavy exercise, for which the physiological adaptations are intended.

Insights into the cellular mechanisms of exercise-induced adaptations in the human heart are sparse, owing to the ethical considerations concerning cardiac biopsies in healthy humans. However, animal studies have shown that subcellular adaptations, for instance in mitochondrial respiratory capacity and capillary densities in cardiac muscle, are minimal (91, 128, 155, 161). Also myocardial contractility appears to be minimally affected (91), although there is some evidence that exercise training enhances myocardial contractility due to enhanced myofilament calcium sensitivity and cardiomyocyte calcium handling (192), whereas there is also an extremely fast relaxation of already very compliant heart of a well-trained subject (27, 31, 95, 96). Thus the increased maximum cardiac output in the trained healthy human appears principally due to an increase in cardiac mass and volume and superior diastolic performance. This is in striking contrast with the adaptations in skeletal muscle, which can be “qualitatively” improved by exercise training.
even without an appreciable increase in muscle mass (e.g., in marathon runners), so that exercise-trained skeletal muscle is capable of performing more work and consuming more oxygen per unit mass than that of sedentary muscle. These adaptations are also coupled with enhanced skeletal muscle vasodilation capacity with increasing fitness (52), whereas coronary adaptations occur commensurately with, but do not exceed, the degree of hypertrophy produced by exercise training (39, 56, 69, 90).

Although there are animal data showing lower myocardial oxygen consumption under resting conditions in trained animals (91), human data are scarce. When the metabolic milieu was made comparable between trained and untrained subjects by producing euglycemic hyperinsulinemia, endurance-trained heart showed lowered cardiac oxygen consumption per unit mass (171), which appeared as the result of exercise-induced bradycardia since other determinants of oxygen consumption were unaltered (171). However, whether oxygen consumption is also lowered in the trained heart without insulin stimulation remains uncertain, since substrate utilization is well known to affect cardiac energetics (110, 126, 160). It is possible that a lower oxygen consumption in the trained heart is not as pronounced in the basal fasting state. Thus, in contrast to skeletal muscle, utilization of energy substrates in the heart is principally determined by their availability in arterial blood (5, 30, 193). In view of the higher levels of circulating free fatty acids and lower insulin levels in trained subjects, the resultant increase in free fatty acid utilization will result in slightly higher levels of oxygen consumption per high energy phosphate produced (110, 126, 160), thereby mitigating the lower oxygen consumption in trained subjects. Paradoxically, this condition resembles obesity, where there is an excessive myocardial uptake of free fatty acids, although it can, however, be corrected by weight loss (186).

Additionally, although studies on structural adaptations of the right ventricle have emerged (137, 163), basic adaptations of right ventricular blood flow and oxygen utilization in response to acute exercise and long-term training warrant further investigation. Such studies would be particularly relevant in view of emerging evidence suggesting that the right ventricle may undergo remodeling in response to physical training to an even larger extent than the left ventricle (137). Several PET tracers are also available for the investigation of neural innervations of heart (92), enabling the study of possible modification by exercise training due to exposure to high levels of stress hormones during exercise.

Finally, although higher fitness is well known to be associated with higher insulin sensitivity and insulin resistance ameliorated by physical activity (149), fitness affects insulin sensitivity differently in skeletal and cardiac muscle (123). Insulin-stimulated whole body and skeletal muscle glucose uptake at rest is namely substantially higher in endurance-trained but not resistance-trained subjects (172), compared with untrained controls, but is markedly reduced in myocardium on both groups, likely due to decreased wall stress and energy requirements or the use of alternative fuels (123). Exercise is also known to potentiate insulin-stimulated glucose uptake in skeletal muscle but more so in already insulin-sensitive subjects (124). When continued as regular physical activity, improved insulin sensitivity is evident particularly by lower serum insulin levels, whereas circulating fasting glucose is also lowered but not to that extent as insulin (103). Improved insulin sensitivity by physically active lifestyle is the hallmark in the prevention of Type 2 diabetes in obese risk profile subjects (179), although exercise training, even when combined comprehensively with other lifestyle adjustments, does not provide any benefits for mortality once diabetic (175, 181).

Bone

The Effects of Acute Exercise

Exercise is known for its benefits in strengthening bone, the tissue that provides the basic framework for human movements with muscles. The beneficial changes in bone mineral content and structure are likely made possible by increased acute exercise-induced and recovery phase blood flow that supplies bone with nutrients in accordance with its metabolic needs (23, 26, 106). However, as is the case with basically every organ located deep in the human body, the study of the regulation of blood flow to bone in humans has been hampered by limitations in technology. However, we have recently begun investigating the responses of femoral bone to exercise and other physiological perturbations, and found that human bone is surprisingly active tissue as its blood flow and glucose uptake clearly increase in response to acute exercise (51). Nevertheless, blood flow levels off with increasing exercise loads, likely due to sympathetic nervous system restraints, which direct flow to active muscles rather than to bone and other less active tissues. This phenomenon appears to be analogous to metabolism in human tendons (37). Furthermore, human bone also has substantial capacity for vasodilation (higher than that induced by exercise), as assessed by direct pharmacological determination, but its blood flow does not change when humans are challenged with acute systemic hypoxic gas mixture breathing (51). This is likely due to constrictive stimulation of arterial...
chemoreceptors that predominate over a local hypoxic vasodilation in bone.

It is likely that exercise-induced enhanced bone perfusion is also responsible for enhancing the eflux of stem cell from bone marrow. As recently reviewed by Schuler et al. (156), acute physical exercise has been shown to mobilize stem cells such as endothelial precursors from bone marrow. The mechanism underlying this recruitment appears to be principally through endothelial nitric oxide synthase-derived nitric oxide (89), although sympathetic nervous system may also contribute (73). However, it remains to be established to what extent these exercise-mobilized stem cells are capable of incorporating into the vascular wall and contribute to end-organ adaptations (138). Moreover, we have recently investigated that, although nitric oxide synthase inhibition reduces bone blood flow at rest, it does not affect bone blood flow during exercise even when combined with inhibition of prostanoids, whereas the inhibition of adenosine receptors reduces bone blood flow during exercise significantly (Heinonen I, Saltin B, Kaskinoro K, Knuuti J, Boushel R, Hellsten Y, Kallokoski KK, unpublished observations). Adenosine receptors are known to be expressed in bone and adenosine acting as primary signaling molecule (35), and in future mechanistic studies that could be performed in humans it might be fruitful to try to relate exercise- and inhibition-induced changes in bone blood flow with simultaneous sampling of peripheral (femoral) venous blood to gain insights into their possible associations.

The Effects of Long-Term Exercise Training

Although repeated exposure to exercise-induced mechanical stress improves the physical characteristics of bone, we are not aware of any studies that have investigated the effects of exercise training on blood flow or metabolism of human bone. Such studies would be particularly timely and important because a role for bone in influencing whole body metabolism is increasingly being recognized (72, 111, 198). The bone plays an important role in releasing (vascular) precursor cells into the circulation, and there is evidence that exercise can enhance this mobilization of stem cells from bone marrow, possibly through nitric oxide (89). However, studies in humans are still scarce. Similarly, the effects of exercise training on vascularity and its integrity in bone marrow remain largely unstudied in humans. Such studies would be important since exercise training could potentially correct vascular impairments and attenuate endothelial progenitor cell release observed in bone marrow in disease states such as diabetes (125, 190). Taken together, exercise-induced physiological adaptations in bone (marrow) have remained largely ill-studied in humans to date, and many of these issues should clearly be the subject of future studies.

Liver, Pancreas, and Gut

The Effects of Acute Exercise

Although we are not aware that tissue perfusion in liver, pancreas, and gut has been determined in response to acute exercise in humans, there are studies that have elucidated that arterial inflow in arteries supplying these organs is decreased (79, 133, 153). These studies also support the concept that overall metabolism, as estimated from total oxygen consumption, of these splanchnic organs is unaffected by exercise. Blood flow can, however, be reduced to as low as 20% of its resting value, but, at least up to moderate-intensity exercise, this is more apparent in splanchnic organs other than gut (133), which may help to prevent intestinal hypoperfusion. Nevertheless, when exercise intensity further increases, it may lead to gut hypoperfusion and gastrointestinal compromise, which could have a negative impact on exercise performance and subsequent recovery (184). Furthermore, epithelial integrity and gut wall barrier function might also be compromised with repeated exposure to strenuous physical stress (184), which may explain why some subjects may have to avoid intense exercise (184).

Although the overall level of metabolism does not change in response to acute exercise, especially pancreas and liver perform important functions during exercise. Thus, although the production of insulin from pancreatic β-cells is blunted mainly by sympathetic stimulation, there is an increased production of glucagone from pancreatic α-cells. The latter allows maintenance of blood glucose levels and effective mobilization of free fatty acids and their utilization, particularly during prolonged exercise. The capacity of the liver for gluconeogenesis from lactate and branched-chain amino acids during exercise is also well recognized. Conversely, the mechanism by which the uptake of energy substrates, mainly glucose and free fatty acids, changes in these tissues themselves in response to acute exercise remains poorly understood. In the fasting state, the liver consumes mainly free fatty acids and amino acids, but from the total amount of free fatty acid oxidation, the liver uses only a small portion of fatty acids for its own intrinsic metabolic processes (112). Future studies are required to investigate the effects of exercise on substrate uptake and utilization.

The Effects of Long-Term Exercise Training

Increasing insulin resistance due to physically inactive lifestyle is likely not only due to augmented
insulin resistance in skeletal muscles but also in the liver, where insulin no longer normally suppresses the production of glucose. Although exercise training effectively improves insulin sensitivity in muscles (149), it remains incompletely understood whether training similarly ameliorates insulin resistance in the liver. This question is important since hepatic insulin sensitivity plays a pivotal role in controlling whole body metabolism. Hence, it is likely, but remains to be investigated, that exercise leads to improvements in liver insulin sensitivity that are similar to those produced by bariatric surgery in obese and diabetic subjects (66). This same holds true for pancreas and gut, where insulin resistance is also present in obesity (9, 64, 185). In the gut, insulin resistance develops even before the deterioration of systemic glucose tolerance (64), and it is plausible that physical activity could maintain the normal metabolic state of this important tissue for early absorption of food and handling of pathogens and immunity.

Interestingly, endurance-trained subjects show increased free fatty acid uptake in skeletal muscle but lower uptake in the liver during hyperinsulinemia (67). This exercise-induced reduction in free fatty acid uptake in the liver was also observed in twins who were discordant for recreational physical activity, and who showed no difference in free fatty acid uptake in skeletal muscle (42). Furthermore, liver free fatty acid uptake was associated with body fat percentage (38), whereas liver and pancreatic fat percent was also found to be lower in the active twin (38), and pancreatic fat was associated with a subject’s fitness, insulin resistance, and hepatic fat content (38). These findings, together with findings regarding physical activity and liver fat (146), clearly support the concept that accumulation of ectopic fat in visceral organs is generally unhealthy, whereas excess adiposity in these organs can be prevented by regular physical activity.

By using PET for noninvasive measurement of renal blood flow (83), it has been demonstrated that renal blood flow is reduced in response to acute (static) exercise (108, 109). It has also been shown that chronic endurance training decreased renal sympathetic nervous activity in sedentary normotensive men, which was associated with a decrease in renal (but not cardiac) vascular resistance (107). To the best of our knowledge, no study has addressed whether perfusion of adrenal glands is altered in response to training. Alterations would be plausible since repeated exposures to extremely high blood flow (∼300 ml·min⁻¹·100 g⁻¹) are common during high-intensity exercise (102), co-existing with a higher epinephrine secretion capacity in endurance-trained individuals compared with sedentary subjects (77).

### Adipose Tissue

**The Effects of Acute Exercise**

There are two types of adipose tissue in humans, white and brown adipose tissue. White adipose tissue is distributed mainly subcutaneously throughout the entire body and in most of the subjects has the capacity to undergo expansion when energy is in surplus. Nevertheless, when the largely genetically determined capacity of subcutaneous fat storage is exceeded, fat starts to accumulate in a form of white fat around and within organs and as visceral fat, the phenomenon that is associated with impaired health and metabolic diseases (135, 174). Conversely, brown adipose tissue is localized only in special small depots, mostly in the neck area, and is activated by cold exposure (187). In contrast to white fat, which stores fat, brown fat is energy, which is released as heat. Interestingly, it was recently proposed that brown fat in adult humans may not be exactly similar to the brown fat found in small animals such as mice, and hence has been named “beige” fat (196). In contrast, in human infants, the brown fat does closely resemble the brown fat of rodents (97), suggesting that not species differences but also age differences in expression exist. In humans, brown or beige fat has also been proposed to play a role in body weight control (197). As mentioned, cold stress is capable of inducing the activation of this fat, but it is currently unknown whether acute physical exercise can activate brown fat depots in humans.

It is well known that lipolysis in white fat is activated by exercise (176), which releases free fatty acids into the circulation to be consumed by other tissues, a phenomenon that is particularly pronounced when the duration of exercise increases. During prolonged exercise, lipolysis and associated changes in adipose tissue blood flow (13–16) are driven largely by a decrease in plasma insulin and circulating catecholamines (165), particularly epinephrine (21). However, although adipose tissue blood flow increases from rest to light- and moderate-intensity exercise (47), it has been speculated that a reduction in adipose tissue blood flow during high-intensity exercise results in decreased free fatty acid release (150) at a time when it is energetically no longer efficient to burn energy from fat. This phenomenon might be mediated by sympathetically mediated vasoconstriction in white adipose tissue, since norepinephrine reduces adipose blood flow acutely, both at rest and during exercise (60). Sympathetically mediated vasoconstriction is also likely to contribute to hypoxia-induced adipose tissue blood flow reduction during exercise (50). Adipose blood flow is also regulated by nitric oxide (58), but only at rest, whereas adenosine regulates adipose blood flow...
during exercise (47). Other factors, such as natriuretic peptides released from the heart, are also likely to contribute to adipose tissue blood flow regulation (176).

**The Effects of Long-Term Exercise Training**

Although it is well known that exercise training can lead to reductions in fat mass and associated biological adaptations (176), including an increase in capillary density due to fat cell size reduction, the elucidation of physiological adaptations to long-term physical activity in adipose tissue is still in its infancy. This is the case, for instance, in regard to adipose tissue blood flow at rest and during exercise (176). As an endocrine organ, adipose tissue can, however, secrete various adipokines (176) that can trigger important physiological functions in various other tissues in the body, which can be modulated by endurance training (11). Recent animal studies suggest that training can modulate several aspects of metabolism within the fat tissue (169). In humans, both glucose (188) and free fatty acid (40) uptake were shown to be higher in visceral than in subcutaneous fat. However, subcutaneous fat contributed more to circulating levels of free fatty acids owing to its larger total mass (40). Interestingly, aerobic endurance exercise-induced improvement in insulin-stimulated glucose uptake was confined to skeletal muscle, with no detectable change in glucose uptake in adipose tissue (147). The latter may have been due in part to the reduction in adipose mass, which occurred to a similar extent in subcutaneous and visceral depots. Although adipose tissue is likely not the main tissue mediating the amelioration of systemic insulin resistance as a result of exercise training, it may participate in maintaining and prolonging postexercise oxygen consumption and therefore overall energy metabolism leading to weight loss. In this respect, it would be important to investigate whether endurance training can change the phenotype of white fat to a more beige or even brown phenotype. Recent investigations in animals support this concept (10, 148), but recent studies in humans either did not see any signs of browning (151) or only saw signs to a minimal extent (121). Moreover, browning of white fat, and to a substantial extent, would be needed to show physiologically relevant effects on whole body metabolism, as a recent human investigation has shown that purely brown fat thermogenesis can only account for energy consumption of <20 kcal/day (113). This amount of energy consumption can be achieved by performing moderate physical exercise, such as brisk walking or moderate-intensity running, for only 2 min (113), highlighting the potential of physical activity per se in burning excess calories and preventing and treating associated metabolic diseases.

Finally, although obesity is generally considered unhealthy, it has been postulated over the years that being physically fit protects against the associated consequences (93). Furthermore, during recent years, a concept of “metabolically healthy obesity” (MHO) has emerged, meaning that, despite increased body weight and adiposity, classical cardiovascular risk factors remain normal. Questions, however, remain, such as whether MHO is just an incomplete clinical characterization (inflammatory status, etc.) of subjects or a transition phase (1). Recent studies suggest that, although MHO is associated with lower risk for Type 2 diabetes (63), risk for cardiovascular diseases and all-cause mortality is elevated compared with metabolically healthy normal-weight individuals (63, 82). Nevertheless, one recent study, however, also importantly suggests that higher physical fitness is a characteristic of MHO, since once fitness is accounted for, MHO appears as a benign condition (127). Furthermore, a recent study in weight-discordant monozygotic twins suggests that sport activity (but not necessarily other physical activity disciplines) is important in MHO, since sport activity appeared to be one of the few protective lifestyle factors against fatty liver (116). However, physical activity and fitness are not only important characteristics of MHO but are protective also in subjects with clustered metabolic abnormalities (36). This effect is likely mediated by physiological responses other than influence on conventional risk factors (68), supporting exercise as an important lifestyle behavior, particularly in primary prevention of cardiovascular diseases.

**Conclusions**

Based on the available evidence obtained in human subjects, we conclude that many of the main regulatory aspects, especially in cardiac and skeletal muscles, in response to acute exercise and long-term physical training have been fairly well characterized. In contrast, many important issues pertaining to perfusion and metabolism in brain, bone, adipose tissue, and splanchnic organs have been comparatively sparsely investigated and hence remain to be elucidated. Although the state of general metabolism does not change substantially in nonmuscular tissues during acute exercise, it is nonetheless conceivable that the alterations in central (blood pressure that is transmitted to the periphery) and local (shear stress) hemodynamics, as well as changes in energy substrate and hormonal milieu, produce adaptations in these tissues. These intriguing organs should therefore be the focus of future research to even more
comprehensively enhance our understanding of the physiological adaptations to voluntary physical exercise in humans. A deeper understanding of the exercise training-induced adaptations will hopefully ultimately enable us to improve health and well being of the general population as well as a wide variety of patient populations.

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References


