Lactate: A key metabolite in the intercellular metabolic interplay.

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Commentary

Lactate: a key metabolite in the intercellular metabolic interplay

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Abstract

Most physicians involved in intensive care consider lactate solely as a deleterious metabolite, responsible for high morbidity and bad prognosis in severe patients. For the physiologist, however, lactate is a key metabolite, alternatively produced or consumed. Many studies in the literature have infused animals or humans with exogenous lactate, demonstrating its safety and usefulness, but the bad reputation of lactate is still widespread. The metabolic meaning of glucose–lactate cycling exceeds its initial role described by Cori and Cori. According to recent works concerning lactate, it can be predicted that a new role as a therapeutic agent will arise for this metabolite.

Keywords brain, Cori cycle, exogenous substrate, kidney, lung, metabolic shuttle

A satellite meeting on lactate was organized during the 8th International Symposium on Shock and Critical Care, August 2001, Bali, Indonesia. The aim of the symposium was to highlight lactate from a different standpoint to the classical view of being a prognosis marker, often solely considered by many physicians involved in intensive care medicine. The review papers on lactate in the present issue discuss four of the lectures presented in this symposium by Cano [1], Bellomo [2], Iscra *et al.* [3], and Schurr [4].

Lactic acid, which is mostly present in biological fluids as its dissociated cationic form (lactate$^-$), is widely distributed among the pathways involved in the intermediary metabolism of living systems. While, from the physiologist point of view, it is one of the most crucial intermediates of carbohydrate and nonessential amino acid metabolisms, for most physicians it is merely considered as a marker of bad prognosis significantly related to a high mortality rate in acutely ill patients [5–7]. Although several works in the literature have shown the safety, and sometimes the usefulness, of administration of exogenous lactate [8–13], it is very often considered a highly 'toxic' compound. Even in sport physiology, the 'lactic threshold' as a marker demonstrating a sharp switch from aerobic to anaerobic metabolism is very popular, and lactate increase is often believed to be the cause of side effects observed after exhausting exercise [14,15].

When recently explaining the design of studies where patients received a bolus of exogenous sodium–high lactate to one of our friends, a very experienced physician from the intensive care unit, his instant reaction was 'in my institution, I would never get an agreement from the ethical committee for such a study involving exogenous sodium–high lactate infusion'. Of course, it is easy to demonstrate that high lactate infusion is actually safe, even in very sick patients [9]; it is indeed a metabolite like glucose, amino acids, fatty acids or ketones. Nevertheless, lactate is often intuitively considered as 'the devil in metabolism' by many physicians or scientists, this probably resulting from confusion between cause and consequence.

Lactate is alternatively consumed and produced in the body, as is the case for every intermediate involved through the vast circuit of the intercellular and interorgan metabolic interplay. This notion is actually the basis of the concept of '*milieu intérieur*' as described by the French physiologist Claude Bernard more than a century ago. Hence, lactate can be considered as a wastage product when released from one cell, but it becomes a very useful substrate when taken up by another cell [16,17]. In fact, the extent of lactate turnover *in vivo* in humans is of a similar order of magnitude to that of glucose, alanine or glutamine (i.e. it has one of the highest recycling rates in the intermediary metabolism). The main question therefore remains as to understanding precisely the

role of lactate as one of the main actors of the energetic homeostasis in both physiological and pathological conditions [18].

Lactate is actually a metabolic '*cul de sac*' because it is metabolized by one single enzyme, lactate dehydrogenase. But, since the first description many decades ago by Cori of interorgan glucose–lactate recycling, it is clear that lactate has a real physiological meaning. The role of energetic shuttle is classically considered between organs responsible for a net lactate release and the liver. Every organ is able to release lactate because all cells contain the different enzymes allowing the conversion of glucose into lactate; pancreatic islets are an exception since they are deficient in lactate dehydrogenase [19]. However quantitatively, muscle and red blood cells are probably the main tissues in physiological conditions, but other organs (such as the lung, for instance [3]) could be of importance in pathological states. The liver is often regarded as the main organ for lactate disposal because of its prominent role in gluconeogenesis. The kidney, although recognized for a long time also as a gluconeogenic organ, has probably been underestimated [1]. Moreover, it was recently shown that even during the anhepatic phase occurring during liver transplantation, plasma lactate was maintained at a higher but constant value, indicating that the liver is not mandatory for lactate clearance [20].

Lactate also appears to possess some specific effects besides its role in redox and carbon shuttle between organs involved in the global energy metabolism. Different interesting works have emphasized a role of lactate in the brain as a protective substrate not only in animal studies [4,21–23], but also in humans [10,13]. The description of coordinated glucose and lactate metabolisms between neurons and astrocytes in relation to neuron excitation has revealed a new and fascinating side of brain lactate metabolism [24,25]. Concerning heart metabolism and cardiovascular function, it has recently been shown that lactate improves cardiac function in a model of hemorrhagic shock [26]. Also, sodium–lactate infusion in humans increases cardiac output not only in postoperative patients [12], but also in cardiogenic shock [9].

In conclusion, this satellite meeting led to the feeling that our view of lactate will probably change in the near future. Lactate, instead of being only considered as a marker of severity in critically ill patients, might be a metabolite used as a substrate for specific purposes.

Competing interests

None declared.

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