Where does the lactate come from? A rare cause of reversible inhibition of mitochondrial respiration

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See related research by Protti et al., http://ccforum.com/content/14/1/R22

Abstract

Biguanide poisoning is associated with lactic acidosis. The exact mechanism of biguanide-induced lactic acidosis is not well understood. In the previous issue of Critical Care, Protti and colleagues demonstrated that biguanide-induced lactic acidosis may be due in part to a reversible inhibition of mitochondrial respiration. Thus, in the absence of an antidote, increased drug elimination through dialysis is logical.

The problem encountered with sepsis is more complex, although at least two situations are usually accompanied with hypoxia-associated hyperlactatemia. The first situation is septic shock with catecholamine-resistant cardiocirculatory failure, especially in situations of low cardiac output. The second circumstance is septic shock pre-emptively observed prior to volumetric expansion, as illustrated in the study of Rivers and colleagues in which hyperlactatemia was associated with signs of poor oxygen delivery [6]. These two situations are nonetheless close to low-output states.

By definition, hypoxia blocks mitochondrial oxidative phosphorylation [7], thereby inhibiting ATP synthesis and reoxidation of NADH. This leads to a decrease in the ATP/ADP ratio and an increase in the NADH/NAD ratio. A decrease in the ATP/ADP ratio induces both an accumulation of pyruvate, which cannot be utilized by way of phosphofructokinase stimulation, and a decrease in pyruvate utilization by inhibiting pyruvate carboxylase, which converts pyruvate into oxaloacetate. An increased NADH/NAD ratio also increases pyruvate by inhibiting pyruvate dehydrogenase, and hence its conversion into acetylcoenzyme A.

Consequently, the increase in lactate production in an anaerobic setting is the result of an accumulation of pyruvate that is converted into lactate, which stems from alterations in the redox potential. This conversion allows for the regeneration of some NAD+, enabling the production of ATP by anaerobic glycolysis – although the process is clearly less efficient from an energy standpoint (two ATP molecules produced versus 36). It is important to consider that the modification of the redox potential induced by an increase in the NADH/NAD ratio activates the transformation of pyruvate into lactate, and consequently increases the lactate/pyruvate ratio [8].

All in all, anaerobic energy metabolism is characterized by hyperlactatemia associated with an elevated lactate/pyruvate ratio, greater glucose utilization and low energy production [9].

The exact mechanism of biguanide-induced lactic acidosis is not well understood. This infrequent complication is associated with high mortality. Biguanide drugs
mainly exert their therapeutic effect by impairing hepatocyte mitochondrial respiration [10]. Recent observations have suggested that metformin, similarly to phenformin, may also inhibit mitochondrial respiration in tissues other than the liver [11].

In the previous issue of Critical Care, using indirect measurement of oxygen consumption, Protti and colleagues found that body oxygen consumption was markedly depressed despite a normal cardiac index evoking an inhibition of mitochondrial respiration [1]. Unfortunately, arterial lactate/pyruvate and acetoacetate/β-hydroxybutyrate ratios, as reflections of cytoplasmic and mitochondrial redox states, were unavailable. Interestingly, there was a clear correlation between drug clearance, correction of lactic acidosis and normalization of oxygen consumption. Clearly, the inhibition of mitochondrial respiration is not the unique mechanism involved in biguanide-induced lactic acidosis, since pure inhibition of mitochondrial function during cyanide poisoning is associated with death in the absence of antidote [12], and, similarly, since lactic acidosis associated with the use of nucleoside analogue reverse transcriptase inhibitors is due to an impairment of mitochondrial oxidative phosphorylation and is also associated with high mortality despite prompt therapy [13].

To conclude, when looking at the literature, pure hypoxic causes of lactic acidosis are relatively rare in clinical practice. In the case of biguanide-induced lactic acidosis, the fact that the inhibition of mitochondrial respiration is reversible should encourage the early use of dialysis [14] in order to accelerate drug elimination.

Abbreviations
NAD, nicotinamide adenine dinucleotid; NADH, reduced form of NAD.

Competing interests
The authors declare that they have no competing interests.

References

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