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PGC-1α and exercise in the control of body weight

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Abstract

The increasing prevalence of obesity and its comorbidities represents a major threat to human health globally. Pharmacological treatments exist to achieve weight loss, but the subsequent weight maintenance is prone to fail in the long run. Accordingly, efficient new strategies to persistently control body weight need to be elaborated. Exercise and dietary interventions constitute classical approaches to reduce and maintain body weight, yet people suffering from metabolic diseases are often unwilling or unable to move adequately. The administration of drugs that partially mimic exercise adaptation might circumvent this problem by easing and supporting physical activity. The thermogenic peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) largely mediates the adaptive response of skeletal muscle to endurance exercise and is a potential target for such interventions. Here, we review the role of PGC-1α in mediating exercise adaptation, coordinating metabolic circuits and enhancing thermogenic capacity in skeletal muscle. We suggest a combination of elevated muscle PGC-1α and exercise as a modified approach for the efficient long-term control of body weight and the treatment of the metabolic syndrome.

Key words: PGC-1α, obesity, thermogenesis, energy expenditure, exercise, weight control

Introduction

Metabolic disorders are increasingly recognized as major threats to public health. Almost two thirds of the adult Americans are already overweight (body mass index >25 kg m^{-2}) and the prevalence will presumably rise in the future[1]. Projections indicate that 86.3% of the adult American population will be overweight and 51.1% will even have to be classified as obese (body mass index >30 kg m^{-2}) by the year 2030[2]. Importantly, excessive body weight fosters the development of comorbidities such as hypertension, dyslipidemia, cancer, cardiovascular disease and diabetes[3, 4] ENREF 2.

A protracted energy imbalance where energy intake exceeds expenditure is considered as a key element in the etiology of metabolic impairments[5, 6]. Reducing energy intake (by nutritional intervention), increasing energy expenditure (by physical activity) or the combination of both thus constitute cornerstones in the treatment of metabolic disorders[7]. Such lifestyle interventions generally lead to weight loss initially [7] and improve metabolic parameters[8], but the majority of patients regain their weight in the long run[9, 10]. A meta-analysis of studies published between 1931 and 1999 reveals a median success rate to maintain body weight after weight loss of a moderate 15%[11]. This impressive recidivism rate after otherwise successful weight loss is partially due to poor adherence to lifestyle interventions and potently facilitated by coordinate actions of ancestral physiological responses designed to powerfully defend and restore body energy stores[12].

Indeed, weight loss initiated by reduced energy intake rapidly turns on a “thrifty” program which favors the eventual restoration of energy stores (Figure 1, outer circle)[13]. To this end, energy expenditure is suppressed in skeletal muscle, which is an important site of energy conservation during food restriction[14]. Concomitantly, adipose tissue increases its responsiveness towards the action of insulin[15]. Upon energy re-availability, energy is diverted from muscle to adipose tissue for accelerating fat mass replenishment[13, 15, 16] ENREF 10. While such adaptive traits allowed the hunter-gatherers to deal with intermittent periods of famine and feast, and had thus survival value during human evolution, they nowadays strongly counteract any attempt to maintain body weight following successful weight loss[17].

Similarly, the life of hunter-gatherers was characterized by alternating periods of high physical activity (hunting and searching for food) and rest (Figure 1, inner circle). Although these habitual physical activity-rest cycles have a shorter term (hours) compared with feast-famine cycles (days), the underlying mechanisms are reminiscent of those that operate during famine and feast[18]. During physical activity muscle energy stores like glycogen and triglycerides are depleted, but subsequently replenished in the resting phase. Such oscillations of muscle glycogen and triglyceride levels with physical activity-rest cycles during tens of thousands of years resulted in the selection of a "thrifty" program with a high proficiency to restore muscle energy stores. A decreased turn-over in muscle glycogen and intramyocellular lipids (IMCLs) is postulated to ultimately impair skeletal muscle insulin sensitivity[18, 19] ENREF 17.

A successful long-term body weight control, with concomitant prevention of metabolic derangements, consequently has to fulfill two requirements: a) avoidance of energy conservation in muscle tissue following weight loss in order to prevent obesity relapse and b) regular metabolic cycling in skeletal muscle in order to prevent excessive accumulation of glycogen and lipids.

Intriguingly, life-long regular exercise would meet both demands (Figure 1), but the long-term adherence is prone to failure. Exercise pills that mimic the plastic adaptations to exercise would be an alternative treatment of choice, but the high complexity of exercise hampers the unraveling and pinpointing of a single pathway that mimics all effects of exercise[20, 21] ENREF 19. Nonetheless, targeting key mediators of physical activity in skeletal muscle constitutes a promising approach to support, facilitate and/or amplify the effects of exercise in manipulating energy expenditure, promoting metabolic cycling and thus finally controlling body weight and promoting metabolic health. In the following section, we will outline why the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) represents an excellent target and summarize the central role of PGC-1α in mediating exercise adaptation, coordinating metabolic circuits and enhancing thermogenic capacity in skeletal muscle.

PGC-1α is a central, integrative hub in exercise adaptation

Physiological induction of PGC-1α by exercise

Muscle contraction activates a myriad of signaling cascades and many of those ultimately converge on PGC-1α to increase its expression levels and activity[22]. The AMP-dependent kinase (AMPK) and the mitogen-activated protein kinase (MAPK) p38 are both activated in response to contraction[23, 24] and subsequently phosphorylate the PGC-1α protein[25]. Exercise also leads to de-acetylation and activation of PGC-1α. Different mechanisms regulating the acetylation level of PGC-1α have been proposed involving direct de-acetylation of PGC-1α by SIRT1 (silent mating type information regulator 2 homolog 1)[26, 27] or inhibition of acetylation by exclusion of the acetyltransferase GCN5 from the nucleus[28].

Transcription of PGC-1α is regulated by the motor-neuron-induced rise in intracellular calcium, which leads to activation of calcium/calmodulin dependent protein kinases (CaMKs) and of the protein phosphatase calcineurin A (CnA)[25, 29]. Subsequently, the altered phosphorylation status of MEF2C/D and the cyclic AMP-responsive element binding protein (CREB) result in an activation of these transcription factors, binding to the PGC-1α promoter and induction of PGC-1α transcription. In addition, exercise-induced activation of AMPK, p38, β_2-adrenoceptor signaling, reactive oxygen and nitrogen species promote the transcription of PGC-1α[30, 31]. Three different splice variants of PGC-1α (PGC-1α-a, PGC-1α-b and PGC-1α-c) are induced by exercise[32]. Compared with PGC-1α-a mRNA, PGC-1α-b or PGC-1α-c mRNAs are transcribed from a different exon 1[32]. In mice, activation of AMPK increases the levels of all three PGC-1α isoforms, while β_2-adrenoceptor signaling acts on the expression of PGC-1α-b and PGC-1α-c[32]. Similarly, in human muscle PGC-1α-a and PGC-1α-b are both activated by AMPK, while β_2-adrenoceptor signaling seems to act mainly on PGC-1α-b[33]. Effects of other exercise-induced stimuli on the expression of different isoforms have not been examined to date. After bouts of endurance exercise, the total PGC-1α levels and its activity in skeletal muscle are consequently elevated. An auto-regulatory loop exists where PGC-1α further increases its own expression[29]. Once transcribed and activated PGC-1α carries out its various functions as summarized below.

92 ***PGC-1α in fiber type switching***

93 Type I and IIa slow-twitch, high-endurance muscle fibers express high levels of PGC-1α, which largely
94 determine the fiber-type composition of skeletal muscle. Ectopic expression of PGC-1α in skeletal muscle
95 *per se* is sufficient to promote fiber-type switching[34]. Indeed, overexpression of PGC-1α shifts muscle
96 appearance from a white to a reddish color[34], promotes mitochondrial biogenesis of intramyofibrillar and
97 subsarcolemmal mitochondria with concomitant reductions in myofibrillar volume[35], alters myosin heavy
98 chain (MHC) composition from MHC IIb and x towards more IIa and I[34], switches metabolism from
99 glycolytic to oxidative[34] and slows down calcium handling[35]. Consequently, endurance performance is
100 improved, while maximal force generation is significantly reduced[35]. Inversely, PGC-1α muscle-specific
101 knock-out animals exhibit a shift from oxidative type I and IIa towards type IIx and IIb muscle fibers, and
102 a reduced oxidative capacity[36, 37]. Thus, PGC-1α seems to drive fiber-type conversion in all its facets.

103 ***PGC-1α in angiogenesis***

104 PGC-1α regulates the angiogenic vascular endothelial growth factor (VEGF). This induction of VEGF by
105 PGC-1α is independent of the canonical hypoxia response pathway and hypoxia inducible factor (HIF).
106 Instead, PGC-1α co-activates the orphan nuclear receptor ERRα (estrogen-related receptor α, NR3B1) on
107 conserved binding sites found in the promoter and in a cluster within the first intron of the VEGF gene[38].
108 Consequently, PGC-1α promotes vascularization of skeletal muscle and thereby supports oxygen and
109 nutrient supply.

110 ***PGC-1α and myokines***

111 Skeletal muscle emerged furthermore as an endocrine organ, which releases myokines (cytokines from
112 muscle) in response to exercise[39]. Given that PGC-1α mediates the effects of exercise to a high extent, the
113 question arose, whether PGC-1α is involved in myokine production and release. Loss-of-function studies
114 of PGC-1α gene expression in murine skeletal muscle revealed a systemic, low-grade, chronic
115 inflammation characterized by elevated circulating levels of interleukin 6 (IL-6) and tumor necrosis factor

α (TNFα)[36, 37]. It remains currently unresolved, whether ectopic expression of PGC-1α, in turn, diminishes the production and release of these cytokines.

PGC-1α in coordinating muscle metabolism and enhancing metabolic flexibility

In respect to metabolism, PGC-1α exerts very versatile effects on skeletal muscle. It coordinately increases the expression of key regulators of lipid oxidation (MCAD; Medium Chain Acyl CoA Dehydrogenase, CPT1b; Carnitine palmitoyltransferase), Krebs cycle (Citrate synthase) and oxidative phosphorylation (Subunits of complexes I to IV)[40].

However, a careful regulation of this process is important since excessive or dysbalanced oxidative metabolism impairs insulin sensitivity. Acylcarnitines are generated when the amount of lipids fluxed into β-oxidation exceeds the capacity of the Krebs cycle and/or oxidative phosphorylation (OXPHOS)[41]. These detrimental lipid species are subsequently released into the circulation and contribute to the development of insulin resistance[41-43]. Similarly, the proton gradient that generates the mitochondrial membrane potential is a potential source of reactive oxygen species (ROS), which are also implicated in the etiology of insulin resistance[44].

Intriguingly, PGC-1α restrains these processes from excessive activation by concomitantly boosting the expression of negative regulators of lipid catabolism. The levels of inhibitors of lipid oxidation (ACC2), antagonists of ROS generation (UCP3; Uncoupling Protein and ANT; Adenine Nucleotide Translocator), and ROS-detoxifying enzymes are all elevated by PGC-1α[40, 45]. While the overall gene expression pattern is ambiguous, the net rates are nonetheless clearly showing an increased oxidation of fatty acids and an elevated mitochondrial membrane potential[40]. Therefore, the increased β-oxidation and the subsequent Krebs cycle and OXPHOS are tightly regulated and balanced by PGC-1α. The concomitant induction of both positive and negative regulators of fatty acid oxidation and OXPHOS through PGC-1α boosts metabolic flexibility and restrains excessive oxidation[40].

In addition, PGC-1α drives glucose uptake and determines fuel selection[46]. Glucose is diverted away from glycolysis and oxidation by inhibiting the activity of the pyruvate dehydrogenase complex through PDK4

(pyruvate dehydrogenase kinase 4)[47, 48] _ENREF_44. This is further substantiated by the reduced lactate production and glucose oxidation rates following overexpression of PGC-1α[47]. Rather glucose is used to replenish glycogen stores or shunted towards the pentose phosphate pathway to serve as substrate for *de-novo* lipogenesis[46, 47]. Indeed, PGC-1α regulates the expression of the fatty acid synthase promoter through its interaction with liver x receptor α (LXRα, NR1H3)[46]. Furthermore, PGC-1α drives the expression of genes involved in lipid esterification into triglycerides[46, 49] _ENREF_39. Subsequently, intramyocellular lipids accumulate. PGC-1α is therefore a metabolic master regulator that induces and controls catabolic and anabolic pathways in skeletal muscle.

Is there a role for muscle PGC-1α in energy expenditure?

Total energy expenditure consists of various components. Principally, there are three major components of energy expenditure: basal metabolic rate (BMR), diet-induced thermogenesis (DIT) and activity thermogenesis (AT)[50]. BMR is the energy expended when an individual is lying at complete rest, in the morning, after sleep, in the postabsorptive state. In individuals with sedentary occupations BMR accounts for approximately 60% of total daily energy expenditure. DIT is the energy expenditure associated with the digestion, absorption, and storage of food and accounts for approximately 10–15% of total daily energy expenditure. AT has to be further separated into two sub-components: non-exercise activity thermogenesis (NEAT)[51] (including fidgeting, muscle tone and posture maintenance, and other low-level physical activities of everyday life[52]) and exercise-related activity thermogenesis (ERAT). In the following we will mainly refer to energy expenditure in the sedentary state (i.e. the total of BMR, DIT and NEAT), and energy expenditure in response to exercise (ERAT).

Skeletal muscle comprises 40% of body weight and, in the absence of physical activity, accounts for 20-30% of energy expenditure[53]. The possibility arises that by altering skeletal muscle function, PGC-1α might increase energy expenditure in the sedentary state. Indeed adenoviral over-expression of PGC-1α in muscle cells *in vitro* elevates oxygen consumption and proton leak[54, 55] _ENREF_22. Consistently, physiological overexpression of PGC-1α increases oxygen consumption in isolated mitochondria[56]. In

mice with ectopic expression of PGC-1α in skeletal muscle, energy expenditure is, however, not elevated[49, 57] _ENREF_46, indicating that the increase in muscle oxygen consumption is possibly too moderate to influence whole body energy expenditure, not detectable or compensated. Thus an effect of PGC-1α on energy expenditure in the sedentary state -although likely- could so far not conclusively been demonstrated *in vivo*.

Originally, PGC-1α was discovered as a mediator of adaptive thermogenesis in both brown fat and skeletal muscle of mice upon cold exposure[58]. The underlying mechanism in brown adipose tissue rapidly emerged. Brown adipose tissue is innervated by the sympathetic nervous system (SNS) and upon cold exposure, SNS nerve endings in BAT release noradrenaline, which activates β-adrenergic receptors. The subsequent induction of PGC-1α increases expression and activation of the uncoupling protein 1 (UCP1), dissipation of the electron gradient and an increase in oxygen consumption[58, 59] _ENREF_52. For a long time, similar mechanisms were believed to act in skeletal muscle and the discovery of the UCP1 homologue UCP3 in muscle has further spurred this idea. In the meantime, conflicting results pertaining to the role of UCP3 as an uncoupler have been reported and interest has waned[60-63] _ENREF_52.

The molecular mechanisms that mediate adaptive thermogenesis in skeletal muscle remain obscure. A model has been proposed implicating futile substrate cycling between lipid oxidation and *de-novo* lipogenesis in response to hormonal stimulation[64, 65]. Given that PGC-1α concomitantly promotes lipid oxidation and lipogenesis the possibility arises that PGC-1α has the potential to modulate oxygen consumption via substrate cycling upon adequate stimulation (e.g. exercise). During acute exercise, the PGC-1α-supported catabolism will prevail, leading to ATP generation for muscle contraction, while PGC-1α-supported anabolism will further consume ATP post exercise. This temporal dissociation might allow optimal energy utilization during acute exercise and concomitantly energy dissipation during entire activity-rest cycles.

ERAT constitutes the component of energy expenditure that can volitionally be modified by increasing the level of muscle work. Upon physical activity, skeletal muscle metabolism changes dramatically and

muscle oxygen consumption can account for up to 90% of the whole body oxygen uptake during this period[53]. Exercise depletes ATP, glycogen and IMCL stores and complements the action of PGC-1α, which, besides promoting oxidative metabolism, drives the refueling of energy stores. These concerted processes result in a high turnover of metabolic cycling and are thermogenic (Figure 2). In response to exercise, the respiratory exchange rate (RER) (ratio VCO_2/VO_2) is diminished and the peak oxygen consumption elevated in PGC-1α transgenic compared to wild-type animals[57].

Taken together, muscle PGC-1α in the absence of stimulation (cold exposure or exercise), seems not to affect whole body energy expenditure.

Muscle PGC-1α in the regulation of whole body glucose homeostasis

By modulating skeletal muscle function, PGC-1α plays an important role in regulating whole body glucose homeostasis. Indeed, muscle PGC-1α and overall metabolism seem to be highly interrelated. Abnormally low PGC-1α levels have been described in the skeletal muscle of type 2 diabetic patients and physically inactive individuals[66, 67]. Direct evidence for a role of muscle PGC-1α in controlling whole body glucose homeostasis derives from studies in mice where reduced or ablated expression of the gene encoding PGC-1α results in abnormal systemic glucose and insulin homeostasis[36, 37]. Inversely, transgenic mice with elevated muscle PGC-1α levels do not display improved whole body glucose homeostasis in the sedentary state, and even develop peripheral insulin resistance on a high-fat-containing diet, possibly due to increased lipid accumulation in skeletal muscle[40, 49, 57] ENREF 15.

Exercise is the real thing: PGC-1α- a partial exercise mimetic, not a substitute

Exercise induces a complex pleiotropic response in skeletal muscle. Even one single bout of endurance exercise comprises changes in the expression of more than 900 genes[68]. To a considerably high extent PGC-1α mimics the effects of exercise, yet PGC-1α induction is not a replacement for exercise. In the following section we will highlight the most prominent differences between exercise as a physiological stimulus of muscle contraction and muscle-specific over-expression of PGC-1α as an "exercise mimetic".

Intriguingly, ectopic expression of PGC-1α can exert positive feedback on some of its alleged upstream activators. The neuromuscular junction program is regulated by PGC-1α[69]. Furthermore, the activity of calcium-dependent signaling pathways via prolongation of myoplasmic calcium transients is increased by PGC-1α and similarly PGC-1α activates the transcription of nitric oxide synthase (inducible and endothelial, but not neuronal), which promotes elevated levels of nitric oxide[35, 70]. By contrast, some other upstream activators, namely AMPK and p38 are not affected by ectopic expression of PGC-1α[49, 71]. On the contrary, glycogen levels are elevated in response to PGC-1α and an inverse correlation between muscle glycogen content and AMPK activity has been established[47, 72, 73] ENREF 34. AMPK has a glycogen binding domain on its β-subunit and there is evidence that glycogen- directly or indirectly- inhibits AMPK activity[74]. Furthermore, by tightly balancing ROS levels, PGC-1α might antagonize the activation of ROS-dependent signaling pathways in skeletal muscle[40, 75].

Those signaling pathways (AMPK, ROS and p38), however, mediate contraction-induced glucose uptake and metabolism. Indeed, the inhibition of AMPK abolishes glucose uptake in response to muscle contraction and similarly, inhibition of ROS-p38 prevents glucose uptake induced by muscle stretching[76, 77]. It could be argued that the higher GLUT4 (Glucose Transporter 4) content in muscles of PGC-1α transgenic animals compensates the lack of AMPK and ROS-p38 mediated glucose uptake. However, the relative increase in glucose uptake is smaller in transgenic animals with ectopic expression of PGC-1α (~50%) than the increase in response to contraction (> 100%)[46, 78-80].

Oscillations of muscle glycogen and triglyceride levels occur with physical activity-rest cycles. Energy stores are depleted during physical activity and replenished during rest. Contraction and epinephrine activate the lipolysis of IMCL by activating hormone sensitive lipase (HSL) and by promoting the translocation of HSL to IMCL in skeletal muscle, thereby contributing to the temporary reduction in muscular triglyceride stores[81, 82]. Similarly, exercise stimulates glycogen breakdown[83].

In contrast, PGC-1α, besides promoting oxidative capacity, drives *de-novo* lipogenesis and lipid storage into IMCL in the sedentary state[46]. Furthermore, PGC-1α stimulates glycogen synthesis and restrains glycogen breakdown[47].

Ectopic expression of PGC-1α in the absence of physical activity thus results in a stalling of glycogen and triglyceride stores at high levels in skeletal muscle[46, 47]. Analogously to an imbalance in energy intake and expenditure, the absence of physical activity leads to an imbalance between physical activity and rest. However, these physical activity-rest cycles are the core catalysts to physiologically break the stalling of muscle glycogen and triglyceride stores at high levels[18].

Moreover, energy expenditure of muscle is high during exercise, due to the low efficiency of muscular contraction (~25%) and thus the dissipation of the bulk of energy as heat. Therefore, although PGC-1α increases energy expenditure in muscle cells[54, 55], this contribution to total energy expenditure might be relatively low in the absence of physical activity. Indeed, whole body energy expenditure is not elevated in sedentary mice with ectopic expression of PGC-1α[49].

Importantly, exercise also affects other tissues and thus alters whole-body glucose homeostasis differently than muscle-specific activation of PGC-1α alone[84]. An acute bout of exercise is associated with changes in the metabolism of liver and adipose tissue that result in an increased provision of fuel for the contracting muscle. The liver increases the release of glucose (initially derived from glycogenolysis and later from gluconeogenesis) into the circulation and adipose tissue increases the hydrolysis triglycerides and the release of long chain nonesterified fatty acids (LCFA) into the circulation. A large body of evidence from both humans and experimental animals has linked these changes to activation of the sympathetic nervous system (norepinephrine) and to increases in plasma levels of glucagon and epinephrine[74]. Regular exercise induces increases in AMPK and ACC phosphorylation in visceral adipose tissue and liver[74]. Despite the scarcity of literature concerning the heart, similar effects are expected to occur in the heart, where acute bouts of exercise promote elevated AMPK phosphorylation[85]. Furthermore, chronic exercise affects

mitochondrial biogenesis and thus respiration not only in skeletal muscle, but also in adipose tissue, liver, brain, kidney and cardiac muscle[86-89] ENREF 84.

It is thus conceivable, that PGC-1α increases the capacity of skeletal muscle for substrate catabolism and anabolism, but does probably not substantially alter whole body energy expenditure and metabolic cycling in the absence of exercise (Figure 2).

Current limitations for pharmaceutical targeting of PGC-1α

Our current knowledge of the action of PGC-1α derives mainly from genetic mouse models. The hormetic effect of PGC-1α on skeletal muscle function and integrity emerged as an important insight from these studies in transgenic animals [90]. In mouse models with moderate, physiological expression of PGC-1α (levels comparable to those of an oxidative soleus muscle), PGC-1α was deemed a beneficial modulator of muscle plasticity, while higher levels resulted in adverse effects such as impairments in muscular glucose homeostasis and atrophy[90-92].

A future challenge is the development of safe drugs that increase PGC-1 levels specifically in skeletal muscle to exactly predefined levels[93]. Currently known substances that pharmacologically target PGC-1α are either unspecific or associated with side effects. Metformin and other agents which stimulate AMP-activated kinase, PPARδ (Peroxisome Proliferator-Activated Receptor) agonists, corticosteroids and β-adrenergic agonists have all been shown to increase PGC-1α[94]. However, they are all unspecific and furthermore affect PGC-1α levels in the liver, where PGC-1α enhances gluconeogenesis and hepatic glucose output[95]. Moreover, they potentially also activate PGC-1α in the heart, thereby leading to derangements of mitochondrial ultrastructure and development of cardiomyopathy[96]. The cardiomyopathy is characterized by an increase in ventricular mass and chamber dilatation and seems to be reversible[96].

Conclusion and outlook

PGC-1α evidentially confers a trained state upon skeletal muscle and increases the metabolic capacity without inflicting *per se* positive effects on body weight control and glucose homeostasis when exclusively augmented in this tissue[25, 40, 49, 57]. However, elevated levels of PGC-1α in skeletal muscle can serve to support and facilitate exercise in physically inactive subjects. This is essentially based on the direct demonstration that sedentary mice with ectopic expression of PGC-1α have a higher endurance capacity when they are forced to run and their isolated muscles are resistant to fatigue[34, 35, 57] ENREF 33. Many additional effects of exercise, which are crucial for metabolic health, cannot simply be mimicked by the sole induction of PGC-1α. A trigger, such as exercise, is mandatory to increase energy expenditure and to initiate metabolic cycling. In the absence of this trigger, PGC-1α might even exert detrimental effects by promoting stalling of muscular energy stores at high levels[46, 47].

The combination of targeting PGC-1α to facilitate exercise and a moderate, tolerable level of exercise to avoid energy conservation and initiate metabolic cycling might constitute a promising approach for the treatment of obesity, obesity-associated comorbidities and for long-term body weight control. Importantly, this approach is not restricted to patients with metabolic impairments, but is broadly applicable for other diseased states where weight regain can occur, but where the health status of the patient precludes achievement of adequate levels of physical activity. More specifically, such weight regain in the form of preferential catch-up-fat is well documented after weight loss due to malnutrition, cancer, septic shock or AIDS and thus constitutes a general phenomenon related to weight loss[17].

The potential for such combined treatments might be enormous. The pinnacle for the global prevalence of metabolic disorders has definitely not yet been reached. Future technical developments will further decrease the necessity for daily physical activity and lead to an even more sedentary behavior. An entire evolving scientific branch is dedicated to the investigation of such 'inactivity physiology'[97, 98]. A recent review on the subject addresses the risk of sitting in decreasing energy expenditure by diminishing non-exercise activity thermogenesis and favoring the development of metabolic diseases and a recent study

reported attenuated insulin sensitivity in healthy, non-exercising subjects who went from a normal to a low level of ambulatory activity for 2 wks[97, 99] ENREF 77. In the light of the increasing prevalence of metabolic disorders, the use of adjuvants to enhance exercise effects in people with a low drive to move might therefore gain profound interest for public health management in the coming years.

Conflict of interest

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Figure legends

Figure 1: Cycles of famine/feast (outer cycle) and physical activity/rest (inner cycle). Reductions in energy intake (famine or dieting) induce weight and adipose tissue loss. Concomitantly, the reduced food availability prompts ambulatory activity for the purpose of gathering and hunting. This additionally contributes to weight and fat mass loss. Moreover, physical activity depletes ATP, glycogen and IMCL stores in skeletal muscle. The scarcity of energy ultimately activates a thrifty program in skeletal muscle to conserve energy.

If food becomes available (feast) and dieting is abandoned, the thrifty program supports the replenishment of energy stores and weight regain, which preferentially occurs in the form of catch-up fat and which is driven by a hyperinsulinemic state. Satiety signals during the period of feast automatically lead to rest, which further supports adipose tissue regain and the restoration of glycogen and IMCL pools in the muscle.

Exercise can counteract the energy conservation in skeletal muscle and prevent weight regain. In addition, regular exercise promotes the turnover of ATP, glycogen and IMCLs. The effects of exercise are indicated as dotted lines.

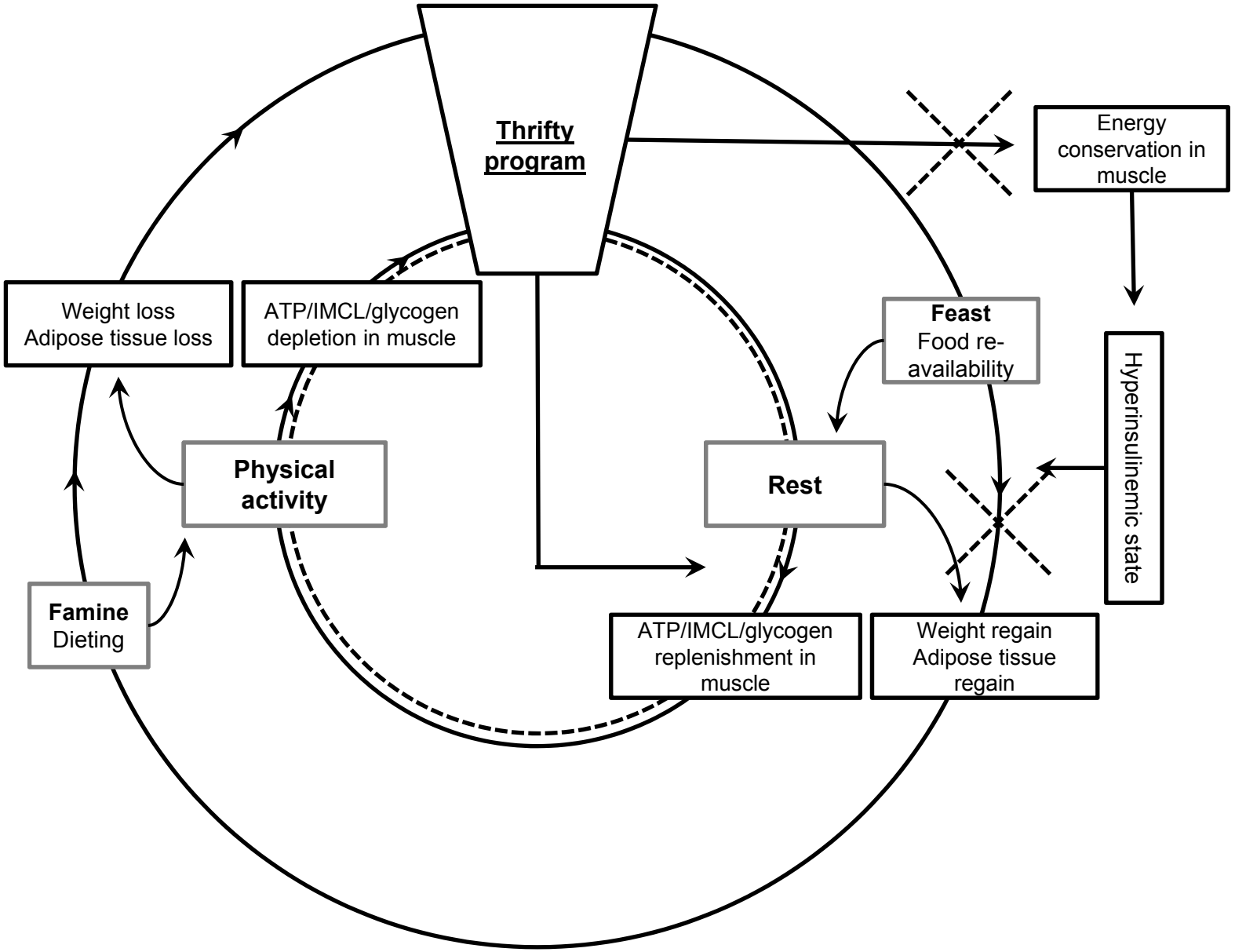
Figure 2: PGC-1α and exercise. Acute bouts of exercise raise myoplasmic calcium levels, increase the activity of p38 and AMPK, and generate reactive oxygen and nitrogen species, which ultimately all culminate in activation of PGC-1α. Subsequently, PGC-1α carries out its various functions.

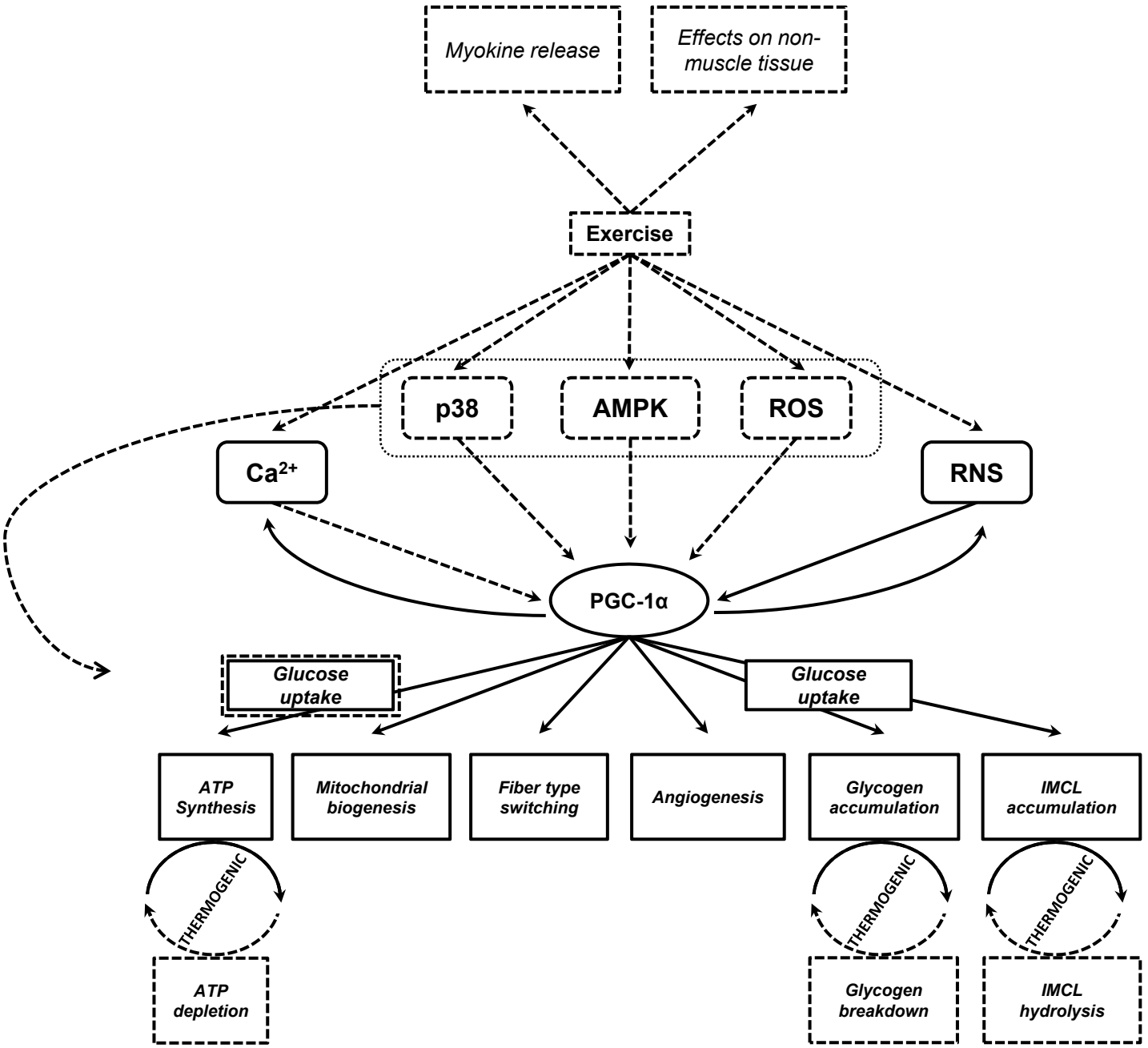
The ectopic expression of PGC-1α alone- even in the absence of exercise- is largely sufficient to mimic exercise-like responses. PGC-1α favors higher myoplasmic calcium and nitric oxide levels by slowing down calcium handling and inducing nitric oxide synthase expression, respectively. Muscle PGC-1α promotes mitochondrial biogenesis, fiber-type switching and angiogenesis. Furthermore, PGC-1α increases glucose uptake in order to generate ATP for later muscle contraction as well as to fuel glycogen

and IMCL stores. In the absence of physical activity, this will result in elevated levels of ATP, glycogen and IMCLs.

In contrast to the sole ectopic expression of PGC-1α, the stimulation of p38, AMPK and ROS by muscle contraction, further increases glucose uptake to quickly generate additional ATP. Moreover, exercise depletes ATP, glycogen and IMCL stores during muscle contraction and thereby induces metabolic cycling between energy depletion during physical activity and energy refueling post-exercise. Due to the low efficiency of muscle work around 75% of the energy is dissipated as heat and therefore these processes increase energy expenditure. Upon exercise, the sympathetic nervous system is activated and releases epinephrine and other hormones. Subsequent lipolysis in adipose tissue diminishes fat mass. In addition, skeletal muscle releases myokines that can act on other tissues.

Continuous lines and boxes with continuous lines: exercise-effects mediated by PGC-1α. Dotted lines and boxes with dotted lines: effects mediated by exercise, but not imitable by ectopic expression of PGC-1α.


Thrifty program
Energy conservation in muscle
Weight loss
Adipose tissue loss
ATP/IMCL/glycogen depletion in muscle
Feast
Food re-availability
Hyperinsulinemic state
Physical activity
Rest
Famine
Dieting
ATP/IMCL/glycogen replenishment in muscle
Weight regain
Adipose tissue regain


Myokine release
Effects on non-muscle tissue
Exercise
p38
AMPK
ROS
Ca2+
RNS
PGC-1α
Glucose uptake
Glucose uptake
ATP Synthesis
Mitochondrial biogenesis
Fiber type switching
Angiogenesis
Glycogen accumulation
IMCL accumulation
THERMOGENIC
THERMOGENIC
THERMOGENIC
ATP depletion
Glycogen breakdown
IMCL hydrolysis