Title
Lactate as a major myokine and exerkine

Journal
Nature Reviews Endocrinology, 18(11)

ISSN
1759-5029

Authors
Brooks, George A
Osmond, Adam D
Arevalo, Jose A
et al.

Publication Date
2022-11-01

DOI
10.1038/s41574-022-00724-0

Peer reviewed

Lactate as a major myokine and exerkine

George A. Brooks, Adam D. Osmond, Jose A. Arevalo, Casey C. Curl, Justin J. Duong, Michael A. Horning, Diana D. Moreno Santillan and Robert G. Leija

The roles of exerkines, factors released from tissues during exercise, in promoting health and longevity were recently addressed in the Review by Chow and colleagues (Chow, L. S. et al. Exerkines in health, resilience and disease. *Nat. Rev. Endocrinol.* **18**, 273–289 (2022)[1]). However, their timely Review did not adequately describe the major and diverse roles of lactate in regulating metabolism and physiology. Here, we highlight important functions of lactate as an exerkine.

Intermediary metabolism

The inevitable product of glycolysis under fully aerobic conditions is lactate[2]. It is exchanged among intracellular compartments, it is exported from sites of production, it fluxes within the muscular interstitium, and it is distributed to organs and tissues via the systemic circulation. Hence, lactate is a myokine and an exerkine with major signalling attributes.

Redox biology

Glycolysis affects the ratio of lactate to pyruvate, which rises two orders of magnitude or more during exercise. The resulting ratio of NAD^+ to NADH, and hence redox change, affects metabolic regulation at the sites of lactate production and disposal. Redox changes have numerous effects on metabolic regulation, including activation of sirtuin 1 and sirtuin 3 (REF.[2]).

Allosteric binding and inhibition of lipolysis

Activation of the lactate receptor HCAR1 inhibits lipolysis in adipose tissues of rodents, and in humans, lactataemia inhibits lipolysis during exercise and following carbohydrate consumption. Hence, in humans, plasma concentrations of free fatty acids fall during hard exercise (here meaning exercise that results in lactataemia) because of the inhibition of lipolysis by lactate in the circulation[2].

Mitochondrial energy substrate utilization

Muscle glycolysis results in the production of malonyl-CoA, which inhibits carnitine palmitoyl transferase 1 (CPT1). Moreover, lactate downregulates CPT2 (REF.[2]); hence lactate limits mitochondrial fatty acid uptake and oxidation.

Mitochondrial biogenesis

Together, AMPK, reactive oxygen species, sirtuin 1 and sirtuin 3 have important roles in activating PGC1α, the master regulator of mitochondrial biogenesis[3]. However, upstream of these factors is lactate[4].

Vascular, cardiac and pulmonary regulation

The angiogenesis that occurs with exercise training is mediated by factors such as vascular endothelial growth factor, which is upregulated by lactate[5]. During exercise, lactate has a dominant role in fuelling the heart[2]. Importantly, in muscle lactate activates the metaboreflex, thereby participating in regulation of cardiac output during exercise[2]. And, as seen in mice, lactate upregulates breathing by stimulating the carotid body olfactory receptor OLFR78 (REF.[6]).

Genomics

Histone lactylation affects the expression of many genes[7], including those of skeletal muscle and skeletal muscle proteins[4].

Lactate and the brain

In the brain, lactate is an energy source and is involved in glutamatergic signalling[2]. Further, in humans the lactataemia of exercise[8], or exogenous lactate vascular infusion[9], stimulates release of BDNF in the brain, which is important for neurogenesis and cognitive function.

Ghrelin, hunger and appetite

Hunger is regulated in the arcuate nucleus of the hypothalamus. Among the signals affecting the arcuate nucleus is ghrelin; its secretion is attenuated by the effect of lactate on the growth hormone secretagogue receptor 1α in the gastrointestinal tract. In rodents and humans, lactataemia inhibits hunger via an effect on lactate-reduced ghrelin signalling[10].

Conclusions

Identifying the roles of myokines and exerkines in promoting metabolic and physiological health is important. Therefore, we offer this commentary as an addition to complement the Review of Chow et al.[1]. Lactate is the greatest myokine in terms of concentration and dynamic range, and the most diverse in terms of metabolic and physiological regulation.

There is a reply to this letter by Chow, L.S. et al. *Nat. Rev. Endocrinol.* https://doi.org/10.1038/s41574-022-00726-y (2022).

George A. Brooks ✉, Adam D. Osmond, Jose A. Arevalo, Casey C. Curl, Justin J. Duong, Michael A. Horning, Diana D. Moreno Santillan and Robert G. Leija
Exercise Physiology Laboratory, Department of Integrative Biology, University of California, Berkeley, CA, USA.
✉*e-mail: gbrooks@berkeley.edu*

https://doi.org/10.1038/s41574-022-00724-0

1. Chow, L. S. et al. Exerkines in health, resilience and disease. *Nat. Rev. Endocrinol.* **18**, 273–289 (2022).
2. Brooks, G. A. The Science and Translation of Lactate Shuttle Theory. *Cell Metab.* **27**, 757–785 (2018).
3. Wu, Z. et al. Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell* **98**, 115–124 (1999).
4. Hashimoto, T., Hussien, R., Oommen, S., Gohil, K. & Brooks, G. A. Lactate sensitive transcription factor network in L6 cells: activation of MCT1 and mitochondrial biogenesis. *FASEB J.* **21**, 2602–2612 (2007).
5. Hunt, T. K., Aslam, R., Hussain, Z. & Beckert, S. Lactate, with oxygen, incites angiogenesis. *Adv. Exp. Med. Biol.* **614**, 73–80 (2008).
6. Chang, A. J., Ortega, F. E., Riegler, J., Madison, D. V. & Krasnow, M. A. Oxygen regulation of breathing through an olfactory receptor activated by lactate. *Nature* **527**, 240–244 (2015).
7. Zhang, D. et al. Metabolic regulation of gene expression by histone lactylation. *Nature* **574**, 575–580 (2019).
8. Hashimoto, T. et al. Maintained exercise-enhanced brain executive function related to cerebral lactate metabolism in men. *FASEB J.* **32**, 1417–1427 (2018).
9. Schiffer, T. et al. Lactate infusion at rest increases BDNF blood concentration in humans. *Neurosci. Lett.* **488**, 234–237 (2011).
10. Torres-Fuentes, C. et al. Short-chain fatty acids and microbiota metabolites attenuate ghrelin receptor signalling. *FASEB J.* **33**, 13546–13559 (2019).

Competing interests
The authors declare no competing interests.