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Exercise and Metabolic Health

Bewegung und Stoffwechselgesundheit

REVIEW

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Summary

- **The awareness** that exercise is an essential means to maintain an adequate response to health challenges is increasing worldwide. Although whole body metabolism is governed by many organs that communicate to ascertain metabolic homeostasis, especially skeletal muscle is central in the response to metabolic changes, since it is the major site of glucose uptake and usage.
- **Thus, metabolic diseases** related to poor lipid/glucose handling due to over-nutrition and insufficient physical activity often trace back to muscle metabolic dysfunction, and vice versa. There is evidence that local thyroid hormone levels in muscle are crucial for the response to exercise, and that metabolically-active thyroid hormones can be considered possible exercise mimetics.
- **Based on data** obtained in rodents as well as humans, this short review aims to shed to light on why muscle metabolic integrity in response to exercise (increasingly studied in combination with restricted nutrition) is crucial for health, ranging from mechanistic aspects of muscle metabolism to the application of exercise to counteract dysfunction of metabolically-active tissues including liver and muscle itself.

KEY WORDS:
Exercise, Fasting, Insulin Resistance, Lipid Metabolism

Zusammenfassung

- **Das Bewusstsein,** dass Bewegung ein wesentliches Mittel ist, um auf gesundheitliche Herausforderungen angemessen zu reagieren, nimmt weltweit zu. Obwohl der Ganzkörperstoffwechsel von vielen Organen gesteuert wird, welche kommunizieren, um die metabolische Homöostase zu bestimmen, ist vor allem der Skelettmuskel zentral für die Reaktion auf metabolische Veränderungen, da er der Hauptort der Glukoseaufnahme und -nutzung ist.
- **So gehen Stoffwechselerkrankungen,** die auf einen schlechten Umgang mit Lipid/Glukose aufgrund von Überernährung und unzureichender körperlicher Aktivität zurückzuführen sind, oft auf eine muskelmetabolische Dysfunktion zurück und umgekehrt. Es gibt Hinweise darauf, dass der lokale Schilddrüsenhormonspiegel im Muskel entscheidend für die Reaktion auf Bewegung ist und dass metabolisch aktive Schilddrüsenhormone als mögliche Trainingsmimetika angesehen werden können.
- **Basierend auf Daten,** die sowohl bei Nagetieren als auch beim Menschen gewonnen wurden, soll dieser Kurzüberblick aufzeigen, warum die metabolische Muskelintegrität als Reaktion auf Bewegung (zunehmend in Kombination mit eingeschränkter Ernährung untersucht) für die Gesundheit entscheidend ist. Neben den mechanistischen Aspekten des Muskelstoffwechsels dient körperliche Bewegung der Bekämpfung der Dysfunktion von stoffwechselaktiven Geweben einschließlich Leber und Muskel.

SCHLÜSSELWÖRTER:
Bewegung, Fasten, Insulinresistenz, Fettstoffwechsel

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Exercise and Energy Metabolism- a Multi-Organ Collaboration with Beneficial Effects for Muscle

Skeletal muscle can switch from lipid to carbohydrate use or vice versa depending on exercise intensity (see for review: (30)). These metabolic switches are reflected by changes in metabolic activity of either glycolytic muscle fibers (type IIb/type IIx) with resistance exercise (17, 24) or oxidative muscle fibers (type IIa and type I) with endurance exercise (24).

Both resistance and endurance exercise have beneficial effects on muscle metabolism in rodents and humans, resulting in fat loss and increased insulin sensitivity (reviewed in: (22)). Metabolic changes during, and in response to, exercise which increase lipid oxidation occur in a variety of organs such as liver (11, 20, 27, 42) and white- (11, 14, 20, 30, 32) and brown adipose tissue (14, 25). ›

This results in an enhanced lipid clearance from the circulation in response to exercise and thus controls fat uptake in muscle. Exposure of muscle to a surplus of fat compromises its metabolic activity (26), and thus one major physiological consequence of the action of the aforementioned metabolically active tissues is the optimization of the muscle's energy metabolism, by preventing overload of fatty acids. This is of importance since skeletal muscle accounts for over 80% of insulin-dependent glucose uptake (8), which makes this tissue an important target in the treatment of diabetes type 2.

Fat Loss by Fasting: a Conserved Role for AMP Activated Protein Kinase?

Fasting and exercise both induce fat loss, and may thus perhaps not be surprising that food deprivation causes metabolic shifts in skeletal muscle that partially overlap with exercise [see for review: (12)]. Food deprivation in rodent muscle results in activation of AMP activated protein kinase (AMPK) (3, 5, 10, 37, 45), considered to be an "energy sensor" (21).

Carbohydrate oxidation during food deprivation is suppressed by up-regulation of the Forkhead transcription factor FOXO1 (FKHR), inducing expression of pyruvate dehydrogenase kinase 4 (PDK4) (18). The subsequent PDK4-dependent phosphorylation of the E1 component of the pyruvate dehydrogenase (PDH) complex causes downregulation of carbohydrate oxidation (36).

The central role for AMPK is further highlighted by the fact that during food deprivation a functional β2 subunit of AMPK in muscle has been shown to be crucial in preventing hypoglycemia (5), and that in addition AMPK controls intramuscular glycogen breakdown in food-deprived muscle (3). Although one study performed in humans did not find direct evidence for a role of AMPK in the fasting-induced metabolic switch from carbohydrate to fat in muscle (43), a recent study in humans reported a 30% increase in AMPK phosphorylation upon fasting in muscle (34).

Similarities and Differences between Fasting- and Exercise-Induced AMPK Signaling

As opposed to fasting, during exercise in mice (progressive treadmill running test starting at 10 m/min upto maximum speed), AMPK has been shown to be essential for glucose uptake in the contracting muscle (31). Recent research has revealed the AMPK γ3 subunit to be crucial for greater Akt substrate of 160 kDa (AS160) phosphorylation at Ser 704, associated with increased glucose uptake in muscle after swimming for 4x30 min bouts, with 5 min rest period between each bout (41).

In response to both food deprivation and exercise, the AMPK pathway overlaps with those induced by the sirtuin SIRT1, a deacetylase that activates peroxisome proliferator activated receptor γ coactivator-1α (PGC-1α), inducing a gene expression program governing the switch toward lipid catabolism (4). In the same study it has been shown that the action of SIRT1 depends on AMPK, since AMPK γ3 KO mice failed to induce SIRT1-dependent deacetylation of PGC-1α (4). PDH inhibition also occurs during exercise in mice (treadmill run of 13 and 18 $m.min^{-1}$) and is shown to depend of the AMPK α2 subunit (16).

Essential Role for Thyroid Hormones in the Muscle's Response to Exercise

Of note, it has been shown in mice that local thyroid hormone 3,5,3'-triiodo-L-thyronine (T3) levels are crucial for the muscle's response to exercise (1). Muscle-specific ablation of deiodinase 2, blocking local conversion of T4 into T3 within the myofiber, impaired acute exercise-induced PGC-1α expression, leading to muscle mitochondrial malfunction (1). In conjunction with this important observation, it has been shown in rats that thyroid hormones can be considered exercise mimetics (13, 29, 33) and that one metabolically active thyroid hormone, 3,5-diiodo-L-thyronine (3,5-T2), tones down fat-induced muscle- (29) and whole-body insulin resistance, in a SIRT1-dependent manner (9).

Combining Exercise with Fasting Affects AMPK Phosphorylation, Metabolism, and Autophagy in Muscle

Skeletal muscle autophagy, induced both by fasting and exercise, is an essential process that ensures both muscle integrity and metabolic homeostasis. During food deprivation, autophagy in muscle fibers is necessary for proteolysis leading to increased circulating levels of alanine, an essential amino acid required for gluconeogenesis thus preventing hypoglycemia.

Again, this process is under control of AMPK, since its muscle-specific ablation in mice results in a block of autophagy during food deprivation accompanied by reduced muscle mitochondrial function (3). Autophagy also occurs during exercise recovery in humans, during which it has been primarily linked to mitochondrial quality-control, and has been shown to be associated with increased phosphorylation of AMPK at Thr 172 as well as that of the autophagy marker UNC51- like kinase (ULK) at Ser 317 (2).

At the structural level, mechanically damaged cytoskeletal proteins in response to resistance exercise (75% to 80% of maximum voluntary force) are degraded by Chaperone-assisted selective autophagy (CASA), a tension-induced degradation pathway, in order to ascertain muscle maintenance (38). The CASA complex is anchored at the Z-disk of the sarcomere by interacting with a protein termed actin-crosslinking protein FLNC (filamin C, gamma), and subsequently recognizes and acts on unfolding protein domains within the filamin rods during contraction of the actin network (38). Given their common features, the effect of combinations of fasting and exercise on the autophagy-muscle repair process has been studied in rodents (45) and humans (15, 28, 39).

Surprisingly, in rodents, exercise (treadmill run at 12 m/min for 2h, with a 10° inclination) has been shown to suppress (24h) starvation-induced autophagy by reactivating mammalian target of rapamycin (mTOR) signaling including Akt, accompanied by increased AMPK phosphorylation over starvation and exercise alone (45). This synergistic increase in AMPK phosphorylation, accompanied by increased PDK4 transcription, has recently also been observed in humans after 15h of fasting and cycling for 1h at 70% W_{max}.

In humans, a 6-week supervised training programme (3x/week, 60–120 min) in combination with fasting during training induces post-exercise reactivation of eukaryotic elongation factor 2 (eEF2), and thus was suggested by the authors to facilitate muscle repair by re-activation of protein translation (39). In apparent contrast, another human study showed that the autophagic signaling through Unc-51 like autophagy activating

kinase 1 (ULK1) induced by exercise (a single bout of cycling exercise at 50% VO_{2max} for 60 min or until fatigued, in concomitance with a continuous glucose infusion after an overnight fast (to mimic the prandial state) or following a 36-h fasting period) is not repressed by fasting (28).

However, a very recent study showed that in trained subjects (based on maximum oxygen uptake, muscle citrate synthase activity, and oxidative phosphorylation protein level) the (36 h) fasting-induced autophagy through ULK1 was repressed (15), showing that combinations of both stimuli can indeed modulate autophagy in humans.

It may be speculated that short-term repression of autophagy under these circumstances may increase muscle mass under specific training conditions, but further studies need to be performed to clarify this issue. A schematic overview of key metabolic and signaling events induced by fasting, (endurance) exercise, and their combination in skeletal muscle is depicted in Figure 1.

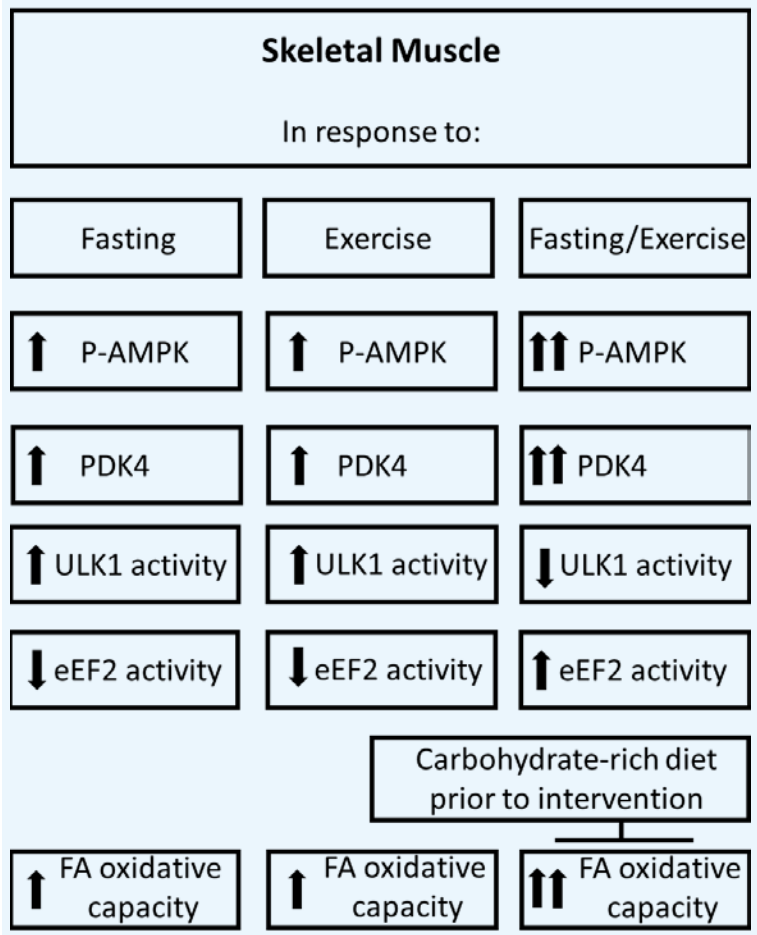

Figure 1

Schematic overview of key metabolic and signaling events underlying the effect of fasting, (endurance) exercise, and their combination in skeletal muscle, involved in fuel-switching (AMPK and PDK4), autophagy (ULK1), and thus muscle repair (eEF2), including the effect of carbohydrate-rich diets prior to intervention. Abbreviations: AMPK, AMP-activated protein kinase; PDK4 , pyruvate dehydrogenase kinase 4; ULK1, Unc-51 like autophagy activating kinase 1; eEF2, eukaryotic elongation factor 2; FA, fatty acid. Double arrows indicate an additive effect of fasting and exercise. The bar-sign underneath the "carbohydrate-rich diet prior to intervention" box depicts an inhibitory effect.

Application of Exercise and Fasting on Heath Parameters, Role Of Diets

Given the metabolic impact of exercise, endurance training has been employed for the treatment of non-alcoholic fatty liver disease (NAFLD), with optimal training programs differing among individuals (see, for reviews: (35, 42)). In addition, recent studies have shown that resistance training increases muscle GLUT4 activity, alleviates insulin resistance and ameliorates lipid profiles in patients with type 2 diabetes (6, 23).

Subjects with NAFLD have been shown to benefit from resistance exercise and show diminished intrahepatic lipids, improved glucose tolerance, and a shift toward whole-body oxidative metabolism (20). Weight loss was not observed, and the authors suggested combined therapy including caloric restriction, having known synergistic effects on metabolism combined with exercise in humans (7, 34, 39).

Importantly, diet compositions change the outcome: carbohydrate-rich diets prior to or during exercise abolish the stimulatory effect of caloric restriction on exercise-induced fatty acid oxidative capacity (19). In this light, it is perhaps not surprising that the diet composition also influences training effectiveness (44). Based on these observations, in the Netherlands a program based on the combination of fasting and exercise is applied on healthy volunteers nationwide (40).

Conclusion

Basic and translational research has made considerable progress in the understanding how exercise, in combination with fasting/caloric restriction, taking the dietary context into account, can ameliorate the metabolic profile of muscle and the whole body to counteract metabolic disturbances including type 2 diabetes mellitus. This is of importance given the recent worldwide increase in the occurrence of obesity and its related complications.

Conflict of Interest

The authors have no conflict of interest.

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