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Insulin resistance, the unbrowning of brown adipose tissue and beige adipose tissue development in obese and obese-diabetic rats: Is there a link?

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Abbreviations: WAT, white adipose tissue; UCP1, uncoupling protein-1; NIDDM, non-insulin dependent diabetes mellitus; MetS, metabolic syndrome, VMA, vanilmandelic acid

Synopsis

The participation of brown adipose tissue thermogenesis during alterations in diet and environment in mammalian species are well cited. Historically only white and brown adipose were known, but recent studies in rodent animal models have proposed a third histologic type of adipose tissue that is morphologically and metabolically similar to brown adipose tissue, and which has become known as beige adipose tissue. The recent reports of beige adipose tissue, also identified as beige, bright, or pink adipose tissue suggest beige adipose tissue may have a role in energy balance vs. energy storage via fat accretion in response to alterations in diet, environment, hormonal and pharmacologic regulation. In addition, activation of beige adipose tissue via pharmacologic, physiologic or hormonal means may also occur via the adrenergic-activated mitochondrial uncoupling protein-1 (UCP1) activity in a manner similar to that of BAT while retaining its multilocular lipid histologic distribution. The morphometric and biological functions of beige adipose tissue in obese and obese-NIDDM rats during over- and undernutrition are reviewed and discussed, with particular reference to the prevalence and role of insulin resistance in various strains of obese and obese non-insulin dependent diabetic (NIDDM) rats in association with brown and beige adipose tissue.

Introduction

Historically, the adipose tissues of man and animals have been divided into white adipose tissue (WAT) and brown adipose tissue (BAT), each with well descried biologic and morphometric features and physiologic functions relating to the partition of lipid energy reserves. The BAT of man and animals has been widely reported to play a key function in the thermal adaptation to alterations to diet and environment in addition to its role in temperature regulation among the newborn of man and animals, and is a likely contributing factor in development of the relative fatness vs. leanness of an animal due to its capacity to expend energy as heat rather than energy storage *per se* when in an activated state.[1–3] The presence of BAT has been observed in cadaveric dissections for many years, but its physiologic role remained unclear until studies reported in recent decades uncovered some of the molecular mechanisms inherent in thermogenic BAT actions in man and animals.[2,4–6] The BAT is now known to play a key role in rodents and other mammalian species during recovery from states of torpor and during recovery from hibernation.[2] In humans, BAT has also been proposed to play a significant thermogenic role in the newborn, where it helps to generate heat to maintain homeothermy during the first stages of life outside the womb.[1,2] The BAT has also recently been proposed as a potential site for obesity therapy due to its capacity to convert stored energy into heat energy which may be readily dissipated from bodily surfaces while maintaining a state of homeothermy.[7,8] The recent recognition and discussion of an intermediate, third type of adipose tissue termed beige, bright or pink adipose tissue (BeAT) has emerged, and has been proposed with the suggestion that it may be able to undergo transdifferentiation to become more thermogenically active as brown adipose tissue under certain environmental, hormonally or pharmacologically activated conditions, or to return to an energy storage role when the thermogenic needs of the organism become less active.[8,9]

Increases in sympathomimetic activity may activate physiologic or environmental conditions that may predispose the differentiation of BeAT from preadipocytes or differentiated BAT adipocytes have been proposed as one of the possible mechanisms to promote development of thermogenic BeAT and BAT tissues, However, factors that impair thermogenic activity of BAT, including β-blockade and excess insulinogenic activity have also been observed to be present where BeAT has been reported, and have been associated with a decreased physiologic capacity for expression of non-shivering thermogenesis characteristic of normally functioning BAT.[9–12] In contrast, pharmacologic actions of both caffeine and ephedrine, which may pharmacologically bypass the normal neuroendocrine activation of BAT have been reported to increase parameters of nonshivering thermogenesis in both lean and obese rats without immediate visible impact on the coloration of BAT, while conditions of short term starvation and experimental protein calorie malnutrition have preserved the pigmented, deep brownish coloration and thermogenic potential of BAT.[13,14]

BAT occurs in the obese phenotypes of several rodent strains

In the obese phenotype of several obese rodent strains summarized in

Table 1 below, the BAT depots are well developed and appear to have undergone significant increases in BAT depot mass and cellularity, consistent with early hyperplasia, hypertrophy and lipid accretion in the BAT depots, particularly the Interscapular depot where most studies have focused.[8,15–20] The histologic features of white and brown adipocytes are markedly different: white adipocytes are readily identified in histologic specimens by their single large lipid droplet, which typically occupies up to 90% or more of the morphology of the adipocyte structure. The single large lipid droplet is typically surrounded with a narrow rim of cytoplasmic material, a defined plasma membrane and a peripherally located and often ovoid-shaped nucleus compressed into the cytoplasmic rim.[12] White adipocytes may continue to form from preadipocytes and via cellular hypertrophy of existing adipocytes throughout much of the adulthood of mammalian species in response to imbalances in energy intake and expenditure. In contrast, brown adipocytes expand via hyperplasia and hypertrophy predominantly during early, preadolescent life, are typically smaller in circumferential diameter, contain a centrally located spherical and dense appearing, nucleus that is surrounded by numerous small lipid locules, in addition to a metabolically active appearing organelle filled cytoplasm containing an abundance of unique, specialized mitochondria that express the thermogenic UCP1 protein, capable of initiating the transformation of lipid energy into heat energy from the lipid locules and carbohydrate energy reserves. Once formed, the differentiated mature adipocytes of both WAT and BAT appear to remain present thereafter where they may contribute to both physiologic and pathophysiologic sequelae well adolescence and throughout much of the adult lifespan (Tables 1&2).[15]

Table 1 Qualitative Summary of Metabolic Parameters in Lean, Obese and Obese-Diabetic rats

Strain / Phenotype / Diet:	IR	NIDDM	RMR	[T3]	Ref
Sprague Dawley-chow diet	No	No		Normal	Normal[26]
Sprague-Dawley-Café' diet	No	No		Increased	Increased[26]
LA/Ntul//-cp					
Lean -chow	No	No		Normal	Normal[14,15]
Obese- chow	Yes	No		Decreased	Decreased[14,15]
SHR/Ntul//-cp					
Lean - chow	No	No		Normal	Normal[16]
Obese-chow	Yes	Yes		Decreased	Decreased[16]
WKY/N-cp Rat					
Lean - chow	No	No		Normal	NR[17]
Obese - chow	Yes	Yes		Decreased	NR[17]
Lean - chow	No	No		Normal	Normal[18]
Obese - chow	Yes	Yes		Decreased	Decreased[18]
Zucker Fatty (fa) Rat					
Lean-chow	No	No		Normal	Normal[19]
Obese -chow	Yes	Yes/No**		Decreased	Decreased[19]

*Indicates visible unbrowing by inspection. IR, insulin resistance as determined by an elevated insulin to glucose ratio; IBAT mass reported in grams/interscapular depot; IBAT, cellularity determine as cells number per depot; IBAT Hypertrophy determined by cell lipid content per cell greater than occurred in normally fed lean animals of the same strain. Correlations between IR and RMR and of IR and increased IBAT, Mass yielded an r^2, 1.0 in these comparisons. NR, not reported. RMR, resting metabolic rate; T3, plasma Triiodothyronine; IBAT, Interscapular brown adipose depot. Ref, denotes reference cited.

Table 2 Qualitative Summary of BAT Characteristics in Lean, Obese and Obese-Diabetic rats

Strain/Phenotype/Diet	IBAT Mass	IBAT cellularity	IBAT Hypertrophy	Ref
Sprague Dawley-chow diet	Normal	Normal	No	[26]
Sprague-Dawley-Café' diet	Increased	Increased ~2-3x	Modest	
LA/Ntul//-*cp*				[26]
Lean - chow	Normal	Normal	No	[14,15]
Obese- chow	Increased ~5x*	Increased ~3-5x	Yes	[14,15]
SHR/Ntul//-*cp*				
Lean - chow	Normal	Normal	No	[16]
Obese - chow	Increased >5x*	Increased ~3-5x	Yes	[16]
WKY/N-cp Rat				
Lean - chow	Normal	Normal	No	[17]
Obese - chow	Increased >2x*	Increased	Yes	[17]
Wistar Fatty(*fa*) Rat				
Lean - chow	Normal	Normal	No	[18]
Obese - chow	Increased ~5x*	Increased ~3-5x	Yes	[18]
Zucker Fatty (*fa*) Rat				
Lean - chow	Normal	Normal	No	[19]
Obese - chow	Increased ~5x*	Increased`	Yes	[19]

*Indicates visible unbrowing by inspection. IR, insulin resistance as determined by an elevated insulin to glucose ratio; IBAT mass reported in grams/interscapular depot; IBAT cellularity determine as cells number per depot; IBAT Hypertrophy determined by cell lipid content per cell greater than occurred in normally fed lean animals of the same strain. Correlations between IR and RMR and of IR and increased IBAT Mass yielded an r^2 = 1.0 in these comparisons. NR, not reported. RMR, resting metabolic rate; T3, plasma Triiodothyronine; IBAT, Interscapular brown adipose depot. Ref, denotes reference cited.

BAT mitochondria express a thermogenic uncoupling protein unique to brown adipose tissue

The specialized mitochondria of BAT exhibit the capacity to convert stored lipid energy into heat energy via a biochemical uncoupling mechanism of oxidative phosphorylation.[1,2] Upon neuroendocrine or noradrenaline-mediated activation by medium and long-chain fatty acids from stored triglyceride, since the smaller lipid structure of the lipid locules allows for a more rapid path and proportionately greater amount of energy production at 9 kcals/g vs. glycolysis at only 4 kcal.g. of substrate. The UCP1 protein increases the rate of proton conductance of the inner mitochondrial membrane to enable BAT mitochondria to generate heat from ATP via a rapid uncoupling process of high energy phosphate bonds and resulting in uncoupling of oxidative phosphorylation rather than generation of ATP that is typical of mitochondria of most peripheral tissues. For each high energy bond of ATP that becomes hydrolyzed in BAT, a net of 7.3 kcal of heat per mole of high energy bonds of ATP to ADP +iP is realized. Because the conversion of stored energy into heat energy initiated via the BAT-unique uncoupling protein (UCP1)-activated hydrolysis of the high energy phosphate bonds of ATP, forming ADP and inorganic phosphate (iP), the releasable heat energy from the high energy bonds of ATP consumed in the reaction may be applied to maintaining body temperature during thermoregulation or dissipated as heat from peripheral tissues.[1,2] BAT is well innervated via noradrenergic sympathetic neurons, and is thus capable of initiating the thermogenic cascade., The released NE diffuses across the synaptic space where it can impinge on stereospecific specialized β3-adrenergic receptors common to BAT and thus to initiate the cascade of thermogenic events.[10,11] In addition, the presence of the uncoupling protein (UCP1) is highly unique to BAT tissues and is not expressed in WAT.[1] In contrast, WAT lacks direct neural innervation and UCP1, has far fewer mitochondria, and can undergo biosynthetic processes of lipid accumulation or mobilization of free fatty acids in response to endocrinologic signals mediated by circulating hormones, especially insulin and catecholamines respectively. Because WAT lacks the capacity for expression of the UCP1 protein, it cannot expresse UCP1 mediated thermogenesis reactions.[2,7,8] Thus, the morphometric, biochemical, physiologic and metabolic characteristics of differentiated BAT and WAT tissues differ very significantly, which contributes to their established and distinct primary physiologic roles in energy metabolism and energy expenditure vs. energy storage. These unique characteristics have contributed to the identification of BAT as a potential mediator of energy balance in response to signals from dietary, environmental and pharmacologic stimuli. Thus, BAT and possibly BeAT are indeed potentially useful pharmacologic targets for altering the balance between energy storage in WAT and energy expenditure in BAT, and as a possible pharmacologic mechanism projected toward reducing the magnitude of adiposity and with a goal toward establishment of a leaner physique.[6–8]

The embryologic origins of Beige adipose tissue transdifferentiation are unclear

The definitive origins and potential roles of the beige adipose tissue are unclear, but the discovery of the presence of the uncoupling protein UCP1 in beige adipose tissue suggests that the tissue is more directly linked to BAT than WAT and may be linked to a histologic form of BAT since the UCP1 protein is unique to BAT.[8,9] Preadipocytes are Stimulation of preadipocytes by expression of the PRDM16 gene is associated with their differentiation into BAT cells. The mechanisms for the proposed transdifferentiation between Brown AT and Beige AT remain unclear, however, but review of the morphometric characteristics and hormonal profiles which occur in animals expressing BeAT vs. BAT suggest that disordered elements of energy metabolism processes likely contribute a decisive role in the development and maturation of the transitional BeAT state. WAT can also express a limited energy-wasting metabolic fatty acid cycle, albeit via a different biochemical mechanism and independent of the actions of the UCP1 protein of BAT, but which likely results in a substantially lesser magnitude of heat generation than can occur in BAT.[20] Pharmacologic agents that bypass the sympathetic neuroendocrine activation of BAT-mediated thermogenesis including caffeine and ephedrine have also been demonstrated to enhance and prolong parameters of nonshivering thermogenesis in both lean and obese rats, suggesting that while the fundamental elements of mitochondrial heat generation remain potentially operable despite impairments in β3-adrenergenic mediated pathways, but that the metabolic activities of other biochemical pathways in non-BAT or BeAT somatic tissues may also independently contribute to the net thermogenic responses of an organism.[3,6,13]

Insulin resistance often develops in obesity

Adiposity has long been associated with the progressive development of insulin resistance in man and animals at least in part via hyperinsulinemia and hyperamylinemia, and a consequent decreased sensitivity to the actions of circulating insulin availability in addition to plasma insulin concentrations. This is associated with increases in insulin secretion in a counter-regulatory loop and together with glucocorticoids implicates the cooperation and impaired participation of intracellular GLUT-4 transporters from the endoplasmic reticulum to the plasma membrane, where they can effect an efficient process of cellular glucose uptake.[10,22,23] Actions of glucocorticoid hormones may also add to the impaired GLUT4 transporter mechanism, further complicating the insulin actions that normally modulate glucose uptake in peripheral tissues.[24] Thus, the dysregulation of the GLUT4 transporter system in association with hyperinsulinemia may impair the glucose uptake in addition to the optimal thermogenic capacity of BAT and likely BeAT cells.[10,11] The decreased cellular capacity to effect efficient glucose uptake and subsequent cellular oxidation contributes to a decreased plasma membrane receptor sensitivity to insulin in many tissues, and in the development of insulin resistance in skeletal muscle and white adipose tissues.[22] Thus, the functional capacity for metabolic energy expenditure in response to alterations in diet and environment diminishes as the onset of obesity and insulin resistance progresses. Insulin resistance in association with dysregulation of glucocorticoid actions is also associated with decreased expression and intracellular translocation of the plasma membrane associated glucose transporter protein, GLUT4, from the endoplasmic reticulum to the plasma membrane, where it normally impacts on the efficiency of cellular glucose uptake from plasma origins.[23]

Expression of GLUT4 glucose transporters of skeletal muscle and adipose tissue become decreased in obesity

Most notable in the elements of disordered energy metabolism are the damaging effects in skeletal muscle and adipose tissue, two of the largest insulin dependent tissues, where the GLUT4 particles are an absolute essential intermediate in transitioning the cellular uptake of glucose in insulin-dependent tissues including both skeletal muscle and adipose tissue.[10,22–24] In addition, the expression of GLUT4 particles has been reported to become decreased by up to 40% in skeletal muscle of NIDDM-corpulent rats.[10] In humans, the continued derangements in insulin sensitivity and insulin action in peripheral tissues in the obese state also contribute to the development of syndrome X, also termed metabolic syndrome (MetS) and to

one of its most common sequalae, Type 2 diabetes (T2DM or non-insulin dependent diabetes mellitus, or NIDDM).[25] The combination of overweight and obese conditions in association with an NIDDM/T2DM milieu is now highly prevalent in Westernized populations and present a serious and costly global challenge to the capacity to deliver health care resources to the affected populations.[26]

Overnutrition and hyperphagia during postweaning and preadolescence growth contributes to hyperplasia and hypertrophy of BAT in rats

Early overnutrition results in hyperplasia and hypertrophy of BAT in lean and obese rats, but the intensity of the brown pigmentation in the BAT of the obese phenotype typically becomes less intense over time however in apparent parallel to the progression of hyperinsulinemia and insulin resistance commonly found in obese rodents and the obese of other mammalian species.[26] The epigenetic expression of an obese phenotype may also develop in the absence of NIDDM in some obesity-prone strains.[14,15,19] The increases in BAT mass in obese rats is disproportionate however to the magnitude of thermogenesis typically observed, in that resting and norepinephrine stimulated VO2 remain depressed among the obese phenotype in spite of the increases in BAT mass and cellularity.[14–19] Insulin resistance occurs in the obese phenotype of several obese rodent strains, including the Obese, non-diabetic Zucker fatty (*-fa*) rat and the LA/Ntul//*-cp* (Corpulent) rat and the NIDDM strains including the T2DM Wistar Fatty Rat, and the obese T2DM SHR/Ntul//*-cp* (Corpulent) rat, and the WKY/N-*cp* rats with the greatest magnitude of IR among the obese+diabetes prone strains.[14–19] Hyperplasia and hypertrophy of BAT occurs in both non-T2DN and in obese-T2DM /NIDDM strains and it becomes visibly evident by inspection during early postweaning and later growth, and by early adulthood hypertrophy of the BAT tissues became readily apparent due to the less intense brown coloration of the tissue noted during gross dissections. In such animals, it has been found in association with a less intense brown coloration as the adipocytes as they accumulate additional lipid reserves when insulin resistance occurs. The hypertrophied brown adipocytes retain fundamental morphometric characteristics typical of brown adipocytes including the multilocularity of small lipid droplets, and a centrally located nucleus. Administration of the β3 blocker propranolol also was found to result in an increases in locular diameters in histologic examinations taken from lean Sprague Dawley rats, but in that study the expansion of the BAT mass and cellularity did not result in adipocyte hypertrophy or significant 'unbrowning' of the brown adipocytes, perhaps to the shorter duration of the β-blockade treatment in combination with the genetically lean phenotype of the animals and protection from cold exposure or experimental over nutrition during housing conditions.[12]

Resting metabolic rates are typically lower and plasma insulin concentrations greater in the obese than the lean phenotype

The observation of decreases in RMR in association with insulin resistance among the obese phenotype of the obese rat strains despite having significant increases in IBAT Mass and cellularity is suggestive of impaired activation of non-shivering thermogenesis in those animals. In contrast, in genetically lean café-fed Sprague Dawley rats, IR was not observed and RMR and IBAT mass and cellularity were increased following a café regimen. Comparing the two variables in obese strains yielded a correlation coefficient r^2 of 1.0, suggestive of a link between the two parameters. Bukowiecki et al[10,11] observed decreased norepinephrine stimulated thermogenesis in isolated brown adipocytes obtained from Insulin resistant obese-NIDDM SHR/Ntul//*-cp* rats and concluded that insulin sensitivity was an essential element in expression of BAT thermogenesis. Glucose uptake contributes to the thermic responses in IBAT and other insulin dependent tissues and is likely an essential significant contributor to the decreases in RMR characteristic of and commonly observed among obese rodent strains.[10,11] Circulating plasma concentrations of triiodothyronine (T3) also contributes to an optimal thermogenic response in rats, and along with RMR are also commonly decreased among the obese phenotype of epigenetically obesity-prone strains.[14–19] Café' feeding regimes in both lean and obese rats results in increases in BAT mass, plasma T3 concentrations, Vanilmandelic acid (VMA) excretion, RMR, and norepinephrine stimulated VO2, while pharmacologic sympathomimetic blockade via α-methylparatyrosine results in decreases in VMA and the magnitude of the sympathetic component of the thermogenic responses.[26–28]

Discussion

The observation of a decreased intensity of robust brown coloration in IBAT depots in combination with insulin resistance as it occurs in multiple obese rodent strains is consistent with a link between hyperinsulinemias-associated insulin resistance and the 'unbrowning' or beigeing of brown adipose tissue with a likely onset early in the postweaning lifespan of the obese animals. In lean animals when offered a highly palatable café diet regimen from weaning or thereafter, RMR, plasma T3 concentrations and IBAT mass and cellularity also became significantly increased, but the insulin resistance and the 'unbrowning' effect noted among obese littermate animals was not observed, suggestive of thermogenically active IBAT in the lean animals in response to the café' overnutrition regimen offered during their postweaning development. The genetically obese animals of the strains cited reported typically demonstrate hyperphagia in the early postweaning growth phase, which may be the likely trigger for the BAT hyperplasia observed. Insulin is a well-documented lipogenic hormone in adipose tissues, where it can facilitate the both *de novo* biosynthesis and cellular uptake of preformed triglycerides, while suppressing both lipolysis and the glucose-dependent elements of the thermogenic response, the combined effects thereby contributing to increased lipid accretion of both white and brown adipocytes. While an undetermined proportion of the decreased brown coloration may be due to infiltration of white adipocyte types in the IBAT mass, the greater lipid content and locule diameters of the brown adipocytes indicate that those cells also play a role in the unbrowning effect. In one study, the lipid content of the IBAT mass and cellularity of the obese phenotype was found to be 1.5-fold greater than occurred in similarly fed lean littermates, while the capacity for nonshivering thermogenesis was significantly decreased, signaling insulin actions as one of several likely possibilities to account for the increased lipid content and decreased brown coloration of the brown adipocytes in concert with the decreased capacity for BAT thermogenesis. The peptide hormone amylin is co-secreted with insulin, and in lean rats acts to aid in satiety responses by slowing the rate of gastric emptying by impinging on amylin receptors in the antrum of the stomach.[29] Obese LA/N-cp and SHR/B-cp rats also develop hyperamylinemia and amylin resistance in concert and accelerated gastric emptying, which likely contributes to the chronic hyperphagia of the obese phenotype.

In lean animals, overfeeding via the café regimen has been shown to increase both sympathetic and thyroidal activity, both of which contribute proportionately to the thermogenic responses.[27–29] At the age of weaning, there is little difference in the body weights and only minimal differences in the adiposity of lean and obese phenotypes, but the hyperphagia common to the obese phenotypes noted above has been observed during early postweaning growth, at an age during post-weaning, prepubertal development where the partial thermogenic responses to exogenous norepinephrine were still apparent.[14,30] At later

ages, the thermogenic responses to diet, norepinephrine and acute cold exposure become progressively decreased in the obese phenotypes.[31,33] Frontini et al have reported that pink adipocytes conveying the thermoregulatory protein UCP1 were observed in omental tissue from human adults with pheochromocytoma, suggesting that the differentiation of brown adipocytes may have been induced by the chronically elevated catecholamine hormone secretions, similar to the hormonal profiles observed during the overfeeding regimens.[9,27,28] Embryologically, both white and brown adipose tissues are thought to be derived from the neural crest during early prenatal development, giving rise to mesodermal and ectodermal preadipocytes. The preadipocyte origin of the omental pink to brown adipocytes remains unclear however, as does the confirmed embryologic origins of the beige adipocytes.[32] The newfound pink to brown adipocytes is small in number however, compared to the mass, cellularity, and distribution of commonly observed primary BAT depots.[9]

Summary and Conclusions

The mechanism of transdifferention to form beige adipocytes remains unclear but appears to be associated with insulin resistance. Thus, the hormonal and metabolic stimulus that is linked to the proposed transdifferentiation of brown or white adipocytes to become beige adipocytes in obese and obese-NIDDM phenotypes, or the proliferation and differentiation of a third class of adipocytes that have now become known as beige, bright, or pink adipocytes remains unresolved. Beige and related descriptions of adipocytes that express the thermogenic UCP1 protein are presumed capable of exhibiting the expression of nonshivering thermogenesis in a manner similar to the known heat-generating functions and capacity of brown adipocytes, although the magnitude of the thermogenic responses of beige adipocytes and their insulin and adrenergic sensitivity remains unknown. The thermogenic potential of beige adipocytes may be less dramatic than that observed in normally active mature brown adipocytes due at least in part to their attenuation of insulin sensitivity, a likely decreased efficiency of GLUT4 transporters and cellular glucose uptake, and greater lipid accretion with an expansion of lipid locule sizes.[31] Lipid locule size in adipocytes is presumed to be a critical factor, as it changes the surface area to lipid content ratios, which may decrease or diminish the sensitivity of lipid mobilization due to the relative decrease in locular surface area to lipid ratio. The metabolic roles of accessory modulators of energy metabolism of the adipokines AMPK and sirtuins in beige adipocytes also remains speculative at best, while their participation in enhancing the metabolic processes of energy metabolism in lean tissues is acknowledged. The GLUT4 intracellular glucose transporter activity is essential in initiating the thermogenic responses in brown adipose tissue, but glucose uptake in BAT is decreased in the obese and obese+NIDDM phenotypes, suggestive of hyperinsulinemia--mediated dysregulation of the GLUT4 transporter mechanism in those animals, resulting in an impaired thermogenic response following perturbations in diet and environment.[31,34–36] The complex molecular mechanisms of expression of nonshivering thermogenesis in BAT, BeAT and other peripheral tissues represents an important aspect of energy homeostasis in response to alterations in diet and environment, and when impaired due to aberrations in hormonal and neuroendocrine factors likely contributes to disordered energy partition between lean and adipose tissues and over time to contribute to excess adiposity, obesity and their common pathophysiologic sequela.

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Conflicts of interest

We declare there are no conflicts of interest.

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