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Exercise, fasting, and mimetics: toward beneficial combinations?

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ABSTRACT: Obesity and type 2 diabetes are associated disorders that involve a multiplicity of tissues. Both fasting and physical exercise are known to counteract dyslipidemia/hyperglycemia. Skeletal muscle plays a key role in the control of blood glucose levels, and the metabolic changes and related signaling pathways in skeletal muscle induced by fasting overlap with those induced by exercise. The reduction of fat disposal has been shown to extend to the liver and to white and brown adipose tissue and to involve an increase in their metabolic activities. In recent years signal transduction pathways related to exercise and fasting/food withdrawal in muscle have been intensively studied, both in animals and in humans. Combining fasting/food withdrawal with exercise in animals as well as in humans causes changes unlike those seen during fasting/food withdrawal or exercise alone, which favor repair of muscle over autophagy. In addition, compounds that mimic exercise have been studied in combination with exercise or fasting/food withdrawal. This review addresses our current knowledge of the mechanisms that underlie the individual and combined effects of fasting/food withdrawal, endurance or resistance exercise, and their mimetics, in muscle *vs.* other organs in rodents and humans, and highlights which combinations may improve metabolic disorders.—Jaspers, R. T., Zillikens, M. C., Friesema, E. C. H., delli Paoli, G., Bloch, W., Uitterlinden, A. G., Goglia, F., Lanni, A., de Lange, P. Exercise, fasting, and mimetics: toward beneficial combinations. FASEB J. 31, 000–000 (2017). www.fasebj.org

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The turn of the century saw a drastic increase in obesity on a global scale. The metabolic disorders associated with obesity such as type 2 diabetes, hypertension, and hyperlipidemia are known signs of what is now described as the metabolic syndrome (1). These disorders occur in a variety of organs, including skeletal muscle, which is responsible for 30–40% of adult resting metabolic rate and for 80% of insulin-stimulated glucose uptake. Insulin resistance in skeletal muscle is a result of increased fat accumulation and because of the organ's metabolic properties, it is the main contributor to the development of type 2 diabetes (2). Skeletal muscle is known for its remarkable flexibility in fuel use (fatty acids or glucose) (3). Food withdrawal and physical exercise trigger this flexibility, which leads to drastic metabolic changes that partially overlap and are prominent in skeletal muscle (for reviews, see refs. 4, 5) but also in other organs, such as liver (5–8), white adipose tissue (WAT) (5, 6, 9–11), and brown adipose tissue (BAT) (9, 12). Most studies focus on skeletal muscle, in which fasting/food withdrawal shifts metabolism toward fatty acid oxidation, oxidative metabolism, and slow myosin heavy chain expression (4), whereas exercise regimens have different metabolic consequences. These are reflected by changes in metabolic activity of either glycolytic muscle fibers (type IIb/IIx) with resistance exercise (13, 14) or oxidative muscle fibers (type IIa/I) with endurance exercise (14). Much attention has been given to endurance exercise in humans because this exercise form leads

ABBREVIATIONS: β-HAD, β-hydroxyacyl CoA dehydrogenase; ADK, adenylate kinase; BAT, brown adipose tissue; BMI, body mass index; CaMK, calmodulin-dependent protein kinase; CPT, carnitine palmitoyl transferase; D, deiodinase (type 1, 2, or 3); GH, growth hormone; GLUT, glucose transporter; MHC, major histocompatibility class; NAFLD, nonalcoholic fatty liver disease; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PGC, peroxisome proliferator–activated receptor γ coactivator; PPAR, peroxisome proliferator–activated receptor; T2, 3,5-diiodo-L-thyronine; T3, 3,5,3′-triiodo-L-thyronine; TR, thyroid receptor; UCP, uncoupling protein; WAT, white adipose tissue

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not only to a higher muscular oxidative capacity enhancing insulin sensitivity (15), but also to increased hepatic fatty acid oxidation, thus counteracting hepatic steatosis and increasing glucose tolerance (for a recent review, see ref. 8). Combining fasting with endurance exercise may bear fruit, given that studies have now emerged on the combined effect of fasting/food withdrawal and exercise in rodents (16) and humans (17, 18), showing that overlapping signaling pathways are enhanced and that new pathways emerge, not seen during fasting/food withdrawal and exercise separately. This has not yet been tested with resistance exercise, but it may be taken into consideration, because this exercise form, analogous to endurance exercise in rodents (7, 19) and humans (8), has been shown to ameliorate nonalcoholic fatty liver disease (NAFLD) in humans (6).

The effect of exercise can, at least in part, be achieved by so-called exercise mimetics, which can either be of endogenous or nonendogenous origin (for reviews, see refs. 20, 21). The sole and combined effects of food withdrawal and exercise with several of these mimetics have been studied in mice with regard to the improvement of muscle performance (22–24) and in rats for the amelioration of NAFLD (7, 19). Thyroid hormones can be considered, at least in part, to be endogenous exercise mimetics (25–27), and so can a recently discovered myokine, termed irisin (28). Knowledge in the field is rapidly progressing, and it seems increasingly clear that beneficial metabolic changes can be induced by combining stimuli through pathways that partially overlap and partially complement each other. Either applied to enhance endurance performance or to counteract obesity or type 2 diabetes mellitus, the combination of food withdrawal with exercise may prove to be favorable, bearing in mind that data from rodents have revealed that not every established or potential exercise mimetic is free of unwanted side effects, such as cancer progression (29) or cardiac disturbances (30, 31). This review deals with the current state of the art of the field, focusing on the separate as well as combined effects of fasting/food withdrawal and endurance as well as resistance exercise on mainly, but not solely, skeletal muscle, with emphasis on fatty acid metabolism and carbohydrate catabolism, autophagy, protein synthesis and breakdown, and mitochondrial biosynthesis.

EFFECTS OF FOOD WITHDRAWAL AND ENDURANCE EXERCISE SEPARATELY: COMPARISON OF METABOLIC SIGNALING MECHANISMS IN RODENTS AND HUMANS

The metabolic effects of food withdrawal and endurance exercise have both been studied extensively, and the following sections show that both conditions cause overlapping effects, which are generally conserved from rodents to humans.

Food withdrawal: animal models

Food withdrawal is a strong trigger of the switch toward oxidative metabolism in skeletal muscle (4). This effect occurs through rapid cellular signaling, activating a shift toward fatty acid oxidation *via* the peroxisome proliferator–activated receptor (PPAR)-δ (5). Upon immediate energy deprivation through nocturnal food withdrawal in the rat, within 6 h, PPARδ mRNA levels have been shown to increase in the gastrocnemius muscle in a transient fashion (32). Simultaneously, carbohydrate oxidation is suppressed during food withdrawal in rodents, by a transient up-regulation of the Forkhead transcription factor FOXO1, inducing an up-regulation of its target gene, pyruvate dehydrogenase kinase (PDK)-4 (33). PDK4 phosphorylates the E1 component of the pyruvate dehydrogenase (PDH) complex, thereby down-regulating carbohydrate oxidation (34). The response to food withdrawal in the rat coincides with transient activation in gastrocnemius muscle of AMPK (32), originally proposed to be an "energy sensor" (35). In recent years, many other studies have reported that food withdrawal is accompanied by an increase in phosphorylation of AMPK in rodent skeletal muscle (16, 32, 36–38), although this effect has not always been confirmed (39, 40). It now becomes increasingly clear that AMPK plays an important role in preserving glycemia and intramuscular glucose during food withdrawal. Dasgupta and coworkers (37) reported that ablation of the β2 subunit of AMPK in mice, which prevents phosphorylation of the AMPKα subunit at Thr^{172}, drastically reduces the animals' glycemia upon food withdrawal compared with that of their wild-type littermates. In addition, it has been shown recently that skeletal muscle AMPK-knockout mice during food withdrawal showed a block in muscle autophagy, leading to reduced proteolysis and circulating levels of alanine, an essential amino acid for gluconeogenesis, resulting in reduced muscle function and mitochondrial activity (38). The AMPK pathway intertwines with the metabolic pathways induced by the sirtuin SIRT1, which deacetylates and activates a key protein involved in the switch toward lipid catabolism—peroxisome proliferator-activated receptor γ coactivator (PGC)-1α—in response to both food withdrawal and exercise (41), which has been shown by the authors to depend on AMPK activity, because AMPKγ3-knockout mice did not display induced SIRT1-dependent deacetylation of PGC-1α in both conditions (41). Recent work has addressed the question of whether SIRT1 could be considered the sole trigger for the adaptations to intermittent food withdrawal (42). Activation of SIRT1 alone is only partially similar to the adaptations to intermittent food withdrawal by every-other-day feeding (a form of caloric restriction) (42). In mouse skeletal muscle, intermittent food withdrawal or SIRT1 overexpression did not significantly change gene expression, and mice subjected to intermittent food withdrawal showed similar decreases in weight gain, epididymal white adipose weight, and hepatic lipid accumulation, as compared with the SIRT1-overexpressing mice. However, whereas regular feeding resulted in reduced lipid droplet size in BAT in the SIRT1-overexpressing mice compared with their wild-type littermates, surprisingly, intermittent food withdrawal resulted in marked increases in BAT lipid droplet size, both in wild-type and SIRT1 transgenic mice (42).

A known food withdrawal–associated marker is uncoupling protein (UCP)-3 (32), a mitochondrial inner membrane protein, the function of which has long been debated (for review, see ref. 43). The predominantly skeletal muscle–expressed UCP3 has originally been compared to its BAT-expressed homolog UCP1, the latter exhibiting a thermogenic action through mitochondrial uncoupling, but data presented more recently in the literature show a role for UCP3 in lipid handling in muscle (43). Indeed, mice deprived of UCP3 show reduced mitochondrial fatty acid oxidation in muscle, closely associating UCP3 with increased lipid metabolism (44), which is a feature of food withdrawal (4). Indeed, time course studies have shown that gastrocnemius muscle mitochondrial levels of UCP3 during food withdrawal correlate well with increased expression of PPARδ and related genes involved in lipid metabolism, and increased serum fatty acid levels (32).

Fasting: humans

Food withdrawal-induced phosphorylation of muscle AMPK in rodents has not been confirmed in fasting humans. One recent time-course study failed to detect AMPK phosphorylation during fasting in human skeletal muscle, whereas the metabolic switch toward the use of fatty acids as fuel was evident, and the authors found decreased Akt/protein kinase B (PKB)-mTor signaling (45), which is associated with AMPK activation during food withdrawal in rodents (16). Analogous to observations in rodents (32, 33), expression of UCP3 (17) and PDK4 (46) is increased in muscle of fasting human subjects. Increased UCP3 levels during fasting in humans correlates with increased serum free fatty acid levels (17), confirming data from the food-deprived rats (32).

With regard to the cardiovascular system, caloric restriction by itself, being a form of food withdrawal generally applied under therapeutic conditions in humans, is beneficial because it reduces aging-related fibrosis and cardiomyocyte apoptosis and preserves or improves left ventricular diastolic function (47).

Endurance exercise: animal models

In rodents, acute exercise has been shown to induce AMPK phosphorylation (48, 49). PGC-1α is both a nuclear and mitochondrial coactivator, and exercise increases the accumulation of PGC-1α in skeletal muscle subsarcolemmal mitochondria in an AMPK-dependent manner (50). It is becoming ever more clear that the mitochondrial network plays a crucial role in the response to exercise and that this response is triggered by PGC-1α, involving increased mitochondrial synthesis, dynamics (fusion and fission), and clearance (mitophagy) (for a recent review, see ref. 51).

In addition to AMPK's playing a key role in mitochondrial biosynthesis and fat oxidation, calcium is likely also to be involved in this regulation. In *ex vivo* rat muscle, PGC-1α was activated by calcium *via* calcium–calmodulin-dependent protein kinase (CaMK) activation of p38 mitogen activated protein kinase (MAPK) (52). However, whether calcium–CaMK signaling is involved in endurance-related signaling in rodents is a subject of controversy. Expression of a constitutively active form of calcium-CaMK-IV in mouse skeletal muscle showed enhanced mitochondrial biosynthesis and elevated expression of enzymes involved in fatty acid oxidation (53). However, CaMK-IV is not endogenously expressed in skeletal muscle (54), and overexpression in rat soleus and gastrocnemius muscle did not result in elevated expression of mitochondrial enzymes (55).

A key mitochondrial fuel-switching response to exercise governed by mitochondria is the inhibition of PDH (and thus of carbohydrate oxidation) (34), which has recently been shown to depend on the activity of the AMPK α2 subunit (56). Whereas AMPK prevents hypoglycemia by intramuscular glycogen breakdown in food-deprived muscle (37, 38), AMPK has been proposed to be essential for glucose uptake in the contracting muscle (57). However, different AMPK subunit knockout models show contrasting results. For instance, knocking out both β1 and β2 subunits (57) results in marked exercise intolerance but the effect is not related to decreased glucose transporter (GLUT)-4 membrane translocation, but rather to decreased mitochondrial activity associated with decreased activity of the α1 and 2 subunits. It has become increasingly clear that the molecular adaptations to food withdrawal, exercise, or both vary over time (acute *vs.* longer term responses), as well as with the intensity of exercise (4, 11). Very recently, it has been shown that ablation of the AMPK α1 and 2 subunits markedly enhances the acute activation of PGC-1α in response to exercise, but not the longer-term metabolic adaptations in mouse skeletal muscle (58), and that the running speed of mice during endurance runs is critical for AMPK activation and expression of SIRT1 and AMPK/SIRT1 target genes related to mitochondrial activity (59, 60). Overexpression of SIRT1 does not mimic the exercise phenotype in skeletal muscle: SIRT1 overexpression has been shown not to significantly change gene expression, but exercise causes drastic increases in the expression of the genes involved in mitochondrial oxidative phosphorylation and respiration (42). In addition, UCP3 has been proposed to mimic the phenotype of endurance exercise: both UCP3 transgenes and exercise (increasing UCP3 protein levels) increase complete fatty acid oxidation and energy expenditure, and the combined events have synergistic effects on these parameters in mice, with a further increase in UCP3 expression (61). Mitochondrial oxidative phosphorylation during aerobic exercise in rats has been shown to be tightly coupled to ATP synthesis in muscle (62) despite the increased levels of UCP3 that are observed under this condition (17, 61). UCP3 has been shown to decrease muscle wasting. Stimulation of UCP3 expression in rats with cachexia has been proposed to reduce lipotoxicity (63); however, despite increased UCP3 expression in cancer-related muscle wasting, mitochondrial respiration is reduced (64). In mice, UCP3 overexpression ameliorates insulin sensitivity (65), whereas its ablation has been shown to worsen it (44, 66, 67), when the animals received a high-fat diet (44); however, this finding is controversial (68, 69).

Target tissues of exercise also include BAT and WAT. BAT is a metabolically active organ, significantly contributing to the organism's energy expenditure, which is conserved between species (12). The gene expression profiles of BAT in SIRT1-overexpressing mice and exercised mice have been shown to be largely similar (42). It has furthermore been shown that exercise in rats increases BAT thermogenesis (9). Moreover, exercise induces a strong adrenergic induction of the conversion of WAT to a "beige" (BAT-like) phenotype, a process referred to as "browning," which is more prominent than the thermogenic effect on BAT (9). Increasing the recruitment of beige adipocytes through browning of WAT by exercise may prove to be a potent means of counteracting obesity. One factor associating exercise and the browning phenomenon in mice is the polypeptide hormone irisin (70) (see Fasting/Food Withdrawal, Endurance Exercise, and Interventions with Nonendogenous Mimetics).

Endurance exercise: humans

Consistent with studies in rodents, endurance training in humans stimulates phosphorylation of AMPK in skeletal muscle (71), which is associated with enhanced expression of genes involved in fat oxidation and mitochondrial biosynthesis (72, 73). The rapid induction of AMPK-induced muscle PPARδ–mediated signaling toward oxidative metabolism is a feature that is shared between the effects of food withdrawal in the rat and those of endurance exercise in humans, in that an increase in PPARδ mRNA is observed in humans within 3 h after a single bout of cycling [180 min at 60% V_{CO_2} peak (72) or 75 min at high intensity (73)]. As in rodents, endurance exercise stimulates expression and activation of CaMK-II in humans (74); however, a role for CaMK-II in the regulation of mitochondrial biosynthesis and fatty acid metabolism in human skeletal muscle, as shown in rodents (52), remains to be established.

Increased muscle AMPK activity after exercise in human muscle is associated with increased expression of PGC-1α and the proteolytic factors atrogin1-MAFbx and MuRF1 (75). In addition, the E3-ligase-induced atrophic reduction in muscle fiber diameter shortens the distance for oxygen diffusion, favoring oxidative metabolism (for a review, see ref. 15). In humans, as in rodents, regardless of the exercise regimen used, there is a consistent initial increase in sarcolemmal levels of GLUT4 mediated by AMPK (76). During prolonged endurance exercise, sarcolemmal GLUT4 levels gradually decrease, which is consistent with the muscles' fuel-switching toward fatty acids (77). Moreover, the inhibition of carbohydrate oxidation through PDK4 induction/PDH inactivation observed during food withdrawal in rats (33) and humans (46) has recently been shown to occur during exercise in humans, as well (78).

Endurance exercise has been reported in various studies to be beneficial in metabolic diseases. Both UCP3 and PPARδ expression in skeletal muscle of diabetic subjects has been shown to increase during exercise, associated with improvement of insulin sensitivity (79). In overweight and obese humans, a 12-wk exercise training program ameliorated the acute response of muscle PPARδ and AMPK expression to a short bout of exercise, measured before and after training, with an amelioration of serum lipid and lipoprotein profiles induced by the training program (80).

Given that endurance exercise leads not only to a higher muscular oxidative capacity (15, 73) and enhanced insulin sensitivity (79), but also to increased hepatic fatty acid oxidation thus counteracting hepatic steatosis and increasing glucose tolerance (8), it is perhaps not surprising that this exercise form has been given much attention in the treatment of NAFLD, although the most beneficial endurance training regimen to counteract NAFLD and obesity is yet to be determined, and may differ among individuals (for reviews, see refs. 8, 81).

Although endurance exercise initially causes a relatively high strain on the cardiorespiratory system (6), regular aerobic exercise training reduces blood pressure through reducing heart rate accompanied by improvement of the sensitivity of aortic baroreceptors and a decrease in peripheral arterial resistance caused by vasodilatation (82). Reductions in blood pressure have furthermore been shown to alleviate insulin resistance, which is of importance in light of the known elevated risk of high blood pressure in obesity/type 2 diabetes (83).

The exercise-induced browning phenomenon of WAT, as seen in rodents (9), has to date not been confirmed in humans. A recent study has revealed that the activity of BAT decreases in endurance-trained athletes compared with lean sedentary men, without recruitment of beige adipocytes (84).

COMBINING FASTING/FOOD WITHDRAWAL WITH ENDURANCE EXERCISE MAY BE BENEFICIAL

Based on the observations that fasting/food withdrawal and endurance exercise have strongly overlapping metabolic features, the impact of their combination has been studied both in animal models and in humans. Results from these studies have revealed that combining fasting/food withdrawal with exercise leads to unforeseen results regarding the adaptive mechanisms that occur in skeletal muscle, which may improve muscle performance and may counteract metabolic disorders.

Evidence from animal models

Although food withdrawal, *per se*, eventually leads to muscle atrophy despite increased autophagy (16, 38, 85, 86), a combined use with other stimuli could be beneficial. An interesting and surprising aspect of combining of food withdrawal with endurance exercise is that this combination induces metabolic changes in skeletal muscles that elicit a more powerful burning of fat compared with food withdrawal alone (16), and attenuate muscle autophagy (16), which is known to occur during exercise and food withdrawal separately (87, 88). Indeed, whereas food withdrawal in mice increases autophagy by AMPK-mediated downregulation of Akt/PKB-mTor signaling (16), treadmill

exercise enhances the food withdrawal–induced AMPK phosphorylation and reactivates Akt/PKB-mTor signaling, thus preventing muscle autophagy (16). Although autophagy-related removal of inactivated mitochondria and clustered myofibers prevent muscle cell death in the long term, the authors reasoned that the lack of autophagy in muscle occurring immediately after exercise combined with food withdrawal would serve to maintain the muscles' functional integrity (also muscle size/mass) related to the increased metabolic demand. Proteomic analysis of the acute effects of swimming on gastrocnemius muscle protein profile in food-deprived rats revealed that expression levels of only 4 proteins were altered. Creatine kinase levels were decreased, whereas the levels of troponin T and a combination of heat shock 20 kDa protein and adenylate kinase (AK)-1 were increased (89), suggesting that most of the acute effects of exercise after food withdrawal is post-translational. The induction of AK1 is indicative of the synthesis of ATP and AMP from ADP under conditions of energy depletion—the ATP being immediately consumed, with the increased AMP subsequently activating AMPK (90).

Evidence from humans

Fasting in humans has been shown to effectively increase muscular oxidative capacity and intramyocellular lipid degradation (especially in type I fibers) in exercised muscle with respect to fed controls (91). The synergistic effect of endurance exercise on AMPK phosphorylation observed in food-deprived rodents (16) was initially also observed in humans, accompanied by a clearly boosted shift toward increased fatty acid over carbohydrate oxidation in vastus lateralis muscle (17). In a study of lean human subjects by the same authors, the increase in AMPK phosphorylation observed by exercise was not further increased by fasting (18). Instead, in this study, it was observed that fasting stimulates, after endurance exercise, dephosphorylation of eukaryotic elongation factor-2, which favors rapid reinitiation of muscle protein translation and repair (18). Whereas endurance exercise in humans *per se* has been shown to increase autophagy (75, 92), the above data suggest that endurance exercise in fasting conditions may circumvent muscle autophagy in humans and shift the balance toward repair and maintenance of mass of existing muscle structures over protein degradation within muscle fibers. A study dating to the 1980s reported that a 23-h fast before exercise induces a relatively high exercise-induced lactate output (93). More recent findings are that lactate induces early differentiation of myoblasts (94) which indicates that activation of muscle satellite cells through increased lactate output by combined fasting with exercise could enhance regeneration of injured muscle fibers. A 23-h fast before exercise was also shown to increase fat mobilization and usage during exercise, evidenced by increased plasma fatty acid concentrations (93). Of note, in a later study, the increase in plasma fatty acid concentrations was not found to parallel the exercise-induced further increase in UCP3 levels with respect to fasting in human muscle, as was seen in fasting-state resting muscle (17), implying that in the contracting muscle, the functional correlation between UCP3 and fatty acid levels, typical of the fasting state at rest, is lost. To maintain glucose homeostasis despite the fasting-induced depletion of liver glycogen (95), exercise has been suggested to increase hepatic gluconeogenesis and to decrease PDH activity and carbohydrate oxidation in muscle (93), which has now been experimentally confirmed (78). The impact of fasting on exercise has been suggested to vary with the nutritional status to which it is compared: carbohydrate feeding *vs.* fasting does not cause differences in fat oxidation during exercise in lean humans, although fasting decreases exercise-induced glycogen breakdown and increased fatty acid oxidation with respect to carbohydrate feeding (96). Instead, in a high-fat diet context, fasting has been shown to be a particularly potent inducer of the effect of exercise. The combination of fasting with exercise in males receiving a hypercaloric (~+30% kcal/d) fat-rich (50% of kcal) diet for 6 wk with respect to low-fat diet–receiving controls increased glucose tolerance and specifically increased muscle AMPK phosphorylation, as well as carnitine palmitoyl transferase 1 (CPT1) and GLUT4 protein levels. No deleterious effects on the cardiovascular system were observed, heart rate was kept below 85% of the maximum value (97). Similarly, obese subjects receiving a hypocaloric diet during a 12-wk exercise training program showed greater improvements in body composition, leptin, and basal fat oxidation compared to controls on a regular diet (98). Based on the observed positive effects of combined fasting and exercise and fasting before exercise, training protocols have been set up in the Netherlands nationwide to have subjects undergo a combined regimen of fasting and submaximal endurance exercise (termed sport fasting), with the aim of improving sports performance in athletes but also a general improvement of physical health in otherwise healthy but overweight subjects (99). See Figure 1 for an overview of the overlapping/distinct metabolic pathways between the response to fasting/food withdrawal, exercise, and fasting/food withdrawal combined with endurance exercise.

FASTING/FOOD WITHDRAWAL, ENDURANCE EXERCISE, AND INTERVENTIONS WITH NONENDOGENOUS MIMETICS

The beneficial effects of fasting/food withdrawal and exercise have led to the question of whether their metabolic effects can be, at least in part, mimicked by factors including pharmaceutical compounds, functional foods, small bioactive natural reagents, or conditions such as hypoxia. As will be discussed in this section, these factors all activate proteins/enzymes (*e.g.*, SIRT1, AMPK, and PPARδ; for reviews, see refs. 20, 21) that determine the effect of fasting/food withdrawal and exercise. Metabolic effects have been assessed either by testing these factors individually or in combination with fasting/food withdrawal or exercise, both in animal models and in humans, producing mixed results. Data from these studies will be discussed in the following sections.

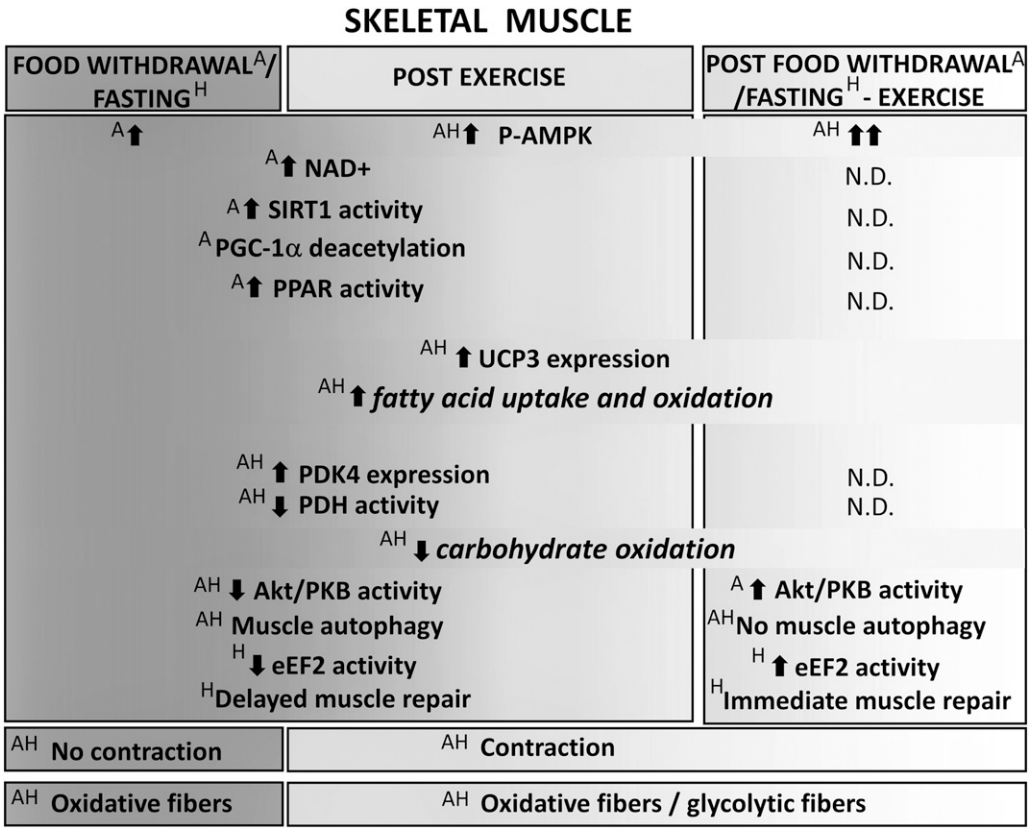

Figure 1. Responses to fasting in humans or food withdrawal in animals, endurance exercise, and their combination: partially overlapping and distinct metabolic signaling pathways in skeletal muscle. Arrows pointing up indicate increases, arrows pointing down indicate decreases. A, evidence from animal studies; H, evidence from human studies; AH, evidence from both animal and human studies. eEF2, eukaryotic elongation factor-2; N.D., not determined.

Applications in animal models

Narkar and coworkers (22) first used mouse models to study whether the PPARδ agonist GW501516 and the AMPK agonist 5-aminoimidazole-4-carboxamide ribonucleotide are exercise mimetics. Indeed, both compounds mimicked the effect of aerobic exercise on the expression of target genes such as UCP3, CPT1, and PDK4, but did not increase endurance performance. Instead, Feige and coworkers (24) have shown that SRT1720, a SIRT1 agonist, increases endurance and locomotor functions in mice, while increasing muscle oxidative phenotype, counteracting hepatic steatosis, and reducing fat mass. Based on the observation in rodents that the natural compound resveratrol improves mitochondrial function and activates AMPK, SIRT1, and PGC-1α, with an accompanying reduction in body weight (23, 100), this compound has been considered to be an exercise mimetic. However, the use of this compound in combination with different intensities of exercise generates different outcomes. Resveratrol has been shown to protect against fatigue and to increases muscle performance in exercised mice (101) and in rats bred for high running performance (102), but the compound attenuates exercise-induced adaptive responses in rats bred for low running performance (103). The compound prevents muscle damage induced by exercise in rats (104); however, although it alleviates oxidative stress, the compound does not attenuate sarcopenia in aged mice (105). Combining lifelong exercise and resveratrol supplementation had no additional effect on skeletal muscle oxidative and angiogenic proteins to that of exercise alone, stimulating these parameters (106).

The effects of hypoxia in part replicate those of exercise. With regard to rodent models, under chronic hypoxia, rat lower limb muscles show muscle fiber atrophy (107, 108), whereas oxidative metabolism and mitochondrial density remain constant or are slightly reduced, depending on the type of muscle (107, 108). When rodents were living and trained in hypoxia, muscle fiber size was still reduced compared to living and training in normoxia (109); however, in different muscles, concentrations of mitochondrial enzymes and of enzymes involved in fatty acid oxidation were increased compared with those in rats that were trained in normoxia (109). Similarly, in obese rats, training in hypoxia showed a synergistic effect on mRNA expression of markers of oxidative metabolism (110). Data from studies in zebrafish have shown that fish move more intensively in chronic hypoxia, which is accompanied by substantial increases in oxidative metabolism and myoglobin expression without muscle fiber atrophy (111), emphasizing the beneficial, synergistic effect of hypoxia and exercise in these fish.

In female Zucker diabetic fatty rats *vs.* lean rats that were subjected to a high-fat diet, it has been shown that the AMPK activator metformin and exercise both reduce muscle FAT/CD36 and lipid accumulation, blunting the

progression of high-fat diet-induced hyperglycemia. In combination with exercise, metformin did not further induce the effect of exercise on these parameters. Whereas exercise training improved insulin-stimulated glucose transport and increased GLUT4 levels in muscle, the combination with metformin did not further improve these parameters, and, in the absence of exercise, metformin was not effective (112). The effects of metformin with food withdrawal/caloric restriction and exercise extend to the liver: when tested for its effect on NAFLD and type 2 diabetes in diabetic Otsuka Long-Evans Tokushima fatty rats, metformin has been shown to enhance the beneficial effects of caloric restriction on parameters, such as increased postchallenge glucose tolerance, lowering of hepatic triglycerides, lowering of the hepatic lipogenesis markers acetyl-CoA carboxylase and stearoyl-CoA desaturase-1 and increased mitochondrial activity [palmitate oxidation and β-hydroxyacyl CoA dehydrogenase (β-HAD) activity] (19). Instead, when metformin was tested in combination with exercise (7), exercise alone had greater positive effects on metabolic parameters (lowering of hepatic triglyceride content and fasting hyperglycemia and improvement in postchallenge glycemic control, hepatic diacylglycerol content, hepatic mitochondrial palmitate oxidation, citrate synthase levels, and β-HAD activities) and in the attenuation of markers of hepatic fatty acid uptake and *de novo* fatty acid synthesis compared with metformin alone. When used in combination with exercise, the compound even inhibited the stimulating effects of exercise on complete mitochondrial palmitate oxidation and β-HAD activities (7).

Evidence presented in the literature shows that exercise mimetics [with the exception of thyroid hormone 3,5,3′-triiodo-L-thyronine (T3); see Fasting/Food Withdrawal, Exercise, and Endogenous Mimetics: Thyroid Homones and Irisin], only mildly affect heart function in rodents. Analogous with the effect of regular endurance training in humans (82), resveratrol reduced heart rate without effects on either blood pressure and related echocardiography parameters or on PGC-1α activity and cardiac gene expression (23). However, the effects of resveratrol on the oxidative capacity of mouse muscle and cadiac myocytes are not always positive (113, 114). In addition, metformin has been shown to improve cardiac function after myocardial infarction induced by isoproterenol in rats (115).

The aforementioned compounds also affect the properties of adipose tissue. The beneficial metabolic effects of combined green tea extract administration and exercise in high-fat diet–fed mice are partially related to the formation of beige adipose tissue (10). In a mouse model, analogs of the red pepper compound capsaicin, termed capsinoids, when supplied in a high-fat diet, significantly activated both the muscle oxidative phosphorylation gene program and fatty acid oxidation when the animals were subjected to (voluntary running wheel) exercise. Furthermore, the capsinoid/exercise combination synergistically suppressed body-weight gain, plasma cholesterol levels, hepatic steatosis, and adipocyte size (116). Capsinoids were shown by the same group to synergistically increase whole-body energy expenditure when mice were cold-exposed (17°C) through β_2-adrenergic–mediated increased biogenesis of beige adipocytes. The underlying mechanism has been shown to involve an increased half-life of Prdm16, a dominant transcriptional regulator of brown/beige adipocyte development (117). SIRT1, a central factor involved in the response to exercise, has been shown to direct the remodelling of WAT (118). In gain-of-function experiments in rodents, it has been shown that the browning of WAT is at least in part governed by SIRT1-dependent deacetylation of PPARγ on Lys^{268} and Lys^{293}, leading to the selective expression of BAT-like genes over the insulin resistance–associated visceral WAT genes through binding of the BAT program coactivator Prdm16 to PPARγ (118).

Applications in humans

Single-protein targets are considered potentially harmful, such as GW501516, one of the first compounds to be tested in combination with exercise and having synergistic effects on muscle endurance in rats (22). Clinical trials with this compound have been abandoned because of safety issues, including cancer progression in rats (29). Nevertheless, there has been increasing interest in the use of functional foods or small bioactive natural reagents that favor the burning of fat (*e.g.*, green tea extracts, capsinoids, and caffeine), and these include the established SIRT1 stimulators α-lipoic acid (119) and resveratrol (120) as exercise and caloric restriction supplements for use in humans (for reviews, see refs. 20, 21). In humans, resveratrol fails to increase performance or muscle fibers responses to high-intensity interval training (121), but does prevent muscle damage induced by exercise (122).

Analogous to findings in rats (107), hypoxia, *per se*, causes muscle fiber atrophy accompanied by a reduction in mitochondrial content in humans (123–125). However, exercise training in hypoxic conditions has been suggested to favor weight loss in humans by increasing the activity of glycolytic enzymes in muscle while enhancing the number of mitochondria and GLUT4 levels, thereby increasing insulin sensitivity (for a review, see ref. 126). Indeed, high-intensity and moderate-duration exercise performed in hypoxia improves endurance performance capacity (127), as well as oxidative capacity and oxygen supply (with stimulated expression of myoglobin and VEGF) without seemingly negative effects on muscle fiber size in human subjects (128, 129). Thus, hypoxia may be a potent exercise mimetic, but the appropriate oxygen tension and exercise duration and intensity must be determined.

The AMPK activator metformin is known to improve insulin sensitivity in humans and is currently used to treat type 2 diabetes (for review, see ref. 100). It has been shown to enhance the time to exhaustion in muscle during high-intensity exercise in humans (130). In addition, it has insulin-sensitizing features that are similar to those seen with exercise, when used at a dose of 2.0 mg/d for 12 wk compared to 12 wk of endurance exercise in humans. However, combining metformin administration and training partially blunted the effect of exercise training on insulin sensitivity (131).

Regarding beneficial effects on the cardiovascular system, metformin administration and exercise in humans have been shown to lower systolic and diastolic blood pressure (118); however, the combination was not more effective (132).

The effects of mimetics on the functional properties of BAT and WAT have been studied in humans. Capsaicin has been shown to increase BAT thermogenesis in humans (133). In addition, a small-molecule stimulator (BAY 41-8543) of soluble guanylyl cyclase enhances differentiation of human brown adipocytes and induces browning of primary white adipocytes acting *via* the NO/cGMP pathway (134). Furthermore, β-adrenergic-independent, increased thermogenic activity through activation of UCP-1 in BAT and recruitment of beige adipocytes has been shown to occur through chronic l-menthol dietary treatment (135). It is conceivable that the use of these compounds combined with exercise could further boost adipose tissue metabolic activity. In line with the central role for SIRT1 in the adaptation to exercise and food withdrawal (41) accompanied by a reduction of fat mass (23) and the browning of WAT in rodents (118), there are indications of a central role for SIRT1 in counteracting obesity in humans, based on population studies of variations in the SIRT1 gene, revealing 2 common genetic variants to be associated with lower BMI in 2 independent Dutch populations, in which carriers of these variants had decreased risk of obesity and weight-gain over time (136). Also, interactions have been reported between dietary vitamin E intake, and genetic SIRT1 variants on BMI (137), and SIRT1 may play a role in the fetal programming of type 2 diabetes through fetal malnutrition (138).

FASTING/FOOD WITHDRAWAL, EXERCISE, AND ENDOGENOUS MIMETICS: THYROID HORMONES AND IRISIN

Because of their metabolic properties, thyroid hormone T3 and the thyroid hormone metabolite 3,5-diiodo-L-thyronine (T2) could be considered endogenous exercise mimetics, and especially the latter is regarded as a promising compound, based on tests in humans (for review, see ref. 30). In addition, the recently discovered polypeptide hormone irisin can be considered an endogenous exercise mimetic, because, especially in animal models, the expression and activity of irisin correlates with exercise (70), which is only partially confirmed in human studies (70, 84). The following sections provide the reader with an update on data from studies in animal models and humans regarding these endogenous exercise mimetics.

Animal models

After caloric restriction, rats gain more weight with respect to regularly fed controls because of accumulation of "catch-up fat" (139). Muscle T3 synthesis decreases during starvation, leading to diminished muscle thermogenesis and enhanced slow-fiber formation (139). Because these phenomena persist during refeeding after the caloric restriction period, the authors concluded that the catch-up fat is associated with diminished T3 neosynthesis in skeletal muscle because of decreased type 2 deiodinase (D2) activity as a result of the caloric restriction stimulus (139). It has recently been shown that addition of T3 can counteract diabetes caused by the muscle atrophy-inducing substance streptozotocin (140) in mice (141). Although T3 levels decrease during intensive exercise in rats (142), pituitary type D1 activity and T3 production are needed to drive growth hormone (GH) release in response to exercise (143). These data suggest that a combination of either food withdrawal or exercise with moderately elevated circulating thyroid hormone levels may be beneficial in specific circumstances. UCP3 is a transcriptional target of T3 in skeletal muscle and heart (144). T3 has been suggested to elicit UCP3-mediated mitochondrial uncoupling in rats, given that T3 induces UCP3 transcription, and the resulting increased mitochondrial UCP3 protein levels are associated with both increased energy metabolism and mitochondrial uncoupling (144), and that, despite the food withdrawal-induced increase in UCP3 levels (25, 145), UCP3-mediated uncoupling activity is unaltered but is increased by T3 administration during food withdrawal (25). In addition, in food-deprived rats, T3 further increases UCP3 expression and increases the expression of a cofactor essential for mitochondrial uncoupling, namely coenzyme Q, which is downregulated in the rat during food withdrawal (25). Because mitochondrial uncoupling leads to decreased ATP formation, one could speculate that it accelerates weight loss with caloric restriction. In analogy with food withdrawal and exercise, T3 administration has further been shown to cause a rapid increase in AMPK phosphorylation in rat skeletal muscle (146, 147). In addition, T3 has been shown to induce GLUT4 translocation to the sarcolemma (147, 148) and to increase insulin sensitivity in rats (148). T3 administration to endurance-trained rats increased palmitate uptake and oxidation in the soleus muscle, indicating that T3 enhances the beneficial metabolic effects of exercise training (149).

In the heart, T3 treatment has been shown to increase myoglobin mRNA and protein content in rat cardiac myocytes (150), which facilitates oxygen transport. In the high oxidative soleus and glycolytic extensor digitorum longus muscle of the rat, T3 stimulates muscle fiber atrophy and a shift from type I to type II major histocompatibility class (MHC) expression (151). A similar shift toward fast-twitch, glycolytic MHCα over slow-twitch, oxidative MHCβ fibers occurs in the heart after T3 administration to mice (152). T3 activity is inhibited by D3, which is expressed locally in the heart *via* a hypoxia-inducible factor-1α–dependent pathway in pulmonary hypertension (153). Whether T3 in combination with D3 mimics the effect of exercise in skeletal muscle, is yet unknown.

The effects of T3 on the heart depend on the action of T3 through binding to one of its receptors, thyroid hormone receptor (TR)-α (152), and for this reason, research has been focusing on the development of metabolically beneficial analogs with increased specificity for a second isoform not involved in cardiac fiber switching but rather in hepatic lipid metabolism, termed TRβ (for reviews, see refs. 30, 31). Indeed, TRβ agonists prevent hepatic steatosis in various rodent models: obese (ob/ob) mice, Zucker diabetic fatty rats, and rats and mice fed high-fat diets, but

do not always prevent insulin resistance (for a review, see ref. 31). An endogenous metabolite of T3, T2, with low-affinity for both TRα and -β (31), has been shown to prevent diet-induced (saturated fat-based) adiposity and hepatic steatosis in rats through a nongenomic effect (154, 155). T2 (26), analogous with T3 (147, 148), induces GLUT4 recruitment to the sarcolemma, indicating increased muscle insulin sensitivity. T2 has been shown to act, at least in part, through SIRT1-mediated deacetylation of PGC-1α and sterol regulatory element-binding transcription factor (SREBP)-1c, with consequential increased expression of genes involved in mitochondrial fatty acid oxidation and decreased expression of genes involved in hepatic lipogenesis, respectively (27). In the same model, on the longer term (after 1 mo of treatment), T2 induced the formation and increased size of gastrocnemius muscle type IIb muscle fibers, associated with a shift of the protein profile toward a glycolytic phenotype (26). Diet-induced insulin resistance was prevented, both in muscle (26) and systemically (27). T2 also increased BAT thermogenesis (156), an effect that is reminiscent of that in exercised rats (9). When administered to rats at an effective daily dose of 25 μg/100 g body weight for 1 mo, T2 did not have deleterious effects on the rat heart (154). On the basis of its metabolic effects (26, 27, 140), T2 may resemble a resistance exercise mimetic (see Resistance Exercise as an Alternative Route to Ameliorate Metabolic Perameters). The fat composition of the diet (monounsaturated over saturated fatty acids) has recently been suggested to be a crucial element determining the metabolic effect of T2 (157), underlining the importance of studying the impact of nutrition on the effect of stimuli, such as fasting/food withdrawal, exercise, their combination, and that of mimetics.

Another example of an endogenous exercise mimetic is irisin, a polypeptide hormone/myokine that has the potential to induce the browning of WAT in mice (66). Irisin levels increase in exercised mice (66). The gene encoding irisin, FNDC5, is up-regulated in exercised, obese rats (158). These observations tightly link this endogenous endocrine compound with exercise-related beneficial effects.

Humans

During fasting, serum TSH and FT4 levels remain normal whereas T3 levels are low, which is likely caused by decreased D1 activity in the liver, as well as decreased uptake of T4 in T3-producing tissues such as the liver (159). By analogy, T3 levels also decline during intensive exercise in athletes (142). Because data from rodents have shown that T3 production during exercise is necessary for the release of GH (143), and that GH release in humans is blunted in human obesity (160), adjusting T3 levels in obese subjects could ameliorate the response to exercise and related metabolic profiles. Although these data show that exogenous administration of T3 to improve exercise-related metabolic parameters may not be recommended because of the cardiac arrhythmias observed in rodents (152), the effectiveness of the response to exercise and ameliorated metabolic profiles may be associated with interpersonal fluctuations in endogenous T3 levels, which in itself justifies basic research on the metabolic effects of this hormone. In this light, it is important to note that, based on studies in rodents and humans, administration of low doses of T3 has been shown to be beneficial when applied to inhibit postinfarct cardiac remodeling, a principle cause of heart failure (161).

Since administration of the endogenous thyroid hormone metabolite T2 causes similar beneficial metabolic changes compared with T3, avoiding T3-related cardiac side effects in the rat (154), T2 could be a candidate for use in the clinic. In this regard, one case report on the administration of T2 in humans (162) showed that this hormone caused the beneficial metabolic effects seen in rats (154) without cardiac abnormalities (162). Based on animal studies (26, 147, 148), it should be considered that T3 and T2 are strong sensitizers of insulin, which should be taken into account, especially during exercise and fasting. Indeed, an extreme case of combined hyperthyroidism and malnutrition has been diagnosed as the cause of comatous hypoglycemia in a 68-yr-old woman (163).

The gene encoding irisin is highly expressed in muscle but also in various WAT in humans (70). Similar to that observed in mice (70), irisin levels have been shown to be up-regulated during exercise in humans (70) although this finding is controversial (84). It remains to be established whether irisin represents a true endogenous exercise mimetic in humans. Should this be confirmed, especially given its potential browning action in humans, irisin could prove to be a strong candidate in counteracting human obesity (for review, see ref. 28).

Taken together, thyroid hormones, especially the thyroid hormone metabolite T2, and the polypeptide hormone irisin, can be viewed as endogenous exercise mimetics, with promising features that may prove to be of use in counteracting metabolic disturbances. The fact that they are endogenous compounds may perhaps add to their safety with respect to nonendogenous compounds, in view of unpredictable collateral effects (29).

RESISTANCE EXERCISE AS AN ALTERNATIVE ROUTE TO AMELIORATE METABOLIC PARAMETERS

In view of the effort needed to sustain the effects of endurance exercise, long-term compliance is poor because the cardiorespiratory demand is high (6), and resistance exercise may be an alternative for maintaining a healthy metabolic profile, which is especially of importance during aging. Because aging is associated with a loss of lean muscle mass and, preferentially, of glycolytic, fast-twitch myofibers (for review, see ref. 164), an interesting question would be whether restoring glycolytic muscle mass during aging could restore metabolic dysfunction. Another issue that has been addressed in humans, is whether resistance exercise can be a useful alternative to endurance exercise regarding the amelioration of NAFLD, and a possible combination with caloric restriction to reduce body weight has been considered (6).

Animal models

Indeed, in aged mice harboring a muscle-specific Akt1-transgene, gastrocnemius muscle type IIb fiber sizes increased, which was associated with an ameliorated glucose metabolism. These mice also showed a reduction in fat mass and hepatic steatosis. The authors concluded that interventions that preserve or restore fast-twitch/glycolytic muscle mass may delay the onset of metabolic disease (165). In apparent contrast to this conclusion, endurance training, but not resistance training, caused recovery from disuse-induced muscle atrophy in old (18 mo) male rats. Muscle regeneration was accompanied by an up-regulation of PGC-1α and inactivation of the FoxO pathway (166).

The structural and metabolic adaptations observed in the Akt transgenic mice are reminiscent of those observed after administration of the thyroid hormone metabolite T2 to rats (26, 27). T2 administration to high-fat diet–fed rats induces formation of type II MHC fibers in gastrocnemius muscle and induces insulin-dependent phosphorylation of Akt (Ser^{473}) and GLUT4 membrane translocation (26), with a strong prevention of hepatic steatosis (154). In rat gastrocnemius high-oxidative muscle fibers, peak power on top of endurance training abolished the endurance-training–induced increase in succinate dehydrogenase (SDH) mRNA levels and prevented the endurance training–induced reduction in receptor-interacting protein 140 mRNA transcription. In low-oxidative type IIb fibers, peak power training substantially decreased SDH activity, and thus decreased oxidative capacity, which was not related to lower SDH mRNA levels (13). This result implies that the intensity of the resistance exercise determines which fiber-type shift and metabolic activity therein occur in muscle and that they vary with age.

Humans

Short-term resistance training in elderly subjects, though accompanied by increased Akt/mTOR activity and improved glucose tolerance (167), leads to a shift in muscle phenotype toward a relatively more oxidative metabolism with an increase in type IIa fibers and a tendency toward a decrease in IIx fibers (167). This effect is partially in contrast to what one would predict based on the results obtained in Akt-overexpressing mice (165) and other mouse models in which type II fiber formation is stimulated with the purpose of mimicking resistance exercise (for a review, see ref. 168). Yet, high force generation over time in humans has been shown to trigger resistance exercise–induced signaling, including Akt phosphorylation at Thr^{308}/Ser^{463}, leading to enhanced responses in type II fibers, whereas highly fatiguing single-set resistance exercise causes less dramatic signaling responses (169). In human skeletal muscle, resistance exercise boosts endurance exercise–induced signaling toward mitochondrial biogenesis (170). It has recently been shown that resistance exercise induces chaperone-assisted selective autophagy as a central adaptation mechanism to repeated mechanical stimulation in human muscle (171). To what extent fasting/caloric restriction modulates this autophagy pathway is presently unknown. One should bear in mind that muscle fiber-type shifts toward a more glycolytic phenotype negatively affect the balance between energy request and intake, which should be especially monitored in elderly subjects. Yet, resistance exercise provokes less acute strain on the heart compared to endurance exercise (6), making this type of exercise favorable in the elderly. Resistance training has been shown to increase active muscle GLUT4 protein levels, alleviate insulin resistance and ameliorate lipid profiles in patients with type 2 diabetes (172). Analogous to endurance exercise (8), resistance exercise performed by subjects with NAFLD has been shown to cause beneficial effects: the subjects contained less intrahepatic lipids after cycling against increased resistance, accompanied by improved glucose tolerance and an increased whole-body oxidative phenotype (6). However, no weight loss was observed, and the authors suggested combined therapy including caloric restriction, which is known to have synergistic effects on metabolism with endurance exercise in humans (17, 18). From the above, it seems plausible to predict that resistance exercise, with or without other stimuli such as caloric restriction, may offer an alternative to endurance exercise in counteracting metabolic disorders.

CONCLUSIONS

Our findings demonstrate that diverse forms of exercise, combined with fasting/food withdrawal, caloric restriction, endogenous mimetics such as thyroid hormones, or food supplements such as resveratrol, can trigger synergistic metabolic effects that, beside improving muscle performance, ameliorate the whole body's metabolic state. Especially the combination of fasting with exercise may prove valuable in this respect, being effective in specific dietary contexts. Both are physiological processes that act on the whole organism, and their application is favorable over the use of ligands that activate single proteins. Natural compounds and emerging endogenous compounds with broad action can also be considered. It becomes ever clearer that individual genetic differences and dietary habits in humans can drastically influence the effectiveness of fasting with exercise and of mimetics and that the effective exercise type (endurance or resistance) and its optimal intensity may thus have to be individually determined. Future research on combinations of fasting/food withdrawal, exercise, and these compounds may prove that they are beneficial for the treatment of metabolic disorders, or, at least, that they prevent their progression. FJ

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AUTHOR CONTRIBUTIONS

R. T. Jaspers and M. C. Zillikens equally contributed to the design and drafting of the manuscript; E. C. H.

Friesema, G. delli Paoli, W. Bloch, A. G. Uitterlinden., F. Goglia, and A. Lanni critically appraised and drafted part of the manuscript; and P. de Lange created the concept and design of the manuscript, prepared the figure, and revised the manuscript in accord with all authors.

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