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Is Lactate a Signaling Molecule (A 'Lactormone')?

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ABSTRACT

Lactate was for a long time considered just a metabolic waste. It was then associated with exercise-induced fatigue and muscle soreness. In recent decades this paradigm has changed and lactate has become a central figure in energy metabolism. More recently, advances in molecular biology and endocrinology studies have shown that lactate also acts to modulate various cellular functions and structures, including gene transcription. These findings allow including lactate as a hormone according to current definitions.

Keywords: Lactate; Hormone; Plasticity; Lactylation; Histones; Epigenetic

Introduction

What does a molecule need to be classified as a hormone? If we adopt the definition of the Biology Dictionary [1] "a hormone is a biological compound used by multicellular organisms to organize, coordinate, and control the functions of their cells and tissues. These chemicals can control everything from metabolism to behavior". It can be argued that this definition is somewhat vague (Stárka [2]), however, it is how it has been used in recent decades. For more than a century, lactate has been considered

(1) A metabolic residue of glycolysis,

(2) A product of anaerobic disease, and

(3) A cause of fatigue in physical exercise and harmful effects (Ferguson, et al. [3]).

Since Archibald V Hill (1886-1977) demonstrated the correlation between discontinuation of incremental exercise (stress testing in which exercise intensity progressively increases) and high lactate levels, the (spurious) lactate-fatigue association has served as a paradigm in the sports sciences (Brooks, [4]).

Discussion

With the advancement of the understanding of metabolism and molecular biology in general, it can be demonstrated that lactate is not a waste product, but an important energy substrate in many tissues (point 1) (Daw, et al. [5]). Which is produced in significant quantities under conditions where the presence of oxygen is plentiful (point 2) (Bertocci, et al. [6]) and has no cause-and-effect relationship with fatigue or other harmful effects during or after physical exercise (point 3) (Bergman, et al. [7]). However, the aim of this assay is to show that the study of the role of lactate only as an energy substrate is limited. Lactate, in addition to its historically described properties, is also a molecule that regulates cellular functions in a variety of other ways (Li, et al. [8]), including plasticity in many of them. One of the mechanisms discovered was signaling through a G protein-coupled receptor 81 (GPR81) (Brown, et al. [9]). A specific example was demonstrated by (Liu, et al. [10]) in which lactate inhibits lipolysis in fat cells through the activation of a GPR81 receptor that acts as a lactate sensor, whose response is to inhibit lipolysis. The class of G-ligand receptor (GPR) proteins present in cells plays an important regulatory role in metabolism. Lactate-specific GPR81 is abundant on the surface of cells in adipose tissue, liver, skeletal muscle, and nervous tissue (Brown, et al. [9]). The GPR81 receptor, when bound to lactate, modulates energy metabolism (inhibiting or activating enzymes), reduces

lipolysis, increases neuroprotection and modifies the action of macrophages and other cells of the immune system (Madaan, et al. [11-14]). On the other hand, cellular plasticity is derived from the ability to respond and adapt to the environment by regulating gene expression.

In the case of macrophage polarization, macrophage activation for an inflammatory phenotype is driven by increased glycolysis, but energy metabolism is relevant for oxidative phosphorylation and β-oxidation in homeostatic macrophages (Chen, et al. [15]). This polarization stems from the regulation of gene expression by lactylation of lysine residues on histones (Zhang, et al. [16]). The addition of lactate in addition to phosphate, methyl, and acetyl tags to histones is an epigenetic way by which the genome and intermediary metabolism are regulated. The increase in histone lactylation in cell lines parallels the increase in cellular lactate levels. Based on these studies (Chen, et al [15,16], a novel modification of histones with special modulation of lactate is established and suggests that lactylation of lysine (Kla) is regulated by changes in glucose metabolic dynamics. As mentioned above, during inflammatory processes, the polarization of M1 macrophages occurs, making the function of these macrophages similar to M2. Macrophage polarization occurs by increasing the rate of glycolytic reactions, consequently increasing lactate production. Higher concentrations of lactate, and its consequent acetylation, contribute to the formation of Kla histones, whose role is to maintain homeostasis by stimulating the translation of genes into mRNA (Zhang, et al. [16]). The function of Kla histones is to make M1 macrophages return to their homeostatic stages, decreasing their inflammatory action, thus functioning as M2 macrophages-like (from the activation of genes other than acetylated histones). In this way, histones Kla synchronize with lactate concentrations and modulate the homeostatic status of the organism.

Conclusion

In this way, we can present lactate not only as a metabolic product but as a signaling molecule. These mechanisms briefly presented allow the inclusion of lactate also as a hormone according to current definitions.

Conflicts of Interest

The author certifies that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

References

1. Biology dictionary.
2. Stárka L, Dušková M (2020) What is a hormone? Physiological research 69(Suppl 2): S183-S185.
3. Ferguson B S, Rogatzki M J, Goodwin M L, Kane D A, Rightmire Z, et al. (2018). Lactate metabolism: historical context, prior misinterpretations, and current understanding. European journal of applied physiology 118(4): 691-728.
4. Brooks GA (2009) Cell-cell and intracellular lactate shuttles. The Journal of physiology 587(Pt 23): 5591-5600.
5. Daw C C, Ramachandran K, Enslow B T, Maity S, Bursic B, et al. (2020). Lactate Elicits ER-Mitochondrial Mg2+ Dynamics to Integrate Cellular Metabolism. Cell 183(2): 474-489.e17.
6. Bertocci L A, Lujan B F (1999). Incorporation and utilization of [3-13C] lactate and [1,2-13C] acetate by rat skeletal muscle. Journal of applied physiology 86(6): 2077-2089.
7. Bergman B C, Wolfel E E, Butterfield G E, Lopaschuk G D, Casazza G A, et al. (1999) Active muscle and whole-body lactate kinetics after endurance training in men. Journal of applied physiology 87(5): 1684-1696.
8. Li X, Yang Y, Zhang B, Lin X, Fu X, et al. (2022). Lactate metabolism in human health and disease. Signal transduction and targeted therapy 7(1): 305.
9. Brown T P, Ganapathy V (2020) Lactate/GPR81 signaling and proton motive force in cancer: Role in angiogenesis, immune escape, nutrition, and Warburg phenomenon. Pharmacology & therapeutics 206: 107451.
10. Liu C, Wu J, Zhu J, Kuei C, Yu J, et al. (2009) Lactate inhibits lipolysis in fat cells through activation of an orphan G-protein-coupled receptor, GPR81. The Journal of biological chemistry 284(5): 2811-2822.
11. Madaan A, Nadeau-Vallée M, Rivera J C, Obari D, Hou X, et al. (2017). Lactate produced during labor modulates uterine inflammation via GPR81 (HCA1). American journal of obstetrics and gynecology 216(1): 60.e1-60.e17.
12. Sun Z, Han Y, Song S, Chen T, Han Y, et al. (2019). Activation of GPR81 by lactate inhibits oscillatory shear stress-induced endothelial inflammation by activating the expression of KLF2. IUBMB life 71(12): 2010-2019.
13. Wu G, Dai Y, Yan Y, Zheng X, Zhang H, et al. (2022). The lactate receptor GPR81 mediates hepatic lipid metabolism and the therapeutic effect of metformin on experimental NAFLDs. European journal of pharmacology 924: 174959.
14. Laroche S, Stil A, Germain P, Cherif H, Chemtob S, et al. (2021). Participation of L-Lactate and Its Receptor HCAR1/GPR81 in Neurovisual Development. Cells 10(7): 1640.
15. Chen A N, Luo Y, Yang Y H, Fu J T, Geng X M, et al. (2021). Lactylation, a Novel Metabolic Reprogramming Code: Current Status and Prospects. Frontiers in immunology 12: 688910.
16. Zhang D, Tang Z, Huang H, Zhou G, Cui C, et al. (2019). Metabolic regulation of gene expression by histone lactylation. Nature 574(7779): 575-580.
17. Troutman T D, Hu W, Fulenchek S, Yamazaki T, Kurosaki T, et al. (2012). Role for B-cell adapter for PI3K (BCAP) as a signaling adapter linking Toll-like receptors (TLRs) to serine/threonine kinases PI3K/Akt. Proceedings of the National Academy of Sciences of the United States of America 109(1): 273-278.
18. Matsumura T, Oyama M, Kozuka-Hata H, Ishikawa K, Inoue T, et al. (2010). Identification of BCAP-(L) as a negative regulator of the TLR signaling-induced production of IL-6 and IL-10 in macrophages by tyrosine phosphoproteomics. Biochemical and biophysical research communications 400(2): 265-270.

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