Strategies to Counter Weight Loss-Induced Reductions in Metabolic Rate

Biff F. Palmer, MD[1] and Deborah J. Clegg, RD, PhD[2]

Abstract

A significant percentage of the population is classified as obese, and there is a growing need to develop novel therapy to reduce body weight. It has long been appreciated that caloric restriction and exercise are the cornerstones of any weight loss method. This review outlines the challenges faced when attempting to achieve weight loss and the metabolic adaptations that ensue upon reductions in body weight which make sustaining weight loss extremely difficult. We discuss the need for novel approaches to weight loss that would increase basal metabolic rate and counter the biological adaptations that provide barriers for maintaining weight reduction. We introduce two metabolic processes, hypobaric hypoxia and cold exposure, which, when activated, cause increased metabolic rate even in the presence of reduced caloric intake. While we do *not* suggest that these are long-term viable options for methods to achieve weight loss, we are introducing these as pathways that may be targeted to eventually develop novel therapies to achieve sustainable weight loss.

Introduction

There is currently a worldwide obesity epidemic with expectations in the United States that the number of individuals considered overweight or obese will exceed 60% of the population by 2020 (1,2). It is, therefore, important to review why obesity has become a worldwide health crisis and why methods to reduce body weight are largely met with failure. Weight gain occurs when energy intake exceeds energy expenditure. Restricting caloric intake to a value below that needed for daily energy expenditure will result in weight loss. Additionally, increasing physical activity to exceed basal metabolic rate (BMR) also will result in reductions in body weight (3–5). Unfortunately, both of these methods are met with reductions in energy expenditure or BMR, making sustainable weight loss achievable only with further reductions in caloric intake or increases in physical activity. Many subjects find it extremely difficult, therefore, to initiate, maintain, and sustain weight loss due to the requirement of consistent caloric deprivation and/or increased physical activity.

There is a large effort from pharmaceutical companies to develop pharmacology to facilitate weight loss; however, drugs to suppress appetite or decrease absorption of nutrients/calories have been associated with modest and nonsustainable weight loss (6). Bariatric surgery is currently the most effective recognized method to achieve weight loss even though it is invasive and can be associated with morbidity and mortality (6). Therefore, new and novel methods are needed to assist those needing to lose weight. Below, we discuss the physiological adaptations that occur when calories are restricted or exercise is increased and use these metabolic adaptations to highlight potential novel pathways that can be capitalized on to activate to achieve sustainable weight loss.

Body Weight Homeostasis

Body weight is maintained by matching caloric expenditure to calorie intake; however, the body defends against weight loss by mounting a biological response to preserve body mass. One component of this response is a reduction in BMR. This change is favorable in the setting of famine and severe caloric deficits but poses a formidable barrier when food is plentiful and one is trying to purposely achieve a reduction in body weight (7,8). This concept is best illustrated by a recent popular television show called "The Biggest Loser" where participants were incentivized to lose weight through caloric restriction and increased physical activity (8). Over the course of 30 wk, the participants lost 57.6 kg or 40% of their initial body weight. The lost weight was mainly comprised of adipose tissue. All participants lost weight, but what was most striking is that when a subset of participants were reevaluated 6 years later, researchers found that 90% of the individuals gained nearly all their weight back and at best, their mean weight was only 11.9% below their starting weight (8). Additionally, when measured 6 years after the subject's significant weight loss, their BMR was *lower* than

[1]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX; and [2]Department of Health Studies, College of Arts and Sciences, American University, Washington, DC

Address for correspondence: Deborah J. Clegg, RD, PhD, Department of Health Studies, College of Arts and Sciences, American University, Washington, DC; E-mail: debclegg@outlook.com.

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individuals who were weight matched but whom had *never lost weight* (8). These findings demonstrate that there are prodigious metabolic adaptations put into place to defend against weight loss. This process is brought about by an increase in "metabolic efficiency" defined as a reduction in the energy required to achieve low levels of activity. Below, we highlight hormones and pathways that lead to metabolic efficiency.

Leptin

Leptin is a hormone made in and released from adipose tissues. Reductions in adipose tissue mass after weight loss lead to reductions in circulating levels of leptin. There are data demonstrating in leptin-deficient states, normalization of leptin levels increases energy expenditure, and therefore, one possibility to prevent reductions in energy expenditure after weight loss might be to restore leptin levels to levels before weight loss (9,10). To demonstrate this, subjects were fed a liquid formula diet to cause a 10% reduction in body weight and were then given twice-daily subcutaneous injections of leptin designed to restore circulating leptin levels to those present before the weight loss (9). When compared with subjects with the same amount of weight loss given a placebo injection, those individuals who received the leptin administration had a reversal in the decline in energy expenditure. These data imply that leptin is one of the regulators of metabolic efficiency in the presence of weight loss (11,12), and that restoration of leptin to the leptin replete state blunts the reductions in energy expenditure seen with weight loss, and this may be achieved by restoration of sympathetic nervous system tone and/or circulating concentrations of T3 and T4 to preweight loss levels (11,12). There are leptin receptors in the central nervous system, and leptin acts by binding to these receptors and increases sympathetic tone (13). One population of leptin receptors critical for leptin's actions are those located in the arcuate nucleus of the hypothalamus specifically on proopiomelanocortin (POMC) neurons that stimulate the release of a cleavage product, α-melanocyte-stimulating hormone (αMSH), which in turn binds to the melanocortin-4 receptor (MCR4) and melanocortin-3 receptor (MCR3), thereby suppressing appetite and increasing sympathetic nerve activity resulting in increased energy expenditure.

To further illustrate the importance of this pathway in humans, defects in the gene encoding POMC lead to hyperphagia and early-onset obesity while heterozygous mutations in the MCR4 are the most common cause of monogenic obesity (14). In fact, there are data demonstrating that patients with POMC deficiency who were treated with the MCR4 agonist setmelanotide, this drug resulted in reductions in sensations of hunger and caused substantial weight loss (15). Additionally, in a randomized, double-blind, placebo-controlled, crossover study of 12 obese human subjects, administration of a MCR4 agonist as a continuous infusion over 72 h increased resting energy expenditure by 6.4% (16). These findings support the notion that there are both direct and indirect effects of leptin in the central nervous system and that stimulation of the MCR4 receptor suppresses appetite and increases energy expenditure, providing an attractive adjunct therapeutic strategy to aid in weight reduction. It is important to note there are not enough long-term data to advocate for leptin/MCR4 activation for sustainable weight loss in all obese subjects, but these data do suggest that this pathway could be potentially capitalized on to prevent the reduction in BMR which occurs after weight loss.

Reductions in Energy Expenditure Associated with Muscle Efficiency

Skeletal muscle is the largest tissue mass of the body and is therefore the primary determinant of the BMR (17). The mass of skeletal muscle is relatively constant, but with the addition of weight-bearing exercise, muscle mass can be increased. Many weight reduction programs combine rigorous weight-bearing exercise in an attempt to increase muscle mass so as to maintain or sustain BMR. Returning to data obtained from the Biggest Loser, the authors found that fat free muscle mass was mostly maintained in the face of weight loss in these individuals and this was largely thought to be due to inclusion of vigorous weight bearing exercise (8). What was a surprising finding from these individuals was that despite preservation of fat free/muscle mass, the resting metabolic rate still *decreased* by 789 $kcal \cdot d^{-1}$, an amount greater than what could be accounted for by the change in body weight (8). One explanation for this metabolic adaptation is that there was a decline in energy expenditure accompanying the weight loss due to "increased skeletal muscle efficiency," suggesting that for every unit of work, muscle was using fewer calories and this is due to changes in fiber type characteristics and energy substrate utilization (17) as will be discussed further below. Furthermore, in response to weight loss, increases in muscle efficiency oppose further reductions in body weight by reducing the caloric cost of muscle contraction (17). In a study designed to focus on the effect of changes in body weight on skeletal muscle efficiency, researchers followed two cohorts of weight stable individuals. One group of otherwise healthy subjects achieved a 10% reduction in body weight after consumption of a calorie-restricted liquid formula and were compared with subjects whose body weight increased by 10% after *ad libitum* food consumption (18). Total energy expenditure decreased in those individuals who lost weight, whereas there was an increase in energy expenditure in those who had gained weight by approximately 15% above baseline (18). The component of energy expenditure that was primarily affected was nonresting energy expenditure, defined as the energy required to perform physical activity. Additionally, the investigators measured whole body energy expenditure while the subjects performed cycle ergometry and determined ATP flux in gastrocnemius muscle with magnetic resonance spectroscopy. Those individuals who gained weight, had an increase in muscle efficiency, as demonstrated by the fact that they burned more calories for any given level of activity when compared with those individuals who had lost weight who had an increase in muscle efficiency and therefore burned less calories (18). Both groups were matched for physical activity during the weight gain/weight loss portion of the study — what is not clear is if exercise had been incorporated into both groups, would there still be differences in muscle efficiency independent of matched activity? The investigators further posited that the muscle efficiency observed in this study was due to altered fuel substrate utilization in the exercising muscle due to a change in muscle fiber type (18).

The above findings highlight that there are changes in muscle efficiency in response to fluctuations in body weight which are linked to alterations in fuel preference by exercising muscle (as demonstrated by exercising muscle associated with activity

of daily living) as well as changes in muscle fiber type (17). Specifically, after weight loss, there is a shift in muscle fuel preference toward fatty acids and away from glucose and a shift to a slower twitch muscle fiber type (18). Slow twitch fibers consume fewer calories and generate less power per muscle contraction and derive a greater proportion of energy from the oxidation of fatty acids in comparison to fast twitch fibers. By contrast, in individuals who gain weight there appears to be a decrease in muscle efficiency, an increase in energy expenditure, a shift in muscle fuel preference to rely more on glycolysis, and an increase in fast twitch muscle fiber type (Table 1) (18).

Biochemical analysis of needle biopsy specimens taken from the vastus lateralis muscle of these individuals also was performed (19). After weight loss, the ratio of glycolytic to oxidative enzyme activity is decreased along with a reduction in the respiratory quotient consistent with a change in fuel preference toward free fatty acids as a primary fuel source (20). Additionally, there were significant increases in relative gene expression of the more efficient myosin heavy chain I (MHC I) mRNA and sarcoplasmic reticulum Ca^{2+}-ATPase SERCA2a (21). This increase in the ratio of MHC I/MHC II and MHC IIa/MHC IIx expression is consistent with a reduction in the oxidization of glucose relative to fatty acids providing a mechanism for prolonged aerobic contractions at a significantly lower energy cost. The substantial increase in muscle efficiency that occurs in response to weight loss likely contributes to the large amount of relapse of lost body weight that occurs in most individuals embarking on a weight loss program.

Potential Pathways to Increase BMR

Hypobaric hypoxia

Ascent to altitude is a nonpharmacological way to increase energy expenditure through effects brought about by hypobaric hypoxia. Exposure to hypobaric hypoxia is associated with an increase in BMR, and at the same time, there is a dose-dependent suppression of appetite (reviewed in 22,23). These effects were demonstrated in a study where obese subjects were taken to altitude and resided in an environmentally controlled station for 7 d (24). The investigators found that these individuals lost weight with concomitant increases in BMR (24). In support of this observation, population studies show an inverse relationship between residing at high altitude and prevalence of obesity, as well diabetes (25–27).

The mechanism(s) by which altitude induced increases in BMR are through activation of hypoxia-inducible factor (HIF) (22,23). Activation of HIF leads to a reduction in appetite as well as an increase in energy expenditure by upregulating POMC. There are HIF response elements in the promotor region of the leptin gene, and therefore, when HIF is activated, there is an increase in circulating leptin that then activates POMC driving reductions in appetite and increases in energy expenditure. In addition, there are HIF response elements in the promotor region of the POMC gene providing a more direct effect of HIF to increase POMC expression. The HIF activation also leads to a shift in metabolism away from oxidative phosphorylation to glycolysis. While this metabolic change is an adaptive response to limited oxygen availability, it is energetically less efficient and creates an energy wasting state which contributes to the increase in energy expenditure (Fig. 1). Where it is admittedly not feasible for all obese individuals to reside at altitude, it is important to note that exposure to altitude not only increases BMR but also reduces appetite and food intake, suggesting that activation of this pathway perhaps by pharmacology might be a viable method for weight loss. In this regard, HIF prolyl hydroxylase enzyme inhibitors are a new class of agents currently being studied for the treatment of anemia. It would be of interest to determine whether these agents have effects on body weight.

Shivering thermogenesis

An additional method to achieve an increase in energy expenditure is through cold exposure. Upon exposure to cold, a number of metabolic and physiologic processes are activated that reduce rates of heat loss and increase rates of heat production to maintain core body temperature at approximately 37°C. One such process is shivering, which is an

Table 1.
Characteristics of skeletal muscle fiber types.

	Type 1	Type IIa	Type IIb, IIx
General characteristics, (analogy to running distance)	Slow twitch, oxidative, efficient* (marathon runner)	Intermediate, oxidative, (400–800 meter)	Fast twitch, glycolytic, less efficient, (100 meter sprint)
Metabolism	High capacity for fatty acid oxidative phosphorylation	Oxidative phosphorylation and anaerobic glycolysis	High capacity for anaerobic glycolysis
Mitochondrial density, myoglobin content, capillary density	High (red)	Moderate	Low (white)
Rate of fatigue	Low	High	High
Myosin heavy chain isoform predominance	MHC I	MHC II	MHC II
Sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) isoform†	Type 2a	Type 1	Type 1

*The ATP consumption rate for MHC 1 predominant muscle fibers is ~ 65% of that of MHC IIa and 40% of that of MHC IIx fibers.

†The type 1 SERCA isoform is uniquely able to uncouple ATP hydrolysis from Ca^{++} transport and generate heat and is therefore less efficient that the type 2a isoform.

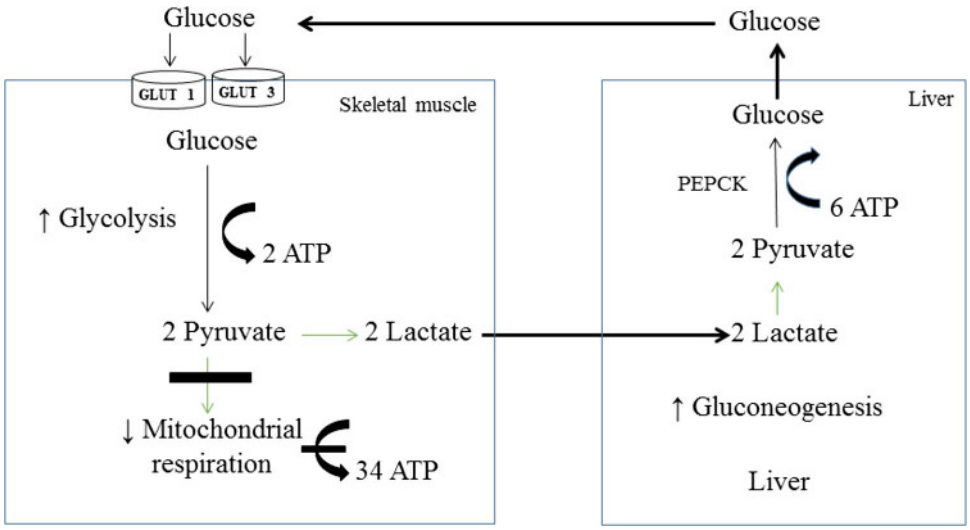

Figure 1: Under conditions of hypobaric hypoxia, activation of HIF leads to a shift in metabolism away from mitochondrial oxidative phosphorylation to production of ATP via glycolysis. The change in metabolism serves to minimize the production of harmful reactive oxygen species that would normally occur during mitochondrial oxidation in a hypoxic environment. The increase in glycolysis necessitates increase glucose uptake and increased glucose production via upregulation in Cori cycle activity. The shift in metabolism comes at the expense of ATP production and results in energy wasting as measured by ATP production and accounts for the increase in BMR at altitude.

involuntary, rhythmic tremor of skeletal muscle that is initiated within minutes of cold exposure and can progress to generalized involuntary movement of all muscle groups (28). Generation of ATP is required to support the energy demands of shivering. The energy supply for ATP production is initially derived from oxidation of glucose and later lipid metabolism (28). Depending on the intensity of shivering, protein oxidation also may contribute to ATP generation (28). Heat production can increase up to five times above baseline values and is associated with increased production of carbon dioxide, consumption of oxygen, and expenditure of energy (29). Since shivering is uncomfortable and prolonged exposure to cold can ultimately lead to hypothermia, this is not a viable strategy for sustainable weight loss. Yet the physiological mechanisms used by shivering may make attractive pharmacological targets to facilitate weight loss without cold exposure. Where admittedly, activation of this pathway may lead to compensatory increases on food intake, perhaps maintaining an increased BMR would make the amount of reduction in caloric intake less onerous if combined with activation of this pathway.

Nonshivering thermogenesis

Induction of nonshivering thermogenesis is a more tolerable method of increasing energy expenditure. This type of thermogenesis is achieved through activation of brown adipose tissue (BAT). There are several adipose tissue types, white adipose tissue primarily functions as an energy storage adipose tissue while BAT is a type of adipose tissue which dissipates energy through the production of heat (30,31). Densely packed with mitochondria, BAT generates heat production through an uncoupling protein called UCP-1 located on the inner mitochondrial membrane. Oxygen consumption is no longer coupled to ATP synthesis because UCP-1 shortcircuits the mitochondrial proton gradient, causing dissipation of chemical energy as heat (Table 2). Mice lacking UCP-1 are severely compromised in their ability to maintain normal body temperature when exposed to cold acutely. Importantly, lacking the ability to activate UCP-1 causes the mice to become obese (32), further supporting the notion that manipulation of UCP-1 may be a strategy to induce weight loss in obese individuals. Adipocytes in BAT are derived from progenitors derived from a skeletal muscle lineage expressing myogenic factor 5 (Myf5) (33). Sympathetic efferent nerve fibers innervate BAT which also is highly vascularized to facilitate dissipation of generated heat. BAT is highly abundant in small mammals or newborns who require BAT to maintain body core temperatures because they have a small body volume to body surface ratio. It was previously thought that BAT was absent or of no relevance in adult humans; however, this view changed after publication of a series of articles using methodology, such as positron emission tomography (PET) images and molecular analysis demonstrating BAT is present in adult humans and can be activated by exposure to cold and some pharmacology (34–36). In fact, cold exposure for as little as 1 to 2 h increases the prevalence of BAT positive scans from a baseline of <15% to as high as 96% in adult human subjects (34). Importantly, short exposures to cold activate existing depots of BAT, and repeated exposure to cold leads to further expansion of BAT mass.

In humans, BAT can be identified around the aorta, common carotid artery, brachiocephalic artery, pericardial mediastinal fat, epicardial coronary artery and veins, internal mammary artery, and intercostal artery and veins (36). In the past several years, using magnetic resonance imaging (MRI), several laboratories have been able to detect intrascapular BAT (iBAT) mass both in thermoneutrality as well as in response to cold stress in humans (37–39).

An additional type of fat is called "beige" or "brite" and is comprised of cells derived from progenitors different from the

Table 2.
Nonshivering thermogenic mechanisms potentially contributing to weight loss.

	UCP-1-Mediated Uncoupling	Skeletal Muscle Thermogenesis	*De Novo* Lipogenesis and Fatty Acid Oxidation	Creatine-Driven Substrate Cycling	Hypobaric Hypoxia
Mechanism	H^+ gradient in mitochondrial dissipated away from ATP synthesis	Sarcolipin-induced Ca^{2+} slippage on SERCA pump in endoplasmic reticulum	Glucose uptake directed to fatty acid synthesis followed by oxidation with net consumption of ATP	Creatine facilitates regeneration of ADP through futile hydrolysis of phosphocreatine leading to increased consumption of ATP	Activation of HIF shifting metabolism away from mitochondrial oxidative phosphorylation toward glycolysis
Location	Beige/brown fat mitochondria	Skeletal muscle	Skeletal muscle, beige/brown fat	Beige/brown fat mitochondria	Effect prominent in skeletal muscle, but present body-wide
ATP formation	Decreased	Increased	Increased	Increased	Decreased
Metabolic effects	Increased glucose and fatty acid uptake	Increased glucose and fatty acid uptake	Increased glucose and fatty acid uptake	Increased glucose and fatty acid uptake	Decreased appetite, increased BMR

classical BAT myf-5 lineage (40). These cells are defined by their multilocular lipid droplet morphology, high mitochondrial content, and exhibit the same properties as classical BAT with respect to UCP-1–mediated thermogenesis. There is a unique pattern of gene expression differentiating beige adipocytes from BAT. Transformation of classical white adipocytes into beige adipocytes is referred to as "beiging," and though controversial, there are data to suggest these pluripotent cells can revert back to white adipocytes after warm exposure (40,41). After a second period of cold adaptation, these same cells regain the typical multilocular morphology and specific gene expression profile of beige adipocytes (42). Other studies suggest cold-induced beige cells are derived from *de novo* differentiation from adipogenic precursor cells (43). While the precise origin of these cells is debated, the presence of brown, beige, and white adipocytes highlights the heterogeneity of adipose tissues and links their diverse functions to energy metabolism.

Activation of the sympathetic nervous system plays a key role in the ability of cold exposure to activate and expand BAT and beige cells in both rodents and humans (44). Stimulation of β-adrenergic receptors on adipocytes through cAMP-dependent protein kinase A activates p38 MAPK which in turn mediates a transcriptional response cascade resulting in increased expression of UCP-1 and PGC-1α (45,46) in beige adipose tissues. UCP-1 dissipates the proton gradient along the inner mitochondrial bilayer, such that lipid oxidation is redirected away from ATP synthesis and toward generation of heat. PGC-1α activates mitochondrial biogenesis, thereby enhancing the magnitude of the thermogenic response (47).

The ability to acutely activate BAT after cold exposure can be accounted for by the densely innervated nature of adipose tissue. Under conditions of chronic cold exposure, increased arborization of nerve fibers can be demonstrated in the beiging fat depots mediated by adipocyte derived factors, such as nerve growth factor, brain-derived neurotropic factor, and neuregulin 4 (48,49). A similar program of acclimatization occurs with regard to vascularity of beiging fat (50), where cold exposure leads to increased expression of vascular endothelial growth factor (VEGF), which plays a critical role in expanding the thermogenic capacity of BAT by promoting angiogenesis and increasing the density of blood vessels, providing an avenue for heat dissipation.

The cellular energetics and fuel utilization of BAT and beige cells are similar. In response to cold, activation of BAT mostly relies on lipid metabolism to generate fatty acids which directly activates UCP1 (51). In unstimulated BAT, the source of fatty acids is mostly from stored triglyceride within BAT itself, and in part, from *de novo* synthesis from glucose cleared from the circulation by upregulation of glucose transporters. Norepinephrine, which is upregulated by cold exposure, increases the amount of lipoprotein lipase gene expression through a cAMP-dependent mechanism (52). BAT activation after cold exposure corrects hyperlipidemia and improves the deleterious fatty acid effects on insulin resistance in animal models of diet-induced obesity and insulin resistance (53,54). A great deal of interest is now focused on ways to increase the mass of beige cells and capitalize on their thermogenic potential as a method to increase total body energy expenditure and reduce body fat mass through enhanced lipolysis (55–57).

Does skeletal muscle "beige" in a similar way to that which occurs in adipose tissues?

Since BAT and skeletal muscle are derived from a common progenitor (Myf5 expressing progenitor), it is not surprising that they might share the common property of thermogenesis. While the method of heat production differs, both tissues are richly innervated by sympathetic nerves, are capable of responding to circulating adrenergic factors, are mitochondrial rich, and both have a high capacity for lipid oxidation. As previously indicated, skeletal muscle is the most abundant tissue in the adult human body; therefore, small changes in the rate of heat production would bring about substantial changes in whole-body thermogenesis. Proton leak also is present in skeletal muscle which accounts for approximately 50% of resting muscle respiration and approximately 10% of total body resting metabolic rate. While UCP3 may be able to uncouple oxidative phosphorylation and dissipate energy as heat (58), similar to what occurs in beige adipose tissues, this effect is likely secondary to its primary role which is to control mitochondrial-reactive oxygen species production and regulate mitochondrial fatty acid oxidation (59,60).

Since altering mitochondrial leak as a mechanism to generate heat could adversely affect the availability of ATP necessary for skeletal muscle contraction, attention has turned toward changes in Ca^{2+} transport across the endoplasmic reticulum as a mechanism for skeletal muscle thermogenesis. Studies in fish and birds have identified sarcoplasmic reticulum Ca^{2+} cycling as a mechanism for heat generation that would not interfere in ATP synthesis (Fig. 2). Sarcolipin is a protein that binds to a Ca^{2+} pump (SERCA) on the endoplasmic reticulum of skeletal muscle causing slippage of Ca^{2+} back into the cytoplasm (61,62). As a result, a greater amount of ATP hydrolysis is required to transport the released Ca^{2+} with the net effect being increased heat production. The importance of sarcolipin in skeletal muscle thermogenesis has been demonstrated in transgenic animal models. Mice lacking sarcolipin when exposed to cold are not able to maintain core body temperature and develop hypothermia (61). The cold sensitive phenotype is rescued after muscle-specific overexpression of sarcolipin in sarcolipin null mice. In addition, sarcolipin-mediated skeletal muscle thermogenesis is recruited to a greater extent after cold exposure in mice lacking UCP1 or when BAT is surgically removed (63–66).

An intrinsic property of skeletal muscle is the ability to rapidly shift between fat and glucose as a preferred substrate to accommodate the needs of other organ systems. Sarcolipin increases the oxidative capacity of skeletal muscle and shifts substrate utilization toward a greater reliance on fat (66). Oxidative muscles are well suited to generate heat because of their ability to cope with greater energy demand while at the same time demonstrating less vulnerability to fatigue. This sarcolipin-induced shift in metabolism is accompanied by increased exercise endurance capacity when compared with control littermates (66). While BAT is the primary source of heat production in small mammals, sarcolipin-dependent nonshivering thermogenesis is dominant in animals where BAT is absent (birds and pigs) or where BAT content is reduced as in large mammals to include adult humans (67).

Increasing skeletal muscle thermogenesis through upregulation of sarcolipin could be a potential strategy to promote

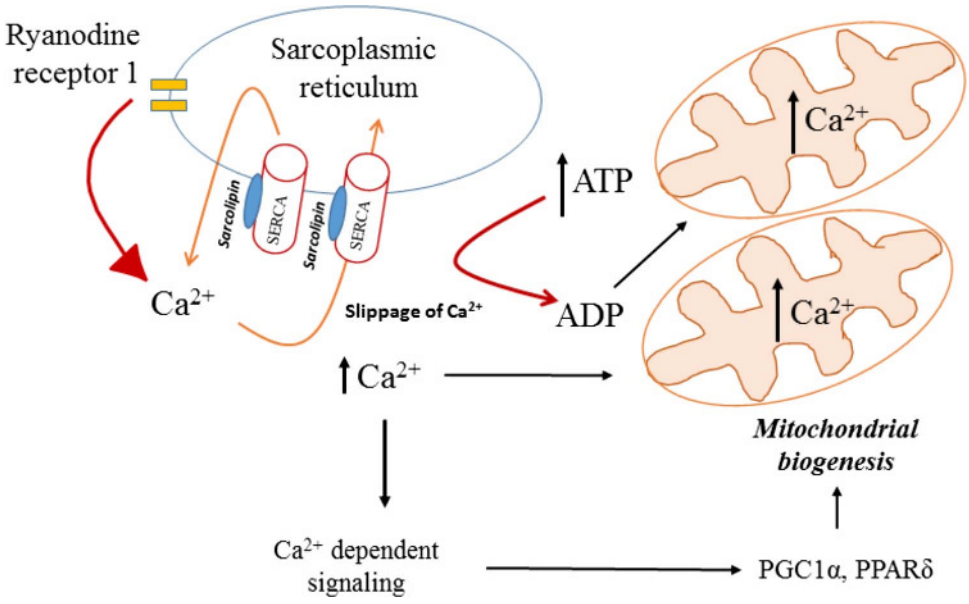

Figure 2: During muscle contraction membrane depolarization activates a voltage-dependent L-type Ca^{2+} channel on the T-tubules which in turn leads to the release of Ca^{2+} from the sarcoplasmic reticulum (SR) into the cytoplasm via the ryanodine receptor 1 containing Ca^{2+} release unit. In the cytoplasm Ca^{2+} binds to myofilaments to bring about contraction. Increases in cytosolic Ca^{2+} also can activate Ca^{2+}-dependent signaling pathways and stimulate mitochondrial oxidation. The SR Ca^{2+} transport ATPase (SERCA) pumps Ca^{2+} back into the SR when the level of cytosolic Ca^{2+} exceeds the activation threshold of the pump. SERCA 1a is an isoform predominately found in fast twitch glycolytic fibers while SERCA 2a is predominate isoform in slow twitch oxidative fibers. The activity of SERCA in skeletal muscle is regulated by the protein sarcolipin. When sarcolipin binds to SERCA it allows ATP to be hydrolyzed but Ca^{2+} transport into the SR is decreased due to slippage of Ca^{2+} back into the cytoplasm. As a result, a greater amount of ATP hydrolysis is required to transport the released Ca^{2+} as compared to when sarcolipin is absent. Heat generation results from the increase in ATP hydrolysis due to the sarcolipin-induced futile SERCA activity.

weight loss (68). In response to a high-fat diet, mice with skeletal muscle-specific overexpression of sarcolipin consume more calories but gain less weight in comparison to wild type or sarcolipin null mice (66). When paired fed, the overexpressing mice lose weight compared to wild type while null mice gain weight. Overexpression of sarcolipin is associated with increased oxygen consumption and a lower respiratory exchange ratio consistent with a shift toward fatty acid oxidation. An increase in sarcolipin-mediated futile cycling of the SERCA pump results in increased ATP hydrolysis. Capitalizing on this futile cycle is a novel and potential therapeutic option to increase energy expenditure in the face of caloric restriction thereby creating an environment for sustainable weight loss (Table 2).

Muscle/adipose tissue communication to facilitate increased BMR

A number of myokines, or circulating factors released from muscle, have been identified that enable skeletal muscle to communicate with adipose tissue and initiate a thermogenic programming response. Specifically, the fibronectin type III domain containing 5 (*FNDC5*) gene encodes a skeletal muscle protein that is proteolytically cleaved into irisin. This protein is an exercise-induced myokine that drives beiging of adipose tissues and UCP1 expression in the subcutaneous depot (69). Cold exposure induces irisin secretion in proportion to the intensity of shivering and of a magnitude similar to exercise stimulated secretion (69). Meteorin is another myokine that is induced after exercise and upon cold exposure and causes an increase in whole-body energy expenditure associated with beiging of adipose tissues.

Conclusions

There is currently an estimated prevalence of obesity which will top 60% of the U.S. population. There are biological forces at play that enhance muscle and metabolic efficiency at a time in which weight loss is being attempted which thwart the individual's ability to maintain and sustain any substantial weight loss. There are few pharmacological remedies for this, and to date, the most efficacious way to lose weight is through surgical options which have significant morbidity and mortality associated with them. It is time therefore, to begin to explore novel mechanisms by which to achieve sustainable increases in metabolic rate in the face of caloric restriction. Here, we discuss several mechanisms to achieve this to include ascent to altitude, exposure to cold, transformation of storage adipose tissues into metabolically active tissue through the process we describe as "beiging" of adipose tissue, and we discuss a novel and potentially important concept, "beiging" of muscle to increase futile energy loss while maintaining elevations in energy expenditure. Now is the time to focus on methods to increase energy expenditure to facilitate sustainable weight loss.

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