The Liver as a Hub in Thermogenesis

Nada A. Abumrad[1,*]
[1]Medicine and Cell Biology and Physiology, Washington University School of Medicine, St. Louis, MO, USA
*Correspondence: nabumrad@wustl.edu
http://dx.doi.org/10.1016/j.cmet.2017.08.018

Manipulating thermogenesis could increase energy expenditure and improve metabolism. Brown fat is a major site of nonshivering thermogenesis, but other tissues, notably muscle and liver, can contribute to cold adaptation. In this issue, Simcox et al. (2017) demonstrate in cold-exposed mice that liver-generated acylcarnitines are required to fuel thermogenesis.

Maintaining body weight requires balancing the energy from food intake with energy expenditure. This balance is difficult to achieve nowadays as we lead a more sedentary lifestyle and reside in a near-constant postprandial state promoted by the excessive exposure to appealing food. As prevalence of obesity and its associated complications continues to increase, strategies advocating reducing energy intake and more physical activity have had limited success in achieving sustained weight loss. This has led to alternative approaches such as bariatric surgery, which remodels the gut to force a reduction of food intake. Another noninvasive strategy that has generated interest is to increase energy expenditure by enhancing adrenergic activation of nonshivering thermogenesis (NST). The major NST site is brown adipose tissue (BAT), which has a rich sympathetic innervation. The abundant mitochondria in BAT are rich in uncoupling protein 1 (UCP1) and dissipate the energy generated by oxidative phosphorylation as heat. Although BAT stores are limited in humans, in individuals exposed to cold temperatures, BAT volume was found to be associated with increases in lipolysis, triglyceride fatty acid (FA) turnover, and FA oxidation (Chondronikola et al., 2016). While NST increases total daily energy expenditure by 12%–20%, the increase contributed by BAT ranges between 2% and 17% (Tan et al., 2011), suggesting input from other tissues such as skeletal muscle and liver (van Marken Lichtenbelt and Schrauwen, 2011). However, the role and physiological impact of muscle or liver in cold adaptation remain unclear. In this issue of *Cell Metabolism*, Simcox et al. (2017) provide strong evidence for a critical role of the liver in providing acylcarnitines as a fuel for NST by BAT in cold-exposed mice.

In rodents, BAT is more abundant than in humans, and its activation by cold exposure contributes to whole-body lipid clearance and glycemic control. Although tissue crosstalk is a significant component in most aspects of energy metabolism, studies of thermogenic regulation in cold-exposed rodents have rarely considered potential contribution of organs other than BAT despite early suggestive evidence. For example, cold exposure in rats was shown to increase hepatic gluconeogenesis, total liver and mitochondrial mass, respiration capacity of hepatocytes, and liver temperature (Rolfe and Brown, 1997; Shiota et al., 1985; Stoner, 1973). Cold adaptation at the level of the liver could provide BAT with glucose and FAs from very low density lipoproteins (VLDLs) and perhaps contribute to heat generation (Stoner, 1973) (Figure 1).

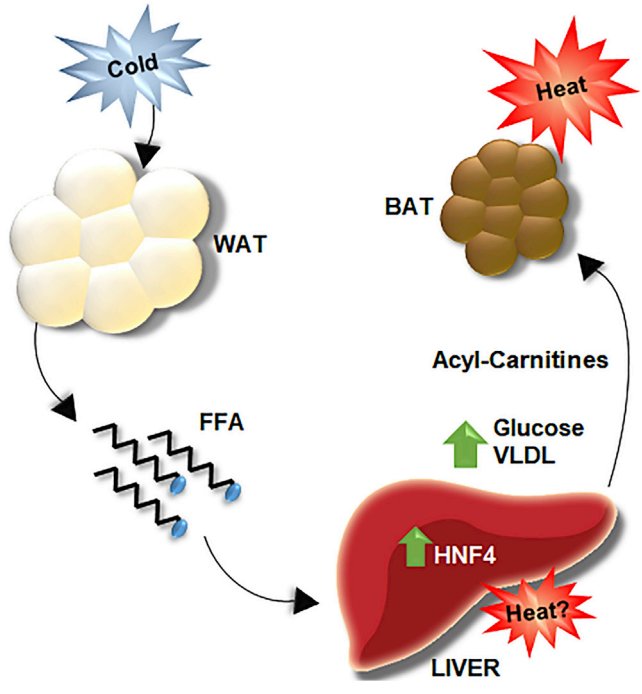

Figure 1. The Liver as a Thermogenic Hub
During cold exposure, FAs from hepatic VLDL are rapidly extracted by BAT. Adrenergic stimulation activates hepatic gluconeogenesis, providing glucose for BAT thermogenesis, and early evidence also suggests that the liver might contribute to heat generation in cold-exposed rodents. In this issue of *Cell Metabolism*, Simcox et al. (2017) show that FAs mobilized from cold stimulation of WAT activate HNFα in the liver, leading to increased FA oxidation and the production of acylcarnitines that serve to further fuel BAT metabolism and NST.

Using non-targeted metabolomics of plasma in cold-exposed mice, Simcox et al. (2017) identified acylcarnitines as a novel fuel for BAT thermogenesis. They showed that acylcarnitines are generated from enhanced hepatic FA oxidation in response to cold-induced FA release by white adipose tissue (WAT). The authors proposed that FAs activate the nuclear receptor HNF4α in the liver, which increases hepatic FA oxidation and results in release into the circulation of acylcarnitines that partition more to BAT and muscle and less to liver or WAT. The increase of acylcarnitine levels, together with induction of hepatic genes of acylcarnitine

metabolism, was diminished in mice with liver-specific deletion of *HNF4α* or *Cpt1a/b*. Similar findings were obtained with deletion of adipose triglyceride lipase (*ATGL*) in adipocytes, and cold intolerance was observed in all conditions. Simcox et al. (2017) speculated that during initial thermogenesis, CPT1 activity in BAT might be inhibited by high levels of cytoplasmic malonyl-CoA and acylcarnitine usage could facilitate the switch from glucose to more FA utilization. Although the quantitative contribution of acylcarnitines to BAT NST remains to be determined, the findings broaden our understanding of thermogenic regulation.

An important contribution of the study by Simcox et al. (2017) is its identification of the liver as a site crucial for cold adaptation and the emergence of the cold-exposed liver as a metabolic hub (Figure 1). It is well established that FAs from hepatic VLDL are rapidly extracted by BAT (Khedoe et al., 2015) and that cold-induced adrenergic stimulation of the liver provides glucose from activated gluconeogenesis (Shiota et al., 1985). We now learn that activation of hepatic HNF4α by cold-stimulated release of FAs from WAT is required to provide BAT with acylcarnitines. The findings suggest potential benefits in humans of manipulating the adaptive capacity of the liver or of providing the thermogenic fuel L-carnitine to increase energy expenditure. Indeed, a 12-week L-carnitine supplementation to healthy volunteers has been found to increase energy expenditure during low-intensity exercise, and it prevented fat mass gain from carbohydrate overfeeding (Stephens et al., 2013). Thus, L-carnitine might have beneficial effects on energy metabolism in humans similar to those reported by Simcox et al. (2017) in mice. However, L-carnitine is converted by gut microbiota to trimethylamine *N*-oxide (TMAO), which is associated with adverse cardiovascular outcomes, but a mechanistic understanding of this association and its relevance at L-carnitine levels used in health supplements is lacking (Zeisel and Warrier, 2017).

The inter-tissue regulation of thermogenesis highlighted by Simcox et al. (2017) suggests importance of further studies that assess the potential roles played by liver or muscle in humans. Provision by the liver of fuel in addition to its possible contribution to heat production (Stoner, 1973) could enhance thermogenesis during cold exposure. Skeletal muscle might also have a significant role in people where BAT stores are scarce. In mice in which 60% of BAT was surgically ablated, skeletal muscle was identified as an important NST site, capable of generating heat from sarcolipin-mediated uncoupling of the SERCA Ca^{2+} pump (Bal et al., 2012). Energy expenditure by liver and muscle in addition to that by BAT could potentially be manipulated to modulate and improve metabolism in obesity.

REFERENCES

Bal, N.C., Maurya, S.K., Sopariwala, D.H., Sahoo, S.K., Gupta, S.C., Shaikh, S.A., Pant, M., Rowland, L.A., Bombardier, E., Goonasekera, S.A., et al. (2012). Nat. Med. *18*, 1575–1579.

Chondronikola, M., Volpi, E., Børsheim, E., Porter, C., Saraf, M.K., Annamalai, P., Yfanti, C., Chao, T., Wong, D., Shinoda, K., et al. (2016). Cell Metab. *23*, 1200–1206.

Khedoe, P.P., Hoeke, G., Kooijman, S., Dijk, W., Buijs, J.T., Kersten, S., Havekes, L.M., Hiemstra, P.S., Berbée, J.F., Boon, M.R., and Rensen, P.C. (2015). J. Lipid Res. *56*, 51–59.

Rolfe, D.F., and Brown, G.C. (1997). Physiol. Rev. *77*, 731–758.

Shiota, M., Tanaka, T., and Sugano, T. (1985). Am. J. Physiol. *249*, E281–E286.

Simcox, J., Geoghegan, G., Maschek, J.A., Bensard, C.L., Pasquali, M., Miao, R., Lee, S., Jiang, L., Huck, I., Kershaw, E.E., et al. (2017). Cell Metab. *26*, this issue, 509–522.

Stephens, F.B., Wall, B.T., Marimuthu, K., Shannon, C.E., Constantin-Teodosiu, D., Macdonald, I.A., and Greenhaff, P.L. (2013). J. Physiol. *591*, 4655–4666.

Stoner, H.B. (1973). J. Physiol. *232*, 285–296.

Tan, C.Y., Ishikawa, K., Virtue, S., and Vidal-Puig, A. (2011). J. Diabetes Investig. *2*, 341–350.

van Marken Lichtenbelt, W.D., and Schrauwen, P. (2011). Am. J. Physiol. Regul. Integr. Comp. Physiol. *301*, R285–R296.

Zeisel, S.H., and Warrier, M. (2017). Annu. Rev. Nutr. Published online July 17, 2017. http://dx.doi.org/10.1146/annurev-nutr-071816-064732.