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Can Brown Fat Win the Battle against White Fat?

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Abstract

A rapid growth in the overweight and obese population in the last few decades suggest that the current diet, exercise, awareness or drug strategies are still not effectively restraining the obesity epidemic. Obesity results from increased energy intake, and the body's energy balance shifts towards energy abundance. Therefore, current research is focused on developing new strategies aimed at increasing energy expenditure. As a result, brown adipose tissue (BAT) is receiving tremendous attention since the major function of BAT is to dissipate energy as heat. For example, mouse models that have increased BAT activity or increased numbers of brown-like adipocytes within the white adipose tissue (WAT) are lean and protected from obesity. Alternatively, mouse models that lack BAT activity are more susceptible to age and diet-induced obesity. However, a significant loss of BAT mass during the natural growth process in humans has created enormous challenges in effectively utilizing this tissue to increase energy expenditure. New strategies are primarily focused on expanding the BAT mass and/or activating the existing BAT. In this regard, recent finding that expression of early B cell factor-2 (Ebf2) reprograms the white pre-adipocytes into brown adipocytes is a significant break-through in developing BAT-mediated strategies to treat obesity. Here we review the major biological functions of WAT and BAT, which play critical but opposing roles in the energy spectrum, energy storage versus energy expenditure, and we evaluate whether activation and/or expansion of BAT is practically achievable to treat obesity in humans.

Keywords

Leptin; Ucp1; Thermogenesis; PGC1α; Beige fat

Introduction

Obesity is rapidly emerging as the greatest challenge to human health worldwide. According to the World Health Organization (WHO), there are currently approximately 1.5 billion overweight adults in the world and of those ~500 million are obese. In addition, ~42 million children under the age of 5 are overweight or obese. The situation in the United States is

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Conflict of interest

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rather alarming, with ~65% of US adults either overweight or obese. Obesity is a substantial risk factor for a number of diseases and numerous cancers (Hursting, 2014; Mirza, 2011; Poirier and Eckel, 2002; Vucenik and Stains, 2012). At the biological level, a shift in the energy balance of the body results in obesity. If the energy (food) intake consistently surpasses energy expenditure, the extra energy is transported and stored in the form of triglycerides in the white adipose (fat) tissue (WAT) (Hursting, 2014). A number of factors, such as genetic, environmental, behavioral and life style and biological factors, play a major role in increased food consumption and/or overeating disorders (Dhurandhar and Keith, 2014; Singh, 2014; Waalen, 2014). For example, according to recent studies, certain types of foods such as those found in fatty and sugary diets, are as addictive as sex and drugs and stimulate the pleasure centers of the brain (Avena et al., 2012; Volkow et al., 2013). In the course of time, this permanently alters feeding behavior, and individuals are addicted to consume high energy fatty diets. Therefore, understanding the physiological and molecular mechanisms of energy intake, storage, and expenditure has become an intense area of research. Although a number of metabolic, hormonal and neuronal signals arising from different organs contribute to the overall body energy homeostasis (Pang and Han, 2012; Sisley and Sandoval, 2011; Suzuki et al., 2010), in this review, we mainly focus on two tissues, WAT and BAT (brown adipose tissue), that play crucial roles on the opposite ends of the energy spectrum – storing energy versus wasting energy.

White adipose tissue (WAT)

The major function of WAT is to store extra energy in the form of triglycerides, which form large unilocular lipid droplets in white adipocytes. WAT represents ~10% of the body weight of healthy adult humans. WAT stores energy when there is a surplus and breaks down triglycerides and supplies fatty acids to other organs when needed. Thus, WAT functions as the energy storage and supply center of the body. Although WAT consists of a small fraction of immune and stromal cell populations (Gimble et al., 2011; Lolmede et al., 2011), it is predominantly composed of white adipocytes. In adults, most of these adipocytes are mature, fully differentiated cells and their size is directly proportional to the amount of stored lipids. The white adipocytes are capable of storing a large amount of energy by hypertrophy (MacKellar et al., 2010). WAT also consists of a preadipocyte population and/or adipose progenitors that reside along the adipose tissue vasculature. Under conditions of increased energy influx, when the existing adipocytes reach their maximum storage capacity, the preadipocytes are induced to differentiate into mature adipocytes in order to accommodate the incoming energy. Therefore, in addition to adipocyte hypertrophy, the preadipocyte/adipose progenitor population plays a predominant role in meeting the demands of increased energy influx (MacKellar et al., 2010; Wang et al., 2013b). Together, WAT has an enormous ability to expand by both hypertrophy and hyperplasia to house extra energy with little or no wastage (Hausman et al., 2001). This efficient capture and storage of energy appears to be an evolutionarily conserved phenomenon to cope with periods of food scarcity. However, in the current times of relatively easy availability of cheap energy-rich food, this energy storage efficiency is, not surprisingly, contributing to the process of moderate weight gain to overweight and ultimately to obesity.

It appears that the WAT has an unrestricted ability to expand; morbidly obese individuals can gain as much as several tens of kilograms of extra WAT tissue, which can exceed more than 50% of the body weight, suggesting that WAT continues to expand as long as excessive energy intake persists. What happens if we target and inhibit WAT expansion? Do we lose extra energy due to lack of storage space in the WAT? These questions are quite elegantly answered by two studies in mouse models. In the first study, a fatless mouse was generated by selectively expressing a dominant-negative protein, A-ZIP/F-1, in adipocytes (Moitra et al., 1998). A-ZIP/F-1 prevents DNA binding and thereby suppresses the function of several B-ZIP transcription factors in the C/EBP and AP1 families. These transcription factors are required for normal adipogenesis. As a result, the A-ZIP/F-1 mice have absolutely no white fat tissue and thus no energy storage capacity (Moitra et al., 1998). In the absence of WAT, these mice accumulate lipids in a number of tissues such as liver, muscle, heart and kidney and suffer increased levels of inflammation, develop diabetes, and are also susceptible to spontaneous and induced carcinogenesis (Nunez et al., 2006). In another study, PPARγ, a crucial regulator of adipocyte differentiation, was specifically deleted from the adipocytes. This causes severe loss of WAT (lipoatrophy) in these mice. Nevertheless, surprisingly, the body weights of adult adipocyte-specific PPARγ-null mice are similar to wild-type mice. The adipose-specific PPARγ-null mice suffer from severe insulin resistance, diabetes and a fatty liver due to ectopic accumulation of lipids. These mice also display abnormalities of bone, skin, and mammary glands, all of which contain adipose tissue (Wang et al., 2013a). These studies clearly indicate that in the absence of the energy store house, WAT, the extra energy may not be just eliminated from the body; thus interfering with adipogenesis and/or WAT expansion can have severe deleterious consequences. In the absence of WAT, cells of other tissues could be forced to capture and store energy, which in turn severely impairs their basic biological functions. It appears that the evolutionarily conserved mechanisms favor energy storage over energy loss even though abundant energy has detrimental effects on the overall function of the body.

Leptin vs Ghrelin

Is there a mechanism whereby WAT communicates stored energy levels to the brain, thereby suppressing energy intake? WAT is not just a simple storehouse of energy. It also functions as an active endocrine organ and secretes a number of cytokines, such as leptin, adiponectin, resistin, IL-6, IL-10 and TNFα (Guerre-Millo, 2004). Of these, leptin and adiponectin are predominantly secreted by adipocytes, and their circulating levels oscillate in response to stored energy levels. These adipokines communicate with other organs, such as brain, muscle, liver and other endocrine organs, to regulate energy homeostasis (Trayhurn and Wood, 2004). The adipokine that is primarily responsible for communicating WAT stored energy levels to the brain is leptin. Secreted from the adipocytes of the WAT, leptin signals the hypothalamus in the brain of energy abundance and thereby controls appetite (Attele et al., 2002). On the other side, ghrelin, a peptide hormone secreted from the endocrine cells of the stomach, signals hunger or energy insufficiency to the hypothalamus, thereby regulating short-term appetite and energy distribution. After a meal, when the stomach is full, ghrelin levels are reduced. Although ghrelin and leptin transmit opposite signals to the brain, they activate a number of overlapping signaling pathways (Klok et al.,

2007). Does leptin play a role in suppressing ghrelin levels and ghrelin-mediated appetite signaling? It was shown that leptin, indeed, could suppress ghrelin-mediated signaling (Barazzoni et al., 2003; Kalra et al., 2005; Kohno et al., 2007). However, leptin appears to function mainly in long-term appetite control and might not regulate short-term hunger. For example, administration of leptin to animals starved overnight does not prevent them from consuming food, suggesting that leptin may not override the hunger signals initiated by ghrelin.

Leptin levels are directly proportional to the amount of stored energy, and its levels continue to rise as the storage increases. However, although in the obese condition the circulating levels of leptin are very high, leptin fails to suppress appetite. This is due to the development of leptin resistance (DePaoli, 2014; Myers et al., 2008). For example, daily administration of leptin to obese animals reduces their food intake for few weeks before they develop leptin resistance and resume their normal food consumption rates. If energy levels are very high, do ghrelin-mediated hunger signals continue to be elicited? Ghrelin levels are lower in the obese condition where the energy levels are very high (Tschop et al., 2001). In certain studies, it was described that ghrelin-mediated appetite is reduced in the obese condition; however, it was also shown that ghrelin stimulates appetite and food intake even more in obese than lean humans (Druce et al., 2005). It appears that ghrelin-mediated signaling fails to recognize the presence of enormous stored energy in the WAT and continues to signal hunger when the stomach is empty. This could be partly due to the breakdown of leptin signaling, and under conditions of leptin resistance, ghrelin might be more potent, even at low levels, in inducing appetite. The inability of leptin to sustain its action on ghrelin-mediated hunger and the relatively rapid development of leptin resistance suggest that the evolutionarily conserved mechanisms favor continuous energy intake and storage, resist tapping into the stored energy, and instead stimulate hunger. It appears that the intake and storage of energy are evolutionarily favored mechanisms that require a breakdown of leptin signaling. These rigid mechanisms that favor energy intake and storage contribute to weight gain and ultimately obesity (Figure 1). Therefore, the only path to balance body energy and prevent obesity is finding a way to waste energy.

Brown adipose tissue (BAT)

The most efficient way to waste body energy is by increasing physical activity. Rigorous physical activities, such as running, swimming and biking, can burn off hundreds of calories and thus facilitate balancing excessive energy intake with energy expenditure (Strasser, 2013). Although it is a very well-known fact that regular physical exercise prevents weight gain, the majority of the humans are unable to follow it due to a number biological, behavioral and lifestyle reasons. If we did, we would not have the problem of obesity. Therefore, we need to find a way to waste energy without extensively participating in physically demanding activities. Is BAT the solution for this problem? The primary function of BAT is to dissipate energy in the form of heat, a process called adaptive thermogenesis. For example, by effectively utilizing BAT, small mammals living in cold environments produce heat for their survival. Thus, the idea of wasting body energy by employing BAT is very appealing. Despite the fact that the existence of BAT in rodents and newborn humans has been very well known for a long time (Cannon and Nedergaard, 2004), its exploitation

to increase energy expenditure and treat obesity has not been taken very seriously. This is mainly because of the belief that BAT mass is steadily lost during the natural human growth process, which leaves very little or no BAT in adults, and, therefore, strategies aimed at activating or expanding BAT in adults may not be feasible. By debunking this belief, recent PET-CT (positron emission tomography) studies demonstrate the existence of metabolically active BAT in adult healthy humans, and the mass and activity of this tissue is declined in obese and aged subjects (Virtanen et al., 2009). These findings reenergized the practical feasibility of increasing the amount and/or activity of BAT in the body in order to waste energy and thus treat obesity (Figure 1). The idea of activating BAT to treat obesity seems to be realistic, since in humans as little as 50 g of BAT (~0.1% of body weight) is estimated to burn ~20% of the basal caloric needs if fully stimulated (Rothwell and Stock, 1983). This is further supported in a number of mouse models where enhanced activity of BAT or increasing the number of brown-like cells or transplantation of BAT protected mice from diet and age-associated obesity (Seale et al., 2009).

What makes BAT so unique and how does it dissipate energy? BAT is specialized in performing a physiological mechanism called adaptive thermogenesis, during which energy is dissipated to generate heat in response to cold and/or diet (Cannon and Nedergaard, 2004; Seale et al., 2009). BAT is densely packed with mitochondria and executes heat production through a unique protein called uncoupling protein-1 (UCP1), which is located in the inner mitochondrial membrane. UCP1 uncouples mitochondrial oxidative phosphorylation from ATP production and dissipates chemical energy as heat, which significantly increases energy expenditure (Klingenberg, 1999; Kozak and Anunciado-Koza, 2008). Consequently, genetic deletion of *Ucp1* leads to impaired ability to produce heat in response to cold exposure (Enerback et al., 1997), and the *Ucp1* knockout mice gain more body weight when they were housed at thermo-neutral temperature (Feldmann et al., 2009). These observations suggest that UCP1-triggered BAT-mediated thermogenesis can be activated by both cold and diet. These findings in animal models further support the idea of expansion of BAT and activation of BAT-mediated thermogenesis to achieve energy balance and to treat obesity in humans (Costford et al., 2007; Kozak and Anunciado-Koza, 2008). But the most important question is how do we specifically expand and/or activate BAT?

Cold-induced thermogenesis

The easiest way to activate and expand BAT is exposure to cold temperatures. For example, exposing rodents to cold temperatures not only activates BAT in the short-term but also increases the total BAT mass in the long-term (Klingenspor, 2003; Morrison et al., 2012; Nakamura and Morrison, 2011). Cold exposure studies in human subjects also showed similar activation and an increase in BAT mass with a concomitant loss of body weight (Cypess et al., 2009; Nedergaard et al., 2010; van der Lans et al., 2013). Conversely, exposure to warmer temperatures results in suppression of thermogenesis due to a reduction in the sympathetic drive to BAT (van der Lans et al., 2013). How does cold temperature induce BAT activation? Exposure to cold causes release of catecholamines such as norepinephrine from the sympathetic nerve terminals that act on the β-adrenergic receptors of the brown adipocytes (Cannon and Nedergaard, 2004). Activated β-adrenergic receptors stimulate the cAMP/PKA/CREB signaling pathway, which ultimately induces peroxisome

proliferator activated receptor γ coactivator 1α (PGC1α), the master regulator of UCP1-mediated thermogenesis (Herzig et al., 2001). The β-adrenergic receptor/cAMP pathway also induces PGC1α through p38 MAPK, which activates PGC1α by removing p160-mediated repression, thereby increasing PGC1α protein stability (Cao et al., 2004). Overall, PGC1α expression as well as its transcriptional activity is greatly induced in response to cold exposure. PGC1α in turn activates a number of nuclear and non-nuclear factors and functions as the central regulator of numerous pathways involved in mitochondrial biogenesis and thermogenesis (Austin and St-Pierre, 2012; Delerive et al., 2002; Finck and Kelly, 2006; Handschin and Spiegelman, 2006; Huss et al., 2002; Knutti et al., 2000; Lin et al., 2005a; Lin et al., 2005b; Puigserver et al., 2003; Puigserver et al., 1998; Vega et al., 2000; Wang et al., 2003). For example, PGC1α directly induces the expression of *Ucp1*, and it also coactivates nuclear respiratory factors 1 and 2 (NRF1 and NRF2), which regulate the expression of genes encoding respiratory chain subunits and other factors essential for mitochondrial biogenesis and oxidative phosphorylation (Austin and St-Pierre, 2012; Wu et al., 1999). By regulating all these factors, PGC1α has a strong impact on several aspects of mitochondrial energy metabolism. Consequently, deletion of *Pgc1α* in mice results in impaired thermogenesis in response to cold exposure (Lin et al., 2004; Uldry et al., 2006). In contrast, induced expression of PGC1α is sufficient to induce an array of genes involved in mitochondrial biogenesis and thermogenesis, including *Ucp1* in white adipocytes (Puigserver et al., 1998; Tiraby et al., 2003), suggesting a central role for PGC1α in thermogenesis.

Is it practically feasible to conduct prescribed cold therapy procedures on humans to increase thermogenesis and to treat obesity? Although it has been known for some time that cold can effectively induce thermogenesis, so far there are not any reported cases of prescribed cold therapy procedures in clinics, and it might be very difficult to implement such procedures to treat obesity. For example, in most of the animal studies, mice were exposed to cold temperatures for prolonged periods of time (4–24h) in order to achieve significant BAT activation. Alternatively, animals were exposed to cold temperatures for shorter periods of time but it was done repeatedly to achieve significant BAT expansion (Fisher et al., 2012; Ravussin et al., 2014; Whittle et al., 2012). Therefore, similar prescribed cold therapy procedures might be difficult to implement in humans due to our inability to tolerate such cold conditions for such prolonged periods of time or multiple cold exposures. On the other hand, short tolerable levels of cold exposure might not be sufficient to achieve significant BAT activation. In addition, although cold exposure might burn some fat, it can also cause certain unintended medical complications such as stress, hypothermia, changes in blood pressure and respiratory issues. Can we achieve BAT activation without exposure to cold?

Activation of BAT

Is it possible to avoid cold exposure and directly activate the β-adrenergic receptor/PGC1α pathway and induce BAT-mediated thermogenesis? Subsequently, β3-adrenergic receptor (β3-AR) agonists have been identified that were shown to induce thermogenesis and increase metabolic rate in rodents (Arch et al., 1984; Connacher et al., 1992). These β3-AR agonists were able to increase energy expenditure and appeared to be beneficial in

counteracting obesity and diabetes in rodents. However, utilizing β3-AR agonists to increase BAT-mediated thermogenesis in humans was unsuccessful due to the very low level of expression of β3-AR receptors on human brown adipocytes (Arch, 2002). Therefore, these agonists were not able to induce the desired thermogenic response in human BAT and caused several off-target effects (Arch, 2002). Alternatively, attempts to utilize non-specific sympathomimetics, such as ephedrine and sibutramine, to induce thermogenesis resulted in severe side effects, such as stroke and cardiovascular complications, due to broad and nonspecific action of adrenergic stimulation (Di Dalmazi et al., 2013). Therefore, strategies that bypass β-adrenergic stimulation and directly activate PGC1α in BAT might be necessary to develop approaches to pharmacologically activate BAT in humans. However, developing such an approach may or may not be possible because, although PGC1α is the central regulator of UCP1-mediated thermogenesis in the BAT, it is also deeply involved in a number of other cellular mechanisms such as glucose and fatty acid metabolism, mitochondrial biogenesis and oxidative metabolism in other organs such as muscle, liver, heart and brain (Austin and St-Pierre, 2012; Puigserver et al., 2003). Therefore, it will be extremely challenging to identify a pharmacological agent that specifically targets and activates PGC1α only in the BAT without causing inadvertent side effects since it also plays an active role in other organs such as liver and muscle. An alternative approach could be identifying the specific molecular regulators of PGC1α and UCP1 in BAT and target these factors to modulate PGC1α/UCP1-mediated thermogenesis. Due to their critical role in thermogenesis, the expression and activities of PGC1α and UCP1 are precisely controlled by a number of proteins that either positively or negatively regulate PGC1α and UCP1, thus serving as accelerators or brakes and controling thermogenesis. Subsequently, a number of factors such as FOXC2, SRC1, CREB, SIRT3, ERRα and p38 MAPK were identified as positive regulators of PGC1α (Seale et al., 2009). Specific deletion of these factors in mice resulted in impaired PGC1α/UCP1-mediated thermogenesis and reduced energy expenditure, and the mice are prone to diet-induced obesity, indicating the importance of these factors in the activation of PGC1α/UCP1-mediated thermogenesis in BAT (Cao et al., 2004; Picard et al., 2002). Therefore, instead of directly targeting PGC1α, pharmacological activation of these factors could serve as an alternative approach to enhance thermogenesis since they ultimately mediate their effects through PGC1α. Conversely, factors such as pRB, p107, RIP140, Cidea, LXRα, Id1, Twist1 and TRPV4 were identified to function as negative regulators of PGC1α and/or UCP1 and thus suppress BAT-associated thermogenesis. Specific deletion of these factors in mice resulted in increased BAT activation and/or expansion and elevated energy expenditure, and the mice are protected from diet and age-associated obesity (Kiskinis et al., 2007; Pan et al., 2009; Satyanarayana et al., 2012; Scime et al., 2005; Sharma et al., 2014; Villena et al., 2007; Ye et al., 2012; Zhou et al., 2003). Therefore, pharmacological intervention of these factors might function as an alternative approach to enhance BAT thermogenesis. However, unfortunately, most of these positive and negative regulators are not only expressed in BAT and function in PGC1α/UCP1-mediated thermogenesis but they are also expressed in various other tissues and participate in a wide range of cellular processes. Therefore, strategies to specifically target one or more of these factors to modulate thermogenesis in BAT might be extremely challenging, and other organs will face unintended consequences from drugs that are directed towards these factors to activate BAT.

Browning of WAT

Another strategy that is under active investigation is to specifically target preadipocyte and/or adipose progenitors in the WAT and induce them to differentiate into brown-like cells, a process called browning of WAT. This will potentially increase the amount of brown adipocytes/brown-like cells, enhance energy expenditure and reduce body weight (Figure 1). In response to various stimuli such as cold and β-AR or PPARγ agonists, pools of UCP1-expressing brown-like adipocytes were detected in mouse WAT, especially in inguinal WAT (Barbatelli et al., 2010; Himms-Hagen et al., 2000; Vitali et al., 2012). These adipocytes are called 'beige' or 'brite' and, similar to brown adipocytes, these cells have high mitochondrial content and express thermogenic genes such as *Pgc1α* and *Ucp1*. Although beige adipocytes participate in thermogenesis similarly to brown adipocytes, their precise origin is not completely understood. Conversely, the developmental origins of brown adipocytes are relatively well known and are derived from a $Pax7^{+}Myf5^{+}$-expressing progenitor population of the mesoderm that also gives rise to skeletal muscle cells. In these progenitors, by co-operating with PPARγ, EBF2 induces the expression of PRDM16, which determines the brown adipocyte cell fate (Seale et al., 2008; Seale et al., 2007; Timmons et al., 2007). PRDM16 can bind to and modulate the transcriptional activity of numerous factors such as PPARα, PPARγ and PGC1α, thus functioning as a critical regulator of brown adipocyte cell fate (Kajimura et al., 2009; Seale et al., 2007). With respect to beige adipocytes, recent evidence suggests that these adipocytes do not appear to be derived from $Pax7^{+}Myf5^{+}$ precursor cells (Rosen and Spiegelman, 2014; Seale et al., 2008). Initial studies suggested that the mature differentiated white adipocytes in WAT can transdifferentiate into beige adipocytes when stimulated by cold or β3-AR agonists (Barbatelli et al., 2010; Vitali et al., 2012). However, subsequent lineage tracing studies revealed that the beige adipocytes do not arise from the existing differentiated white adipocytes and are indeed derived from the adipose progenitor/precursor cells (Wang et al., 2013b). The adipose progenitors in the WAT are believed to be bi-potential and, under conditions of excessive energy influx, they differentiate into white adipocytes, whereas, in response to cold or β-AR stimulus, they differentiate into beige adipocytes (Wu et al., 2012). As a result, thermogenic genes such as *Ucp1* and the *PGC1α*-network of genes are expressed in beige adipocytes only when there is an external stimulus such as cold or β-AR agonists. This is in contrast to brown adipocytes where the thermogenic genes are expressed all the time, at least at basal levels (Wu et al., 2013). Consequently, the thermogenic capacity of beige adipocytes is reversible, and these cells can lose this ability when the stimulus is withdrawn (Rosenwald et al., 2013). It appears that the beige adipocytes are susceptible to transdifferentiation into white adipocytes when there is high energy influx. Similar to mouse WAT, it is also known that human WAT contains adipose progenitor cells that express UCP1 in response to PPAR-γ activation and display beige adipocyte characteristics (Elabd et al., 2009). Can we force adipose progenitors in WAT to differentiate into brown-like cells in humans? Obviously, cold exposures and β-AR/ PPAR-γ agonists can induce browning of WAT in humans. However, both of these approaches are difficult to implement in humans due to the non-specific nature of β-AR agonists and the inability of humans to tolerate cold conditions for prolonged periods of time. Can we avoid cold exposure and β-AR agonists and still be able to induce browning in WAT? Recent studies successfully identified some of the important genes, such

as *Prdm16* and *Ebf2*, that participate in brown adipocyte programing (Rajakumari et al., 2013; Seale et al., 2008; Seale et al., 2009). These findings will potentially allow us to think beyond cold and agonists and formulate more specific targeted approaches to induce browning of WAT. Not surprisingly, due to their dominant role in brown adipocyte programing, it was demonstrated that induced expression of *Prdm16* or *Ebf2* is sufficient to convert white adipose precursors into brown-like UCP1-expressing cells. Similarly, overexpression of Prdm16 in mouse adipose causes browning of WAT and protects mice against diet-induced obesity (Seale et al., 2011). Based on these studies, it is clear that strategies aimed at inducing the expression of PRDM16 or EBF2 are sufficient to cause browning in WAT, which will have profound implications in the treatment of obesity. Additionally, a number of other factors have been identified to have a positive or negative regulatory effect not only on BAT thermogenesis but also on the browning of WAT. Some of these factors include FOXC2, RIP140, LXR, p107 and pRB, and activation of positive regulators or inhibition of suppressors function as alternative strategies to stimulate WAT browning, enhance energy expenditure and treat obesity. However, so far, pharmacological agents that specifically target any of these known factors to increase browning of WAT in humans are not available and are still an active area of investigation.

Conclusions

A steady growth of the overweight and obese population in the world implies that current diet, exercise and drug strategies are clearly not working in curtailing the obesity epidemic. Obesity results from a shift towards energy abundance in the body; therefore, new strategies must be aimed at enhancing body energy expenditure and/or identifying a way to waste energy. Since the predominant function of BAT is to dissipate energy as heat, new strategies should be designed to exploit this tissue to raise body energy expenditure. Under natural conditions, BAT mass steadily declines during the growth process, and adult humans have a significantly less percentage of BAT compared to newborns. BAT mass is also mostly lost in obese individuals, suggesting that its existence is susceptible to high energy influx. For example, the presence of significant levels of childhood obesity and 65% of adults in the US are overweight or obese clearly indicates that under normal conditions BAT is definitely unable to handle the excessive energy influx. If it did, we would not have the problem of obesity. Moreover, in energy excessive conditions, BAT appears to be prone to transdifferentiation into white-like cells. For example, feeding mice with a high-fat diet for just a few weeks can lead to significant lipid accumulation in BAT, and it appears like WAT, although mice have a much higher percentage of BAT compared to humans. Therefore, strategies to either increasing the amount of BAT or activating the existing BAT are currently under active investigation with the expectation that it will counter-balance higher energy influx. Activation and/or expansion of BAT could potentially work to treat obesity since it has been demonstrated that an increase in the amount and/or activation of BAT causes a lean and healthy phenotype in numerous animal models. Moreover, recent advances in identifying genes that play critical roles not only in the developmental origins of BAT and its activation but also the differentiation and browning of WAT is providing new opportunities to develop specific strategies at the molecular level to activate the existing BAT or to convert WAT into BAT. For example, approaches such as specific activation of

PGC1α in the brown adipocytes or induction of *Ebf2* or *Prdm16* in preadipocytes of WAT to generate more brown-like adipocytes in an obese individual could increase energy expenditure and reduce body fat. However, whether an obese patient still has any brown adipose tissue left to activate is questionable. In addition, converting adipocyte progenitors in the hypertrophic WAT of an obese individual into brown-like cells may not be easy because when there is a constant influx of energy into the body the adipose progenitors might prefer to differentiate into white adipocytes to store incoming energy rather than differentiate into beige cells to burn off the extra energy. At this moment, although BAT-mediated energy expenditure strategies seem to be theoretically possible, it will be extremely challenging to implement any of these strategies in humans to reduce WAT mass and treat obesity. This is mainly due to the fact that not only lifestyle but also biological factors such as development of leptin resistance, unsuppressed continuous ghrelin-induced appetite and unlimited ability of WAT to expand and store energy all favor energy storage over energy expenditure. It will be a monumental challenge for BAT to fight against all these factors and reduce WAT mass and restore body energy balance.

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Abbreviations

β3-AR	Beta 3-adrenergic receptor
BAT	Brown adipose tissue
B-ZIP	Basic leucine zipper
C/EBP	CCAAT/enhancer binding protein
cAMP	Cyclic adenosine monophosphate
Cidea	Cell death-inducing DNA fragmentation factor, alpha subunit-like effector A
CREB	cAMP response element binding protein
Ebf2	Early B cell factor 2
ERRα	Estrogen-related receptor alpha
FOXC2	Fork-head box C2
Id1	Inhibitor of differentiation 1
IL-6	Interleukin 6
IL-10	Interleukin 10
LXRα	Liver-X-receptor alpha
Myf-5	Myogenic factor 5
MAPK	Mitogen activated protein kinase
NRF1	Nuclear respiratory factor 1
NRF2	Nuclear respiratory factor 2
p107	Pocket protein 107
PAX7	Paired box 7

PET-CT	Positron emission tomography-computed tomography
PGC1α	Peroxisome proliferator activated receptor gamma coactivator 1 alpha
PKA	Protein kinase alpha
PPARγ	Peroxisome proliferator-activated receptor gamma
pRB	Retinoblastoma protein
RIP140	Receptor-interacting protein 140
PRDM16	PR domain containing 16
SIRT3	Sirtuin-3
SRC1	Src tyrosine kinase 1
TNFα	Tumor necrosis factor alpha
TRPV4	Transient receptor potential cation channel, subfamily 5, member 4
Twist1	Twist family basic helix-loop-helix transcription factor 1
UCP1	Uncoupling protein 1
WAT	White adipose tissue

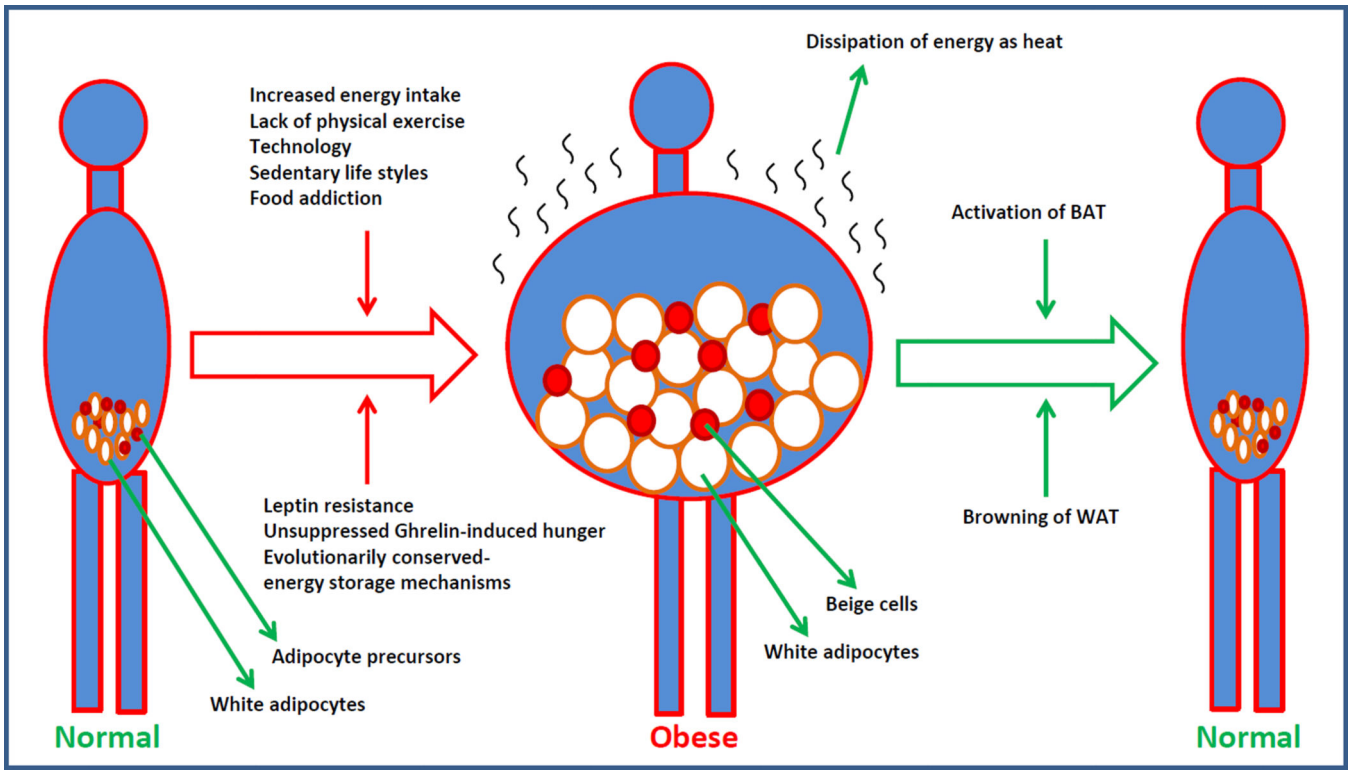

Figure 1.

Cartoon showing an array of factors responsible for causing obesity and the brown adipocyte-mediated energy expenditure strategies to possibly reverse obesity in humans. The detailed mechanisms are discussed in the text.