Commentary

Lactate: a key metabolite in the intercellular metabolic interplay

Xavier M Leverve[1] and Iqbal Mustafa[1,2]

[1]Laboratoire de Bioénergétique Fondamentale et Appliquée, INSERM E0221 & Université Joseph Fourier, Grenoble, France
[2]Intensive Care Unit, Harapan Kita National Cardiovascular Center, Jakarta, Indonesia

Correspondence: Xavier Leverve, xavier.leverve@ujf-grenoble.fr

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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.

References

1. Cano N: **Bench-to-bedside review: Glucose production from the kidney.** *Critical Care* 2002, **6**:317-321.
2. Bellomo R: **Bench-to-bedside review: Lactate and the kidney.** *Critical Care* 2002, **6**:322-326.
3. Iscra F, Gullo A, Biolo G: **Bench-to-bedside review: Lactate and the lung.** *Crit Care* 2002, **6**:327-329.
4. Schurr A: **Bench-to-bedside review: A possible resolution of the glucose paradox of cerebral ischemia.** *Crit Care* 2002, **6**: 330-334.
5. Bakker J, Coffernils M, Leon M, Gris P, Vincent JL: **Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock.** *Chest* 1991, **99**:956-962.
6. Marecaux G, Pinsky M, Dupont E, Kahn R, Vincent J: **Blood lactate levels are better prognostic indicators than TNF and IL-6 levels in patients with septic shock.** *Intensive Care Med* 1996, **22**:404-408.
7. Bellomo R: **Lactic acidosis, sepsis, and anaerobic glycolysis: a continuing controversy.** *Crit Care Shock* 1998, **1**:102-108.
8. Chiolero R, Tappy L, Gillet M, Revelly JP, Roth H, Cayeux C, Schneiter P, Leverve X: **Effect of major hepatectomy on glucose and lactate metabolism.** *Ann Surg* 1999, **229**:505-513.
9. Chiolero RL, Revelly JP, Leverve X, Gersbach P, Cayeux MC, Berger MM, Tappy L: **Effects of cardiogenic shock on lactate and glucose metabolism after heart surgery.** *Crit Care Med* 2000, **28**:3784-3791.
10. King P, Kong MF, Parkin H, MacDonald IA, Barber C, Tattersall RB: **Intravenous lactate prevents cerebral dysfunction during hypoglycaemia in insulin-dependent diabetes mellitus.** *Clin Sci (Colch)* 1998, **94**:157-163.
11. Levraut J, Ciebiera JP, Chave S, Rabary O, Jambou P, Carles M, Grimaud D: **Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction.** *Am J Respir Crit Care Med* 1998, **157(4 part 1)**:1021-1026.
12. Mustafa I, Leverve X: **Metabolic and hemodynamic effects of hypertonic solutions: sodium lactate versus sodium chloride infusion in postoperative patients.** *Shock* 2002, in press.
13. Veneman T, Mitrakou A, Mokan M, Cryer P, Gerich J: **Effect of hyperketonemia and hyperlacticacidemia on symptoms, cognitive dysfunction, and counterregulatory hormone responses during hypoglycemia in normal humans.** *Diabetes* 1994, **43**: 1311-1317.
14. Miles MP, Clarkson PM: **Exercise-induced muscle pain, soreness, and cramps.** *J Sports Med Phys Fitness* 1994, **34**:203-216.
15. Spurway NC: **Aerobic exercise, anaerobic exercise and the lactate threshold.** *Br Med Bull* 1992, **48**:569-591.
16. Leverve X, Mustafa I, Péronnet F: **Pivotal role of lactate in aerobic metabolism.** In *Yearbook of Intensive Care and Emergency Medicine*. Edited by Vincent J. Berlin: Springer-Verlag; 1998:588-596.
17. Leverve XM: **Energy metabolism in critically ill patients: lactate is a major oxidizable substrate.** *Curr Opin Clin Nutr Metab Care* 1999, **2**:165-169.
18. Leverve X, Mustafa I: **From cellular pathways to in vivo considerations (in healthy subject and critically ill patients).** *Crit Care Shock* 1998, **1**:89-95.
19. Sekine N, Cirulli V, Regazzi R, Brown LJ, Gine E, Tamarit-Rodriguez J, Girotti M, Marie S, MacDonald MJ, Wollheim CB: **Low lactate dehydrogenase and high mitochondrial glycerol phosphate dehydrogenase in pancreatic beta-cells. Potential role in nutrient sensing.** *J Biol Chem* 1994, **269**:4895-4902.
20. Joseph SE, Heaton N, Potter D, Pernet A, Umpleby MA, Amiel SA: **Renal glucose production compensates for the liver during the anhepatic phase of liver transplantation.** *Diabetes* 2000, **49**:450-456.
21. Schurr A, Payne RS, Miller JJ, Rigor BM: **Brain lactate is an obligatory aerobic energy substrate for functional recovery after hypoxia: further in vitro validation.** *J Neurochem* 1997, **69**:423-426.
22. Schurr A, Payne RS, Miller JJ, Rigor BM: **Brain lactate, not glucose, fuels the recovery of synaptic function from hypoxia upon reoxygenation: an in vitro study.** *Brain Res* 1997, **744**: 105-111.
23. Schurr A, Rigor BM: **Brain anaerobic lactate production: a suicide note or a survival kit?** *Dev Neurosci* 1998, **20**:348-357.
24. Magistretti PJ, Pellerin L: **Metabolic coupling during activation. A cellular view.** *Adv Exp Med Biol* 1997, **413**:161-166.
25. Tascopoulos M, Magistretti PJ: **Metabolic coupling between glia and neurons.** *J Neurosci* 1996, **16**:877-885.

26. Kline JA, Thornton LR, Lopaschuk GD, Barbee RW, Watts JA: **Lactate improves cardiac efficiency after hemorrhagic shock.** *Shock* 2000, **14**:215-221.