Original Article

MOLECULAR METABOLISM

Neuronal modulation of brown adipose activity through perturbation of white adipocyte lipogenesis

Adilson Guilherme [1,3], David J. Pedersen [1,3], Felipe Henriques [1], Alexander H. Bedard [1], Elizabeth Henchey [1], Mark Kelly [1], Kamal Rahmouni [2], Donald A. Morgan [2], Michael P. Czech [1,*]

ABSTRACT

Objective: Crosstalk between adipocytes and local neurons may be an important regulatory mechanism to control energy homeostasis. We previously reported that perturbation of adipocyte de novo lipogenesis (DNL) by deletion of fatty acid synthase (FASN) expands sympathetic neurons within white adipose tissue (WAT) and the appearance of "beige" adipocytes. Here we tested whether WAT DNL activity can also influence neuronal regulation and thermogenesis in brown adipose tissue (BAT).

Methods and results: Induced deletion of FASN in all adipocytes in mature mice (iAdFASNKO) enhanced sympathetic innervation and neuronal activity as well as UCP1 expression in both WAT and BAT. This increased sympathetic innervation could be observed at both 22 °C and 30 °C, indicating it is not a response to heat loss but rather adipocyte signaling. In contrast, selective ablation of FASN in brown adipocytes of mice (iUCP1FASNKO) failed to modulate sympathetic innervation and the thermogenic program in BAT. Surprisingly, DNL in brown adipocytes was also dispensable in maintaining euthermia when UCP1FASNKO mice were cold-exposed.

Conclusion: These results indicate that DNL in white adipocytes influences long distance signaling to BAT, which can modify BAT sympathetic innervation and expression of genes involved in thermogenesis.

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Keywords Adipocytes; Lipogenesis; Brown adipose tissue; Thermogenesis; Sensory nerve; Sympathetic nerve; SNS outflow

1. INTRODUCTION

Adipose tissue is profoundly expanded in obesity based on greatly increased storage of neutral lipids. This expansion is frequently associated with the onset of metabolic diseases such as type 2 diabetes [1–4]. Thus, understanding the functions and effects of adipose tissue on whole body metabolism is a major goal of this field. Animal studies have provided evidence that there are at least three different types of adipocytes, each presenting clear differences in their thermogenic potential and metabolic functions [5–8]. White adipocytes, for example, display a unilocular lipid droplet with relatively low thermogenic potential and account for the increased stores of fatty acids in the form of triglyceride in obesity. Hydrolysis of this triglyceride in fasting conditions provides fatty acid fuel for other tissues [9,10]. Brown adipocytes, on the other hand, contain multilocular lipid droplets, possess high thermogenic capacity, and constitutively express the mitochondrial uncoupling protein 1 (UCP1). These cells utilize fatty acids and glucose as fuel to generate heat and maintain body temperature during cold-induced adaptive thermogenesis [5,11–13]. White adipocytes can be converted into brown-like adipocytes, known as "brite" or "beige" adipocytes, which are also multilocular cells that express UCP1 and possess high thermogenic potential [5,14]. This browning of white adipose tissue (WAT) is driven by release of catecholamines and perhaps other factors from sympathetic neurons within WAT that occurs during cold stimulus. Catecholamines signal through the cAMP pathway to stimulate lipolysis and upregulate UCP1, as well as other mitochondrial proteins that mediate fatty acid oxidation and the "beige" adipocyte phenotype [5,14,15].

Conversely, multilocular brown adipocytes can be converted into white-like unilocular adipocytes with fewer mitochondria and lower oxidative capacity, UCP1 protein and thermogenic potential. This conversion of brown adipocytes into white-like adipocytes is known as whitening of brown adipose tissue (BAT) and occurs in situations such as at thermoneutral conditions (i.e., 30 °C), in which sympathetic innervation and activation within BAT is diminished. Altogether, these observations support the concept that under different physiological conditions, adipocytes can adjust their appearance and metabolic phenotype as needed [7,14,16]. They are capable of changing from

[1]Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, MA, 01605, USA [2]Department of Pharmacology, University of Iowa Carver College of Medicine, Iowa City, IA, 52242, USA

[3] Adilson Guilherme and David J Pedersen contributed equally to this work.

*Corresponding author. Program in Molecular Medicine, University of Massachusetts Medical School, 373 Plantation Street, Biotech 2, Suite 100, Worcester, MA, 01605, USA. Fax: +1 508 856 1617. E-mail: michael.czech@umassmed.edu (M.P. Czech).

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unilocular to multilocular, from anabolic to catabolic, and from storing calories as lipids to dissipating calories as heat. These interconversions are distinct from differentiation of progenitor cells within adipose tissues which can also give rise to white, beige, or brown adipocytes in response to sympathetic activity [14,17]. Together, the combination of interconversion and differentiation mechanisms control the overall profile of adipocyte types within the tissue and these events are regulated by local sympathetic tone.

Recent work in our laboratory revealed that de novo fatty acid synthesis (DNL) within adipocytes may be linked to control of localized sympathetic nerve activity in adipose tissues [3]. Thus, blockade of adipocyte DNL through selective inducible deletion of fatty acid synthase (*Fasn*) in adipocytes of mature mice enhanced sympathetic neuron innervation and browning of iWAT, along with an improvement of systemic glucose metabolism [3]. Therefore, adipocyte DNL perturbation not only modulates the thermogenic programming of iWAT but also whole-body metabolism. Adipocyte DNL may produce bioactive lipids that alter adipose tissue functions [18], energy balance, and systemic metabolism [3,19,20]. This pathway is also a rich source of metabolites such as acetyl-CoA, malonyl-CoA, palmitate and lipid products, all known to control diverse cellular processes [2,21,22]. These metabolites mediate such post-translational protein modifications as protein acetylation [23], malonylation [24], and palmitoylation [25], which are implicated in histone regulation, gene expression, and other cellular systems. Notably, the adipose DNL pathway is dynamically regulated by nutritional state, insulin, and obesity [2,3,26–28]. In turn, these DNL perturbations may modulate adipose sympathetic activity. Taken together, the data available suggest the hypothesis that signaling by one or more small molecule metabolites connected to the DNL pathway within adipocytes mediates a signaling pathway that confers paracrine regulation of localized neurons.

Interestingly, while inducible deletion of FASN in both WAT and BAT (using adiponectin-Cre mice crossed to flox/flox FASN mice, denoted iAdFASNKO mice) in animals housed at 22 °C caused expansion of sympathetic neurons and browning in WAT, no such effects were observed in BAT [3]. Furthermore, selective deletion of FASN in BAT (using UCP1-Cre mice crossed to flox/flox FASN mice, denoted UCP1-Cre-FASNKO) had no effect on either WAT or BAT in mice housed at 22 °C. This absence of effect of FASN deletion in BAT was somewhat surprising since BAT is highly innervated and responsive to catecholamines. Also, DNL in BAT is vanishingly low at thermoneutrality but highly upregulated in cold-adapted mice. Based on these considerations, the present studies were designed to further investigate the role of DNL in BAT under these more extreme temperature conditions. Remarkably, deletion of FASN selectively in BAT in the UCP1-Cre-FASNKO mice did not decrease survival of mice at 6 °C and had no detectable effect on UCP1 expression. Neither did selective FASN deletion in BAT have detectable effects on BAT function in mice housed at 30 °C. However, deletion of FASN in both WAT and BAT in iAdFASNKO mice at 30 °C did cause detectable sympathetic neuron expansion and increased UCP1 expression in BAT. These data indicate that DNL activity in white adipocytes within WAT can initiate long distance signaling to BAT that enhances its thermoregulation program.

2. METHODS

2.1. Animal studies

Mice were housed on a 12 h light/dark schedule and had free access to water and food, except when indicated. Mice with conditional $FASN^{flox/flox}$ alleles were generated as previously described [18]. To selectively delete FASN in adipocytes from adult mice, homozygous $FASN^{flox/flox}$ animals were crossed to Adiponectin-Cre-ERT2 mice to generate the TAM-inducible, adipocyte-specific FASN knockout mice referred to as iAdFASNKO [3]. At eight-weeks of age, both control $FASN^{flox/flox}$ and iAdFASNKO were treated via intraperitoneal (i.p.) injection once a day with 1 mg TAM dissolved in corn oil for 6 consecutive days. $FASN^{flox/flox}$ animals were also crossed with iUCP1-Cre-ERT2 mice (Jackson Laboratory) to generate the iUCP1-Cre-FASNKO that specifically delete FASN in brown adipocytes upon TAM treatment as described. The UCP1 KO mice were obtained from JAX Laboratory (Jackson Laboratory stock number 017476).

2.2. Mice housing at TN and CL316,243 treatment

For the effects of thermoneutrality on adipose tissue innervation and browning, 8-week-old control mice and iAdFASNKO mice were transferred from 22 °C (mild-cold) to 30 °C (thermoneutrality) and acclimated for 3 weeks. Then, control and iAdFASNKO mice were treated with tamoxifen (TAM) as previously described [3]. Two weeks post-TAM, mice were treated with 20 mg/kg of β3-agonist CL316,243 or PBS (one daily i.p. injection for 6 days). On the next day, adipose tissue was harvested and processed for histological and biochemical analyses.

2.3. Cold challenge

To assess cold tolerance, control and knockout mice were placed at 6 °C in the morning and provided free access to food and water. Rectal temperatures were recorded every 1 h for a total of 24 h.

2.4. Sympathetic nerve recordings

For determination of sympathetic nerve activities in adipose tissue from iAdFASNKO mice, the procedure was performed as follows. Each mouse was anesthetized with intraperitoneal administration of ketamine (91 mg/kg body weight) and xylazine (9.1 mg/kg body weight). Tracheotomy was performed by using PE-50 tubing to provide an unimpeded airway for the mouse to breathe O_2-enriched room air. Next, a micro-renathane tubing (MRE-40, Braintree Scientific) was inserted into the right jugular vein for infusion of the sustaining anesthetic agent: α-chloralose (initial dose: 12 mg/kg, then sustaining dose of 6 mg/kg/h). A second MRE- 40 catheter inserted into the left common carotid artery was connected to a Powerlab via a pressure transducer (BP-100; iWorx Systems, Inc.) for continuous measurement of arterial pressure and heart rate. Core body temperature was monitored through a rectal probe and maintained at 37.5 °C.

Next, each mouse underwent direct multifiber recording of sympathetic nerve activity (SNA) from a nerve innervating white adipose tissue (WAT) followed by SNA subserving brown adipose tissue (BAT). The nerve subserving the inguinal WAT was accessed through a small incision made on the right flank near the hindlimb. The sympathetic nerve fascicle was carefully isolated from surrounding connective tissues. A bipolar platinum-iridium electrode (40-gauge, A-M Systems) was suspended under the nerve and secured with silicone gel (Kwik-Cast, WPI). The electrode was attached to a high-impedance probe (HIP-511, Grass Instruments) and the nerve signal was filtered at a 100- and 1000°Hz cutoff with a Grass P5 AC pre-amplifier and amplified 10^5 times. The filtered and amplified nerve signal was routed to a speaker system and to an oscilloscope (model 54501A, Hewlett–Packard) to monitor the audio and visual quality of the SNA recording. The nerve signal was also directed to a resetting voltage integrator (model B600c, University of Iowa Bioengineering) and finally to a MacLab analog-digital converter (Model 8S, AD Instruments Castle Hill, New South Wales, Australia) containing software (MacLab Chart Pro; Version 7.0) that utilizes a cursor to analyze the total activity and to

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