Laurent Vergnes[1] and Karen Reue[1,2,3]

Adaptive Thermogenesis in White Adipose Tissue: Is Lactate the New Brown(ing)?

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The prevalence of obesity and type 2 diabetes has become a major economic and medical burden worldwide. Increased food intake and reduced physical activity have contributed to a shift in energy balance, resulting in excess energy storage in the white adipose tissue (WAT) depots. In contrast to WAT, brown adipose tissue (BAT) converts excess energy into heat via uncoupled respiration, which is dependent, in part, on expression by brown adipocytes of the uncoupling protein 1 (UCP1). Thus, an attractive strategy to reduce energy storage is to increase the levels of brown adipocyte activity.

Although WAT does not normally express UCP1 or exhibit uncoupled respiration, WAT depots are capable of great plasticity. In response to cold exposure or genetic modifications, mouse white adipocytes can be induced to exhibit brown adipocyte–like character. These cells are known as "brite" (for brown-in-white) or "beige" adipocytes. Factors that are known to increase "browning" in mouse WAT include the transcription factors PGC1α, PRDM16, and members of the PPAR family (1). Additionally, treatment with metabolites, such as bile acids, prostaglandins, and retinoids, promotes the browning of WAT (2). Beige adipocytes express UCP1 and accumulate multilocular lipid droplets similar to genuine brown adipocytes but exhibit a gene expression signature that is distinct from classic brown adipocytes (3,4). The presence of UCP1 and increased mitochondrial activity in beige adipocytes has suggested enhanced "browning" within WAT and may be an important adjunct to classic BAT in vivo.

In this issue of *Diabetes*, Carrière et al. (5) identified a fundamental cellular metabolite—lactate—as a new WAT browning factor. Lactate is well-known as the product of anaerobic glycolysis and is generated in high amounts in skeletal muscle during periods of intense activity. Resulting lactate may be "recycled" by the liver (which converts lactate to glucose) and also can serve as an oxidative substrate for the heart (6). This lactate transport between cells is mediated by monocarboxylate transporters (MCT) 1 to 4 (7). Within cells, high levels of lactate can be oxidized in the mitochondria by the mitochondrial lactate oxidation complex (6,8).

Carrière et al. determined that mice exposed to cold for 24 h to trigger thermogenesis exhibit increased circulating lactate levels and *Mct1* (lactate importer) gene expression in BAT and subcutaneous WAT. Furthermore, lactate treatment of murine and human white adipocytes substantially increased *Ucp1* expression (30-fold in vitro and 2.5-fold in vivo), as well as the expression of fatty acid oxidation and mitochondrial genes. In lactate-treated mice, UCP1-positive cells within WAT depots had multilocular lipid droplets, reminiscent of brown adipocytes. The effects of lactate on *Ucp1* induction required an intact PPARγ signaling machinery, although lactate appears not to act as a direct PPARγ activator.

How do elevated lactate levels influence UCP1 levels in white adipocytes? To investigate this, Carrière et al. ruled out involvement of the lactate-responsive G-protein–coupled receptor GPR81 (9) but demonstrated that modulation of MCT lactate transporter activity altered *Ucp1* expression. Pharmacological inhibition of the MCT1 lactate importer abrogated the lactate induction of *Ucp1* expression, whereas reducing levels of the MCT4 lactate exporter led to a several-fold increase in *Ucp1* mRNA levels. These results suggest that intracellular lactate levels influence *Ucp1* expression and browning in white adipocytes.

An expected consequence of the metabolism of high lactate levels within cells is the production of pyruvate and NADH (Fig. 1). By this means, lactate concentrations may influence the NADH-to-NAD^+ ratio, and hence redox

[1]Department of Human Genetics, University of California, Los Angeles, Los Angeles, CA
[2]Department of Medicine, David Geffen School of Medicine at UCLA, University of California, Los Angeles, Los Angeles, CA
[3]Molecular Biology Institute, University of California, Los Angeles, Los Angeles, CA

Corresponding author: Laurent Vergnes, lvergnes@ucla.edu.

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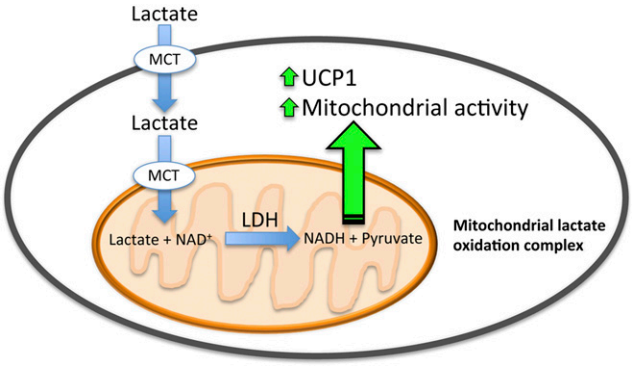

Figure 1—Model for lactate-mediated browning of white adipocytes. Lactate uptake into the cell and mitochondria occurs through MCT proteins. Lactate oxidation in the mitochondria produces NADH, which alters NADH-to-NAD^+ ratio and cellular redox state. Cells increase mitochondrial oxidative activity through the mitochondrial lactate oxidation complex and induce *Ucp1* expression, perhaps as an adaptive response to prevent oxidative damage. LDH, lactate dehydrogenase.

state, of the adipocyte. If so, then modulation of the redox state by an independent means should produce the same effect on *Ucp1* expression as observed with lactate treatment. To test this, Carrière et al. treated white adipocytes with another monocarboxylate, β-hydroxybutyrate, which led to similar increases in NADH-to-NAD^+ ratio as lactate treatment and induced *Ucp1* mRNA levels up to 25-fold. Conversely, treatment of adipocytes with pyruvate or acetoacetate (to reverse the effects on the NADH-to-NAD^+ equilibrium elicited by lactate or β-hydroxybutyrate) negated *Ucp1* induction. The authors hypothesized that UCP1 induction constitutes an adaptive mechanism to alleviate redox stress by lactate-induced NADH accumulation. Consistent with this possibility, the addition of a mitochondrial uncoupler counteracted the lactate effect on *Ucp1* expression. Thus, a potential role for lactate-induced *Ucp1* expression may be to reduce oxidative stress that could occur in the presence of high lactate levels. It has previously been suggested that modulation of *Ucp1* levels may serve as a mechanism to reduce reactive oxygen species levels in situations of oxidative stress, although this hypothesis remains controversial (10,11).

Hashimoto et al. (12) observed that lactate affects mitochondrial gene expression in muscle-derived L6 cells, and it would be interesting to know whether an uncoupling state was also present. The fact that lactate promotes fatty acid oxidation, mitochondrial activity, and *Ucp1* expression raises the possibility that the activation of a master regulator of mitochondrial function occurs. Transcription factors such as PPARs and PGC1α are good candidates. PPARα was ruled out in the current study, but PPARγ and PPARδ could potentially be involved in the browning activation. Interestingly, PPARγ activation was required in vivo to observe a lactate-induced increase in *Ucp1* expression, so the role of PPARγ warrants further investigation. PGC1α also promotes fatty acid oxidation and mitochondrial respiration and is regulated both transcriptionally and posttranscriptionally. It is noteworthy that PPARs and PGC1α regulate *Ucp1* promoter activity.

In conclusion, this discovery by Carrière et al. (5) highlights the role of lactate in energy metabolism and reveals an effect on browning in WAT. Further work is needed to fully understand the mechanism, to determine whether lactate-induced uncoupling is specific to WAT, and to understand the physiological role. Studies in obese mice may help to further determine whether this browning mechanism plays a significant role in energy expenditure.

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