LETTER TO THE EDITOR

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Lactate, not Lactic Acid, is Produced by Cellular Cytosolic Energy Catabolism

In the November issue of *Physiology*, Sun et al. (12) published a review describing the role of lactate as a multi-tissue autocrine regulatory molecule influencing multiple cellular and systemic physiological functions. Such functions included transmembrane H^+ transport, enzyme regulation, downregulation of multi-tissue lipolysis, anti-inflammation, improved immune tolerance, stimulation of long-term memory, and improved wound healing including ischemic tissue injury, while deleteriously supporting cancer growth and metastasis. We acknowledge the detail and quality of the presentation of the contemporary evidence for the involvement of lactate in the regulation of these processes. Nevertheless, it is unfortunate that the authors referred to cellular lactate production as lactic acid, repeatedly associated cellular lactic acid production as a cause of acidosis, and used the term lactic acid within their title. Such repeated use, totaling 50 occurrences of "lactic acid" throughout the entirety of the manuscript, severely detracts from the scientitic quality of their work.

As we will explain, there is no such entity as lactic acid in any living cell or physiological system. Indeed, it is impossible, based on the fundamental laws of physics that underpin the disciplines of organic chemistry, metabolic biochemistry, acid-base chemistry, and physiology, for lactic acid to be produced or present in living systems where cellular and tissue pH is regulated to be between 6.0 and 7.45. Thus Sun et al. (12) repeatedly errored with every mention of the term "lactic acid" within their manuscript, reinforcing the false knowledge of an outdated construct (non-empirically supported concept assumed to be fact). Such content detracted from the quality content for what their article actually focused on: the roles of lactate in metabolic regulation across multiple tissues and regulatory systems.

We will explain the organic chemistry and metabolic biochemistry of metabolite ionization and cation association/dissociation, the H^+ exchange during glycolysis, and the lactate dehydrogenase reaction to document the reality of cellular lactate production and the separate, although coincident, development of tissue and systemic metabolic acidosis. Such commentary was presented in detail by the lead author in 2004 (9), and, for brevity, pertinent figures and tables from this prior publication will be referred to and not repeated here. It is also worth emphasizing that commentary on the false construct of a lactic acidosis dates back to the 1970s (2, 4, 14, 15), and, as such, this argument is not new, although it is bolstered by decades of advancements in our understanding of organic and computational chemistry understanding since this time.

Importance of the History of Lactic Acid and Lactate

The brief history of lactic acid discovery described by Sun et al. (12) was largely accurate. However, a key omission was the fact that the very early discovery and isolation of lactic acid (1780), followed by subsequent refinements in purification and optical isomer detection (to 1869), both occurred 100–150 years before the understanding of acid-base chemistry and physiology. For example, the work and achievements of Haldane in acid-base chemistry did not occur until the 1940s (11), but the impact of World War II (distractions in scientific achievement and dissemination) delayed the understanding and application of this work to chemistry and physiology into the 1960s, and perhaps with regard to lactic acid, to current time. These time discrepancies and delays functioned to indirectly reinforce an assumed cause-effect connection between tissue lactate production and acidosis. However, a fundamental error in science is to assume correlation is cause-and-effect, and despite more than 70 years since the work of Haldane, the error of a lactic acid-derived metabolic acidosis (lactic acidosis) continues to be reported in the basic and applied biochemical, physiological, and clinical sciences.

Organic Chemistry of ATP Hydrolysis, Ionization, Glycolysis, and Lactate Production

Sun et al. (12) explained cellular lactate production as the conversion of pyruvate to lactic acid (not true), that this was a reaction within glycolysis (not true, although there is debate as to what constitutes the true end of glycolysis, pyruvate or lactate), and that because of the low pK_a of lactic acid (pK = 3.86) (true) [although the NIST (8) reference resource has this as pK = 3.67], there was an immediate and near-complete dissociation of lactic acid to lactate and a proton (H^+) (p. 453) (not true because in living systems there is no lactic acid to begin with).

ATP hydrolysis is a chemical reaction, which in living systems is mostly coupled to another reaction via an enzyme, resulting in a phosphate transfer from ATP to another substrate, forming a product with an added phosphate group. During this process, water is involved in the chemical reaction (hence the term hydrolysis), providing a hydroxyl group for addition to the cleaved phosphate group, and releasing a H^+ (see Ref. 9, Fig. 10, p. R509). Such H^+ release is never purely unitary, since the proportion (hence a fractional numeric representation) of ATP molecules that release H^+ is dependent on the localized pH and additional concentrations of competing cations such as potassium (K^+), sodium (Na^+), calcium (Ca^{2+}), and magnesium (Mg^{2+}). Similarly, for any molecule, when exposed to physiological pH that can release H^+ during ionization or because of being ionized associate with a cation, there will be a fractional (~) H^+ exchange that either releases or consumes ~H^+. For these reasons, we present metabolites in their main cation-associated form and for this reaction (*Eq. 1*) with a variable coefficient (~) associated with the released H^+. Furthermore, such an organic and acid-base chemistry fact reveals that the H^+ activity during cellular metabolism is not a dependent entity, as proposed by Stewart (10), but a process