Heart Metab. (2016) 69:34-37

Uncoupling proteins as mediators of mitochondrial metabolic rates

Gary D. Lopaschuk, PhD
Cardiovascular Research Centre, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Canada

Correspondence: Dr Gary Lopaschuk, 423 Heritage Medical Research Centre, University of Alberta, Edmonton, Canada, T6G 2S2
E-mail: gary.lopaschuk@ualberta.ca

Abstract

Mitochondrial oxidative phosphorylation has a key role in cellular energy production. However, proton leak across the mitochondrial membrane can short-circuit this energy production, resulting in an uncoupling of oxidative phosphorylation from adenosine triphosphate (ATP) production. Uncoupling protein 1 (UCP1) that is highly expressed in brown adipose tissue has a key role in this uncoupling process, resulting in thermogenesis. In other tissues, UCP2 (found in the central nervous system, macrophages, heart, and pancreatic β cells) and UCP3 (primarily expressed in skeletal muscle) also may increase mitochondrial membrane proton leak and regulate a number of processes that include decreasing reactive oxygen species generation, glucose sensitivity, insulin secretion, storage of fatty acids, and energy expenditure. As a result, UCPs have emerged as important mediators of energy metabolism and thermogenesis and may be involved in central nervous system control of food intake, and are thus potential targets for treating obesity and diabetes mellitus. ■ *Heart Metab*. 2016;69:34-37

Keywords: mitochondria; mitochondrial membrane potential; thermogenesis; uncoupling protein 1; uncoupling protein 3

Mitochondria have a key role in regulating energy metabolism in most cells. They are best known for their pivotal contribution to energy production (in the form of adenosine triphosphate [ATP]) through the process of oxidative phosphorylation. This occurs via the production of reduced cofactors from oxidizable substrates (such as fatty acids, carbohydrates, proteins, and ketones) that supply electrons for the mitochondrial electron transport chain (ETC). Electron transfer through the ETC results in the conversion of O_2 to H_2O, and the pumping of protons out of the mitochondrial matrix into the intermembrane space (*Figure 1*). This creates a proton motive force, the energy from which is used to synthesize ATP as protons flow back into the mitochondrial matrix. Any disruption of the proton gradient across the inner mitochondrial membrane will end up in a decrease in ATP production.[1] Instead, dissipation of the mitochondrial proton gradient will produce heat.

Uncoupling proteins (UCPs) are a family of mitochondrial anion carrier proteins that are differentially expressed in many tissues.[1] The first UCP identified, UCP1, is predominantly expressed in brown adipose tissue (BAT). As a UCP, it dissipates the mitochondrial proton gradient, and therefore has a thermogenic role (*Figure 1*). Additional UCPs subsequently identified include UCP2 and UCP3.[1,2] UCP3 is expressed mostly in skeletal muscle and heart, whereas UCP2 is expressed in a variety of tissues, including the brain. While UCP2 and UCP3 may also play a role in thermogenesis, these UCPs have also been implicated in

Abbreviations

BAT: brown adipose tissue; **ETC:** electron transport chain; **GSIS:** glucose-stimulated insulin secretion; **ROS:** reactive oxygen species; **UCP:** uncoupling protein

regulating fatty acid oxidation, reactive oxygen species (ROS) production, inflammation, neurodegenerative function, cell proliferation, and metabolic processes.[2-4]

Role of UCP1 in thermogenesis

BAT has a key role in regulating thermogenesis. UCP1 is highly expressed in BAT, which has a high capacity for mitochondrial respiration. Whereas mitochondrial respiration rates are much higher in BAT compared with white adipose tissue, actual ATP synthesis rates are not. This is likely due to the dissipation of the inner mitochondrial protein gradient by UCP1, resulting in the production of heat as opposed to ATP. While a role for BAT in regulating thermogenesis in rodents and human newborns has been recognized for decades, only recently has it been demonstrated that BAT in human adults may also play an important role in energy expenditure and thermogenesis.[5] Using techniques involving positron emission tomography combined with computed tomography, the presence of BAT in the subscapular and cervical regions of adult humans was recently identified.[6] The adipocytes in this BAT are enriched with UCP1, and cold exposure has been shown to increase BAT content.[7] Of importance, an inverse relationship between BAT content and obesity, insulin resistance, and diabetes has been shown.[8] This suggests that increasing BAT and UCP1 content may be an approach to treating obesity, insulin resistance, and diabetes by increasing energy expenditure and thermogenesis.

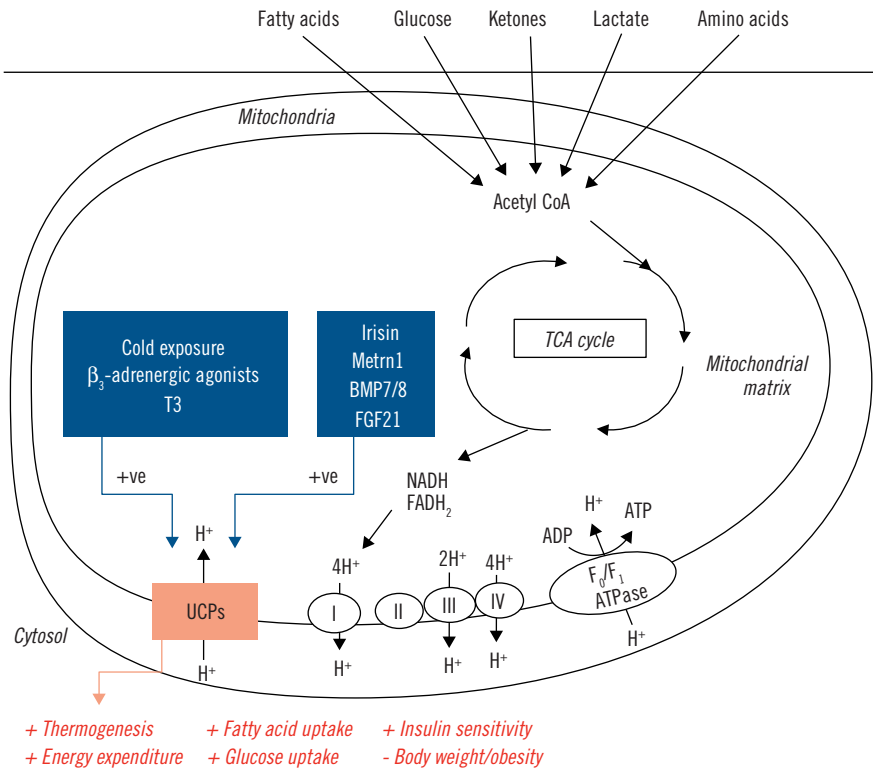

Fig. 1 *Role of uncoupling proteins in regulating mitochondrial metabolism. Mitochondria oxidize various carbon substrates to produce NADH and $FADH_2$. These reduced equivalents feed into the electron transport chain, resulting in the pumping of protons out of the mitochondrial matrix. The flow of protons back through the F_0/F_1 ATPase produces ATP. Uncoupling protons can dissipate the inner mitochondrial membrane proton gradient, thereby decreasing ATP production. The net effect of this uncoupling is to increase thermogenesis, energy expenditure, fatty acid uptake, glucose uptake, and insulin sensitivity. This can result in a decreased obesity and insulin resistance. A number of approaches can be used to increase expression of UCP levels, including cold exposure, β_3 agonism, T3, and peptides such as irisin, Metrn1, BMP7/8, and FGF21.*
Abbreviations: *+ve, positive; I, electron transport chain (ETC) complex I; II, ETC complex II; III, ETC complex III; IV, ETC complex IV; ADP, adenosine diphosphate; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase; BMP7/8, bone morphogenetic protein 7/8; CoA, coenzyme A; $FADH_2$, flavin adenine dinucleotide; FGF21, fibroblast growth factor 21; H^+, protons; Metrn1, meteorin-like protein; NADH, nicotinamide adenine dinucleotide; T3, triiodothyronine; TCA, tricarboxylic acid; UCPs, uncoupling proteins.*

BAT and UCP1 expression can be modified by a number of different mechanisms. Cold exposure is one approach to increase BAT and UCP1 expression,[6] which is inversely related to the body weight index. Cold exposure is also associated with an increase in β_3-adrenergic receptor activation of UCP1 transcription and translation,[9] thereby promoting thermogenesis. Thyroid hormones also promote UCP1 transcription and thermogenesis. Various peptides such as irisin, fibroblast growth factor 21 (FGF21), and bone morphogenetic protein 7/8 (BMP7/8) have also been proposed to promote the "beiging" of white adipose tissue, resulting in increased UCP1 expression.[10] Combined, this is thought to increase energy expenditure,

increase insulin sensitivity, increase glucose and fatty acid uptake, and thereby modulate obesity and diabetes severity.

Role of UCP2 and UCP3 in regulating energy metabolism in skeletal muscle and heart

The close homology of UCP2 and UCP3 to UCP1 resulted in these UCPs also being initially implicated as being primarily involved in thermogenesis.[2] UCP2 and UCP3 have a wider tissue distribution than UCP1, with UCP3 being primarily expressed in skeletal muscle. While these UCPs may have a role in thermogenesis, other functions are also evident. UCP3 has a key role in regulating mitochondrial fatty acid oxidation in heart and skeletal muscle,[11] as well as in preventing mitochondrial ROS production.[12] By reducing mitochondrial membrane potential, UCP3 may decrease ROS production by the ETC. Deletion of UCP3 has also been shown to decrease skeletal muscle fatty acid oxidation, possibly contributing to an increased accumulation and storage of fatty acids. UCP3 may also be a fatty acid anion carrier,[13] resulting in transport of fatty acids out of the matrix of the mitochondria. Combined, these actions of UCP3 (and possibly UCP2) suggest a protective role in preventing obesity and diabetes.

Role of UCP2 in other tissues

UCP2 has a wider tissue expression than UCP1 and UCP3, including the expression of UCP2 in the central nervous system, macrophages, and pancreatic β cells.[14] As such, UCP2 may have an important role in the regulation of food intake, energy expenditure, and glucose homeostasis.[3] In the arcuate nucleus of the hypothalamus, UCP2 is highly expressed, and has an important role in neuronal control of food intake. Activation of UCP2, such as by the orexogenic hormone ghrelin, promotes food intake and decreases energy expenditure.[15] These actions of UCP2 are thought to be mediated by a decrease in ROS production. Hypothalamic UCP2 also decreases glucose sensing in the hypothalamus, and increased UCP2 expression leads to a promotion of appetite and obesity.[16] In the pancreas, UCP2 is also involved in glucose-stimulated insulin secretion (GSIS).[17] Increased UCP2 expression is associated with a decrease in GSIS.

Modifying UCP2 as an approach to modifying energy metabolism

Stimulating UCP1 and UCP3 in BAT has the potential to increase thermogenesis and treat obesity and its associated diseases. The use of β_3-adrenergic agonists to increase UCPs and BAT is one such approach,[18] although this approach needs further study. While thyroid hormone treatment can increase UCP1 and BAT, such treatment is associated with serious adverse side effects, such as tachycardia. The use of irisin to increase BAT and UCP1 has also been proposed,[19] although the role of irisin in controlling BAT and UCP1 levels in humans has recently been questioned.[20] Other peptides such as BMP7/8, meteorin-like protein (Metrn1), and FGF21, as well as small-molecule activators of UCPs are also being tested, although the potential of these approaches to upregulate UCPs and BAT has yet to be established.

Conclusions

UCPs have a critical role in regulating energetics through their action of decreasing mitochondrial coupling and efficiency. In addition to their role in regulating thermogenesis, UCPs have potential roles in regulating mitochondrial oxidative metabolism, as well as central nervous system control of food intake and peripheral control of glucose metabolism. As a result, targeting UCPs is a potentially promising approach to treating obesity and diabetes-related disorders. ■

REFERENCES

1. Brand MD and Esteves TC. Physiological functions of the mitochondrial uncoupling proteins UCP2 and UCP3. *Cell Metab.* 2005;2:85-93.
2. Boss O, Samec S, Dulloo A, Sydoux J, Muzzin P, Giacoboino JP. Uncoupling protein-3, a new member of the mitochondrial carrier family with tissue-specific expression. *FEBS Lett.* 1997;408:39-42.
3. Toda C, Diano S. Mitochondrial UCP2 in the central regulation of metabolism. *Best Pract Res Clin Endocrinol Metab*. 2014;28;757-764
4. Diano S, Horvath T. Mitochondrial uncoupling protein 2 (UCP2) in glucose and lipid metabolism. *Trends Mol Med.* 2012;18;52-58.
5. Nedergaard J, Bengtsson T, Canoon B. Unexpected evidence for active brown adipose tissue in adult humans. *Am J Physiol Endocrinol Metab.* 2007;293:E444-E452.
6. Saito M, Okamatsu-Ogura Y, Matsushita M, et al. High incidence of metabolically active brown adipose tissue in healthy adult humans: effects of cold exposure and adiposity. *Diabetes.* 2009;58:1526-1531.
7. Yoneshiro T, Aita S, Matsushita M, et al. Recruited brown adi-

pose tissue as an antiobesity agent in humans. *J Clin Invest.* 2013;123:3404-3408.
8. Virtanen KA, Lidell ME, Orava J, et al. Functional brown adipose tissue in healthy adults. *N Engl J Med.* 2009;360:1518-1525.
9. Nakamura K, Morrison SF. Central efferent pathways mediating skin cooling-evoked sympathetic thermogenesis in brown adipose tissue. *Am J Physiol Regul Integr Comp Physiol.* 2007;292:R127-R136.
10. Busiello RA, Saverese S, Lombardi A. Mitochondrial uncoupling proteins and energy metabolism. *Front Physiol.* 2015;6:36.
11. Bezaire V, Seifert EL, Harper ME. Uncoupling protein-3: clues in an ongoing mitochondrial mystery. *FASEB J.* 2007;21:312-324.
12. Cioffi F, Senese R, de Lange P, Goglia F, Lanni A, Lombardi A. Uncoupling proteins: a complex journey to function discovery. *Biofactors.* 2009;35:417-428.
13. Goglia F, Skulachev VP. A function for novel uncoupling protein: anti-oxidant defense of mitochondrial matrix by translocating fatty acid peroxides from the inner to the outer membrane. *FASEB J.* 2003;17:1585-1591.
14. Richard D, Rivest R, Huang Q, et al. Distribution of the uncoupling protein 2 mRNA in the mouse brain. *J Comp Neurol.* 1998;397:549-560.
15. Andrews ZB, Liu ZW, Walllingford N, et al. UCP2 mediates ghrelin's action on NPY/AgRP neurons by lowering free radicals. *Nature.* 2008;454:846-851.
16. Kong D, Vong L, Parton LE, et al. Glucose stimulation of hypothalamic MCH neurons involves K_{ATP} channels, is modulated by UCP2, and regulates peripheral glucose homeostasis. *Cell Metab.* 2010;12:545-552.
17. Zhang CY, Baffy G, Perret P, et al. Uncoupling protein-2 negatively regulates insulin secretion and is a major link between obesity, β cell dysfunction, and type 2 diabetes. *Cell.* 2001;105:745-755.
18. Weyer C, Tataranni PA, Snitker S, Danforth E Jr, Ravussin E. Increase in insulin action and fat oxidation after treatment with CL 316,243, a highly selective β_3-adrenoceptor agonist in humans. *Diabetes.* 1998;47:1555-1561.
19. Boström P, Wu J, Jedrychowski MP, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature.* 2012;481:463-468.
20. Elsen M, Rachke S, Eckel J. Browning of white fat: does irisin play a role in humans? *J Endocrinol.* 2014;222:R25-R38.