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REVIEW

Adrenergic regulation of cellular plasticity in brown, beige/brite and white adipose tissues

Vanesa D. Ramseyer[a] and James G. Granneman[a,b]

[a]Center for Molecular Medicine and Genetics, School of Medicine, Wayne State University, Detroit, MI, USA; [b]John Dingell Vet Administration Medical Center, Detroit, MI, USA

ABSTRACT

The discovery of brown adipose tissue in adult humans along with the recognition of adipocyte heterogeneity and plasticity of white fat depots has renewed the interest in targeting adipose tissue for therapeutic benefit. Adrenergic activation is a well-established means of recruiting catabolic adipocyte phenotypes in brown and white adipose tissues. In this article, we review mechanisms of brown adipocyte recruitment by the sympathetic nervous system and by direct β-adrenergic receptor activation. We highlight the distinct modes of brown adipocyte recruitment in brown, beige/brite, and white adipose tissues, UCP1-independent thermogenesis, and potential non-thermogenic, metabolically beneficial effects of brown adipocytes.

Introduction

Interest in understanding adipose tissue biology has increased globally because of the alarming rise in obesity and diabetes. The escalation in obesity is largely attributed to augmented energy consumption and widespread adoption of sedentary lifestyles, with the consequent expansion of adipose tissue and development of metabolic dysregulation. Therefore, research efforts have been focused on elucidating regulators of adipose tissue physiology in the hope of finding novel therapeutic approaches that mitigate the pathological effects of elevated fat mass.

The past 6 y have seen an explosion of interest in brown adipose tissue (BAT) that has been fueled by the unequivocal identification of active BAT in adults,[1-5] and by the growing appreciation of the intrinsic metabolic and cellular plasticity of mammalian adipocytes. Positron Emission Tomography (PET) imaging studies conclusively demonstrated that mild cold stress or selective activation of β3-adrenergic receptors (ADRB3) produces visually impressive increases in uptake of ^{18}F fluorodeoxyglucose (FDG).[3-9] However, direct measurement of oxidative metabolism in BAT by ^{15}O PET (or blood flow) indicate that the level of cold-activatable thermogenesis in most individuals is less than 10 kcal/day.[6,7,9] To put this in perspective, blood flow to BAT of cold-adapted rats can reach rates of 1000 ml/min/100 g[10,11] versus 15–20 ml/min/100 g BAT in cold-stressed, warm-adapted humans.[6,7,9] The clear conclusion is that the abundance and/or magnitude of thermogenic activation of BAT in humans would need to be increased by 40–50 fold to achieve an effect similar to brief exercise. Thus, there is a real need to understand how the brown adipocyte (BA) phenotype is regulated in vivo, and how levels might be expanded by physiological and pharmacological approaches.

The central role of the sympathetic nervous system (SNS) in modulating BAT and white adipose tissue (WAT) energy metabolism is well established (for review see refs.[12-14]). Recent work from our lab and others has demonstrated that the SNS, acting mainly via ADRB, plays a central role in modulating intrinsic cellular and metabolic plasticity of adipose tissues. Importantly, the mode of regulation varies according to depot and nature of activating stimulus. The goal of this article is to provide a focused outlook on how adrenergic receptor activation mediates cellular and metabolic plasticity in adipose tissues with a main focus on research done on rodents.

Modes of adrenergic activation

Adipose tissue ADRB can be stimulated by elevating sympathetic neural activity, for example by cold stress,[15-18]

CONTACT James G. Granneman ✉ jgranne@med.wayne.edu ▣ 6135 Woodward, Integrative Biological Sciences Building, Room 2414, School of Medicine, Wayne State University, Detroit, MI 48202

leptin[19,20] or emotional stress.[21] In rodents, substantial sympathetic innervation of both BAT and WAT has been demonstrated consistently by a variety of methods (for review see refs.[14,17]) including immunochemical detection of tyrosine hydroxylase,[22-26] fluorogold retrograde tracing[27] and electrical recording of nerve activity.[18,28] Direct nerve stimulation of WAT has also been demonstrated in rodents and humans.[29-32] Importantly, the sympathetic innervation of WAT is necessary for lipolysis triggered by stimuli like leptin or cold exposure in rodents.[13,33-36] Nonetheless, it is important to note that the level of sympathetic innervation varies among fat pads, with BAT being the most heavily innervated and abdominal WAT the least.[25,27,37] Furthermore, activation of the SNS varies according to stimulus and fat depot. Thus, cold exposure is a powerful activator of BAT and inguinal WAT (iWAT) and, to a lesser extent, gonadal WAT (gWAT), whereas glucoprivation selectively activates iWAT, but not BAT or gWAT.[16]

A second means of activating the catabolic functions of adipose tissues is by direct adrenergic receptor activation, which overcomes the limitations imposed by differences in innervation and central nervous system (CNS) activation. In rodents, systemic infusion of norepinephrine is sufficient to reproduce most of the effects induced by neural activation.[38-42] Activation of thermogenesis and upregulation of oxidative metabolism is mediated by ADRB and selective ADRB3 agonists are highly effective in elevating whole body thermogenesis in rodents [11,43-46] and humans.[47] Interestingly, experiments involving tissue-selective gene expression indicate that activation of ADRB in both WAT and BAT is required for full thermogenesis, with WAT ADRB3 directly or indirectly accounting for ˜70% of the total response.[48] In this regard, humans express ADRB3 in BAT, but not WAT,[49-51] which may explain why ADRB3 agonists have not been successful as anti-obesity agents in humans.[52]

Modes of modulating adipose plasticity by adrenergic activation

The pioneering work by Cinti highlighted the tremendous plasticity of adipose tissues,[53-55] and many laboratories are now investigating how this intrinsic plasticity might be exploited for therapeutic benefit. Adrenergic activation expands the catabolic character of adipose tissues by interrelated mechanisms, and lipolysis is a major regulator of catabolic activity. In BAs, mobilized fatty acids are direct allosteric regulators of UCP1 [56] and are the principal fuel driving high rates of heat production.[57] Mobilized free fatty acids are also effective ligands of PPARα and PPARδ, which regulate expression of genes involved in the uptake and oxidation of fatty acids,

thereby coupling oxidative capacity to supply.[58] Of course, activation of PKA by ADRB phosphorylates and activates CREB-binding protein,[59] PGC1α [60,61] and p38 MAPK,[62] which are important in establishing the BA phenotype and inducing mitochondrial biogenesis. Interestingly, chronic ADRB3 activation in rodents greatly increases catabolic activity of WAT in a manner that can be largely independent of UCP1.[63-65] Under chronic conditions, this catabolic activity is matched by dramatic increases in de novo lipogenesis in BAT, iWAT, and gWAT.[65] These observations indicate that coupled energy expenditure (i.e., ATP-consuming processes) may be of greater significance in WAT vs. BAT, at least in response to pharmacological activation.[65,66]

In addition to metabolic plasticity, adrenergic activation can alter a number of BAs (defined as multilocular cells expressing UCP1) in classic interscapular BAT (iBAT) and WAT depots. Although the modes of BA recruitment are not fully resolved, in general they involve de novo adipogenesis (i.e., differentiation from progenitors) or upregulation of the BA phenotype in differentiated cells that appear to be white. Importantly, the mechanisms of BA recruitment depend on the nature of inductive stimuli (neural vs. pharmacological) and the specific fat depot.

Cellular plasticity in iBAT

In mice, iBAT develops prenatally and is functionally innervated and fully active at birth.[67] An intact innervation is not required for specification of the BA lineage; however, denervated iBAT is functionally inactive and over time takes on the appearance of white adipocytes.[40] The significance of the SNS in activating and maintaining BA phenotype in adult mice has been firmly established by selective surgical,[68-72] chemical,[73] immunological,[74] and genetic [75] denervation strategies. Importantly, local surgical denervation abrogates induction of UCP1 and tissue hyperplasia in response to cold.[25,69] Similarly, highly selective inhibition of medullary sympathetic efferent neurons eliminates induction on BAT thermogenesis in response to cold.[76,77] Thus, while other cellular sources of catecholamine, such as macrophages, have been proposed based on genetic approaches,[78,79] none is sufficient to mediate the effects of cold in the absence of neural activation.

Adrenergic stimulation induces BA hyperplasia and angiogenesis in iBAT,[25,80-82] leading to pronounced expansion of iBAT mass during extended cold adaptation. Using radioactive thymidine labeling, Bukowiecki found that cold, norepinephrine, or isoproterenol strongly induced cellular proliferation in iBAT, suggesting that ADRB stimulation mediates cellular

proliferation.[80,81] By analyzing the fate of flash-labeled cells, Bukowiecki deduced that BA cells arise from a population of interstitial cells that proliferate during the first 2–4 d of cold stress. More recent work using genetic tracing methods demonstrated that cold exposure or norepinephrine treatment triggers proliferation and differentiation of a subpopulation of Sca1+ stromal cells that express PDGFRα.[25] PDGFRα cells are morphologically and immunologically distinct from closely associated endothelial cells, which also proliferate in response to cold stress.[25] The PDGFRα+ BA progenitors have a dendritic morphology that appears to be characteristic of adipocyte progenitors in various fat pads.[25,83,84] Interestingly, proliferation of progenitors occurs mostly in the dorsal region of iBAT at the white-to-brown interface,[25] suggesting the presence of specific micro environmental factors.

With regard to the identity of the ADRB involved in expansion of BAT mass, it is known that rodents and human iBAT express β1, β2, and β3 receptors (ADRB1, 2 and 3 respectively).[51,85-88] Early in vitro work from the labs of Kozak and Nedergaard suggested that norepinephrine triggers BA proliferation via ADRB1.[88-91] These data are in agreement with the fact that ADRB1 are present in BA progenitors, whereas ADRB3 is a marker of the differentiated state.[91] Recently, we reported that knockout of ADRB1 abrogates cold-induced iBAT hyperplasia.[25] In this regard, it should be noted that ADRB3 agonists do not induce hyperplasia in iBAT, despite intense metabolic activation.[82] Altogether these data indicate that ADRB1 mediate SNS-induced progenitor proliferation in iBAT, whereas both ADRB1 and ADRB3 mediate increases in lipolysis, mitochondrial biogenesis and establishment of oxidative phenotype in mature BAs (for review see refs.[17,92,93]).

Adrenergic regulation of BA phenotypes in subcutaneous WAT

It is well known from the work of Cinti,[53-55] Loncar[94-96] and Kozak[97,98] that neural or direct adrenergic activation of subcutaneous white fat in small mammals can induce the appearance of UCP1 positive multilocular adipocytes. Although this phenomenon can be observed to varying degrees in many depots, it is most robust (defined as fold-induction) in the inguinal fat pad,[97] also known as the mammary fat pad. In mice, the inguinal pad develops prenatally and adipocytes begin to fill with lipid in the first few days after birth.[99] Interestingly, UCP1 expressing multilocular adipocytes appear in abundance during the second post-natal week and by the time of weaning these cells compose about 30% of the total adipocyte population.[34,100,101] The developmental

appearance of BAs in the inguinal pad seems unrelated to perinatal thermoregulation, since these cells appear after the peak activation of classic BAT and after pups have acquired fur. The mechanism for the upregulation of the BA phenotype is not clear; however, expression profiling of whole iWAT indicates that UCP1 expression correlates with upregulation of genes involved in axonogenesis, neuritogenesis, and growth of nervous tissue.[102] It is possible that expression of the BA phenotype requires neural activity and that appearance of iWAT reflects degree of innervation and or activity of the SNS in this depot.

Mice largely lose expression of BA markers in iWAT, like UCP1 and CIDEA, by 3 months of age when reared in the warm;[34,102] however, expression of these markers can be rapidly (within hours) induced by cold stress or ADRB3 agonists.[55,97,103,104] Whether the newly appearing BA cells represent de novo adipogenesis or the induction of BA phenotype in existing cells is controversial. Immunohistological experiments indicate that UCP1 expression first appears in relatively large paucilocular adipocytes that progressively take on the appearance of classic BA.[55] Furthermore, experiments done in UCP1-CreER/tdRFP mice and UCP1-GFP mice indicate that the inguinal fat pad contains a substantial population of UCP1 negative adipocytes having a history of UCP1 expression.[104] Tracing experiments using tamoxifen-inducible Cre also support the notion of conversion between "white" (paucilocular, UCP1 negative) and "brown" (multilocular UCP1 positive) phenotypes.[25,104] Use of tamoxifen for tracing in adipose tissue has been criticized owing to the potential slow clearance.[105] However, use of tamoxifen under conditions in which de novo adipogenesis can be quantitatively demonstrated in iBAT, indicates that most BA cells that appear in inguinal fat during cold stress arise from preexisting fat cells.[25,83,84,104] As mentioned before, UCP1 positive cells that appear in response to 2 single injections of ADRB3 agonist have an appearance (large, paucilocular) that seems inconsistent with de novo adipogenesis.[34] In contrast, Scherer's group has shown that cold and ADRB3 agonist treatment stimulate "massive" de novo adipogenesis in iWAT.[106] This conclusion is based on the appearance of differentiated UCP1 positive adipocytes in iWAT that lack an immediate history of adiponectin expression. Using Lac-Z activity as a reporter, these authors observed that overnight cold exposure was sufficient to produce the appearance of fully formed unilocular (>50 micrometer diameter) white adipocytes in gWAT. In addition, Gupta's group recently demonstrated that Zfp423-PDFGRβ+ mural cells, which also express PDGFRα, give rise to brown adipocytes in iWAT in response to 2 weeks but not 1 week of cold exposure[107] suggesting that

several waves of de-novo adipogenesis may occur in response to cold exposure. However, the nature of early white adipocyte progenitors has not been established, and alternative technical explanations have been suggested.[25,83,84] Since PDGFRα+ progenitors do not contribute significantly to brown adipogenesis in iWAT within a week of adrenergic stimulation,[25,83,84] initial de novo recruitment might involve an intermediate or partially-differentiated phenotype capable of rapid lipid filling, but lacking adiponectin expression.

Regardless of the mechanism of BA recruitment (phenotype reinstatement in existing cells or de novo adipogenesis) the tonic neural activity appears to be important in maintaining phenotype flexibility of WAT. Thus, surgical denervation of iWAT in mice greatly reduces the ability ADRB3 stimulation to upregulate the expression of BA makers.[34] These results suggest that tonic neural activity maintains the BA progenitor pool or epigenetic program that preserve phenotypic flexibility of existing convertible adipocytes.

Cell cloning experiments and expression profiling data has suggested that BA cells derived from inguinal fat pads are distinct in phenotype to BAs from iBAT.[108] Thus, in rodents, BAs from iBAT and iWAT express a distinctive set of body positional markers (e.g, Zic1, Hoxc8, Hoxc9, Tcf21 and Myf5).[109] In spite of those differences, it is uncertain to what degree BAs from iWAT differ fundamentally from classical iBAT with respect to thermogenic mechanisms, lipid metabolism, and hormone secretion. Recent work by Wang et al. indicates that PDGFRα+ progenitors destined to become BAs express Ebf2+, whereas those destined to become white do not.[110] These observations reinforce the fact that the inguinal fat pad is very heterogeneous and that approaches that do not account for this heterogeneity can be misleading (i.e. cell suspensions, RNA extraction and protein homogenates from whole tissue).

Brown in gWAT

GWAT is a major abdominal depot in rodents that develops postnatally, with differentiated adipocytes appearing by day P7 and fully maturing by P14.[111] Among the various fat depots, gWAT is among the least capable of inducing BA phenotype in response to neural or direct adrenergic activation.[55,65,103] The reason for the relative lack of responsiveness is not certain, but could be related to lower density of sympathetic innervation[25,27,37] or differences in specific progenitor pools.[112] Our lab found that mouse gWAT tissue contains populations of bipotential progenitors that can differentiate into brown or white adipocytes depending on inductive signals.[84] Cold exposure, which relies on the activation of

the relatively spare SNS in gWAT, has very little effect on expression of BA makers in existing adipocytes and induces virtually no de novo recruitment of BA. In contrast, direct activation of gWAT by ADRB3 agonist triggers de novo adipogenesis from the bipotential progenitor pool that express PDGFRα on their surface. Activation of ADRB3 with CL-316,243 increases cell proliferation peaking at 3 d after treatment. Interestingly, the effect of ADRB3 agonist is not direct on progenitors, which lack ADRB3, but rather is the indirect response to adipocyte cell death and repair. In particular, chronic infusion of ADRB3 agonist increases lipolysis and adipocyte apoptosis, which signals recruitment of M2 macrophages, formation of crown-like structures and phagocytosis of dead adipocytes.[83] Adipocyte efferocytosis results in the expression of signaling molecules like osteopontin which recruits PDGFRα+ progenitor cells to the site of injury. Recruited progenitor cells divide and differentiate into adipocytes which, in the presence of ADRB3 agonist, adopt a multilocular brown like-phenotype with increased levels of UCP1.[83] Interestingly, brown adipogenesis occurs in small clusters, reflecting proliferation and differentiation driven by microenvironmental factors. In this regard, we recently found that the macrophages which clear dead fat cells upregulate expression of Alox15, which generates the PPARγ agonists 9-HODE and 13-HODE.[113] In vitro experiments established that 9-HODE and 13-HODE are nearly as effective as rosiglitazone in strongly upregulating the BA phenotype of differentiating PDGFRα cells. Since progenitors in the earliest stages of differentiation express ADRB3, it seems likely that the combined effects of adrenergic stimulation and PPARγ activation drive bipotential progenitors to the BA fate.

UCP1-Independent effects: thermogenic and non-thermogenic mechanisms

Historically, nonshivering thermogenesis has been attributed to the presence and activation of UCP1 in BAT. However, depending on background strain, UCP1-knockout mice can adapt to cold by increasing thermogenesis.[114] Indeed, UCP1 mice are resistant to diet-induced obesity under mild cold stress, indicating engagement of inefficient UCP1-independent mechanism.[115] The site(s) of UCP1 independent thermogenesis has(ve) not been fully established. Chronic treatment with ADRB3 agonist elevates oxygen consumption in gWAT and this effect is independent of UCP1.[63] As mentioned above, ADRB3 agonist treatment dramatically increases glyceride-glycerol turnover (to >50 %/day) and simultaneously increases de novo lipogenesis and fat oxidation.[65] Thus, adrenergic activation creates an ATP-

consuming cycle of triacylglycerol lipolysis and fatty acid synthesis and re-esterification (TAG/FA cycle). This cycle is presumably fueled by local fatty acid oxidation and sustained by dramatic expansion of mitochondria.[44,65,116] Whether such dramatic effects can be observed in human adipocytes is uncertain. Human white adipocytes lack ADRB3, so other means of triggering futile cycling selectively in adipocytes would need to be developed.[117]

A positive correlation between BAT mass and insulin sensitivity has been shown in humans and rodents.[118,119] This correlation seems to be independent of total fat mass and points to a still speculative endocrine function of BAs. Research shows that subcutaneous or visceral transplants of BAT or beige/brite tissue improve glucose metabolism in rodents.[120-125] Moreover, a recent report from Stahl's group demonstrated the beneficial effects of matrix assisted transplantation of beige/brite cells on glucose metabolism and insulin sensitivity.[126] Although results from matrix transplants could not be separated from increased thermogenesis, they point to a possible endocrine function of BAs. In this regard, FGF21 and IL6 have been shown to mediate some of the beneficial effects of BAT transplantation,[122] and FGF21 alone can improve insulin sensitivity in a UCP1-independent fashion.[127,128] Altogether recent data suggest that some of the beneficial effects of BAT and beige/brite tissue are not related to increasing thermogenic capacity (for review see ref.[129]).

Some unresolved issues

A significant amount of progress has been done in understanding BAT, WAT and beige/brite tissue physiology and regulation in small mammals. However, we still face challenges when extrapolating those findings to humans. Endothermic thermogenesis plays a much larger role in energy balance of small versus large mammals.[130,131] Therefore, the contribution of iBAT-mediated thermogenesis on energy expenditure is less prevalent in humans than rodents. Thus, it would be necessary to perform studies in larger animals to predict the applicability of the concept in humans.

In addition, another important difference between humans and rodents is body distribution of ADRB. ADRB1 receptors are broadly expressed in the cardiovascular system, so ADRB1 agonists cannot be used to selectively recruit BA progenitors. In rodents, ADRB3 are selectively expressed in BAT and WAT, and combined activation is required for full thermogenesis.[48] Humans express ADRB3 only in BAT, and thus ADRB3 activation cannot rely on WAT-supplied fatty acids to fuel high levels of metabolism. This limitation may explain the failure of ADRB3 agonists in clinical trials.[52] It was recently reported that the ADRB3 agonist mirabegron, currently approved for overactive bladder, increases ^{18}F-FDG uptake in human BAT.[132] However, based on the relationship between standard uptake values (SUV) and blood flow,[6,7] the quantitative significance with respect to thermogenesis is unclear.

Interestingly, several groups have demonstrated a significant increase of about 300 kcal/day in whole body energy expenditure after cold exposure or ADRB3 in individuals harboring cold-activated BAT.[6,132,133] As mentioned earlier, these increases are not likely due to PET-identifiable BAT thermogenesis (which contributes <20 kcal/day). These data suggest that, similar to improved glucose metabolism, an alternative non-thermogenic function of BAT could mediate increases in energy expenditure. Whether this is due to an unknown BAT function or to the secretion of "BATokines" remains unclear.

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