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In Translation

Potential Role of NHE1 (Sodium-Hydrogen Exchanger 1) in the Cellular Dysfunction of Lactic Acidosis: Implications for Treatment

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The development of lactic acidosis in seriously ill patients often is accompanied by impairment in organ function and increased morbidity and mortality. Although hypoxia per se is a crucial factor, detrimental effects also have been attributed to the metabolic acidosis that accompanies lactic acidosis. As a result, ancillary treatment of lactic acidosis has included base administration to improve the metabolic acidosis. However, treatment with base does not necessarily result in improved cellular function or clinical outcome. Recent research suggests that lactic acidosis can be associated with activation of the sodium-hydrogen exchanger 1 (NHE1), potentially giving rise to deleterious increases in cellular sodium and calcium ion concentrations, which can cause cardiac stunning and arrhythmias, extend cerebral damage, and worsen kidney function. Also, experimental studies in animals suggest that selective inhibition of this transporter might decrease the severity of cellular injury in the heart, brain, and kidney. These findings suggest that administration of selective inhibitors of NHE1 to patients with severe lactic acidosis might be beneficial. This article reviews experimental evidence of the role of NHE1 in the pathogenesis of cellular dysfunction with lactic acidosis and potential benefits of treatment with selective inhibitors of this transporter.
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BACKGROUND

Lactic acidosis associated with ischemia or sepsis is associated with mortality that can be as high as 60%-80%.[1] Although tissue hypoxia per se undoubtedly has a major role in producing cellular dysfunction and injury, the accompanying metabolic acidosis also has been considered a potentially important contributory factor.[1,2] In this regard, experimental studies have shown that lactic acidosis produced by lactic acid infusion to dogs, an experimental model in which tissue hypoxia is absent, decreases cardiac contractility and cardiac output.[3,4] This decrease in cardiac output can contribute to the development of hypotension and a further decrease in tissue oxygen delivery,[5] factors contributing to a poor clinical outcome.

Abnormalities in cellular function with lactic acidosis have been presumed to be caused in part by abnormalities in the function of important cellular proteins, including those of important enzymes, arising from a decrease in intracellular pH.[6] Importantly, the decrease in intracellular pH occurring with lactic acidosis will activate the hydrogen ion (proton) and base transporters in the cell that are designed to return cellular pH to its baseline, including sodium-hydrogen exchanger 1 (NHE1; encoded by the *SLC9A1* gene).[7] Activation of this sodium-dependent proton exchanger might not be without cost, but in fact potentially can contribute to cellular dysfunction and injury. Furthermore, experimental studies in animals[8,9] have shown that inhibition of this transporter can attenuate cellular dysfunction and injury, observations suggesting that administration of selective inhibitors of NHE1 might be a useful ancillary treatment of lactic acidosis in humans.

CASE VIGNETTE

An 85-year-old man was brought to the emergency department by his family, who found him in his room unresponsive. He had a long history of atherosclerotic disease, with a previous myocardial infarction and cerebrovascular accident. He also had a history of type 2 diabetes mellitus, for which he was receiving the oral hypoglycemic agent tolbutamide. He generally had blood pressure of 140/80 mm Hg without receiving antihypertensive medications.

On physical examination, temperature was 103°C, blood pressure was 78/37 mm Hg supine, and heart rate was 110 beats/min and regular. Examination of the lungs and heart showed negative findings. The patient was poorly responsive, but neurologic exami-

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nation otherwise showed normal reflexes and no evidence of focal findings.

Blood acid-base parameters on admission showed the presence of severe lactic acidosis with the following values: blood pH, 7.0; serum sodium, 135 mEq/L (135 mmol/L); serum chloride, 100 mEq/L (100 mmol/L); serum bicarbonate, 5 mEq/L (5 mmol/L); $Paco_2$, 25 mm Hg; and serum lactate, 17 mEq/L (1.89 mmol/L). The patient was treated with large quantities of sodium bicarbonate, which increased serum bicarbonate concentrations to 8-9 mEq/L (8-9 mmol/L), but failed to stabilize blood pressure. Despite administration of vasopressor agents and other supportive measures, the patient died 8 hours after admission. Although not proved, lactic acidosis was presumed to be caused by the combination of sepsis and hypotension.

The failure of sodium bicarbonate administration to substantially alter the course of this patient and others with severe lactic acidosis has caused clinicians to explore other potential mechanisms of cellular injury in an attempt to reveal other targets for treatment.

PATHOGENESIS

Lactic acidosis causes a decrease in both extra- and intracellular pH. Alterations in the pH of both compartments can contribute to cellular dysfunction and injury. A decrease in extracellular pH can cause cellular dysfunction by decreasing intracellular pH; however, in vitro studies suggest that it also can affect cellular function by other mechanisms. These include decreasing insulin or catecholamine binding to their cognate receptors[10,11] and enhancing the opening of potassium channels in the heart and blood vessels, predisposing to the development of arrhythmias and hypotension.[12,13] Furthermore, when central nervous system ischemia is present, calcium-permeable acid-sensing ion channels are activated, contributing to tissue damage.[14] An increase in extracellular pH, if of sufficient magnitude, therefore will improve insulin and catecholamine binding to their receptors, decrease the activity of these channels, and potentially decrease cellular dysfunction and injury.

The decrease in intracellular pH also theoretically can produce cellular dysfunction and injury by decreasing adenosine triphosphate (ATP) production because of inhibition of pH-dependent enzymes, such as phosphofructokinase, in several tissues[15,16]; impairing calcium binding to cardiac troponin in the heart[17]; and possibly stimulation of apoptosis predisposing to cellular death in various tissues.[18] The latter action could be mediated directly by cellular pH or in part by stimulation of the mitogen-activated protein kinase pathway.[19] The extent of cellular injury or dysfunction related to these mechanisms theoretically will be a function of the severity of intracellular acidosis. This can be profound in the presence of ischemia and hypoxia with intracellular pH decreasing to as low as 6.5,[20] although it might be less severe with other causes of lactic acidosis. Because of the importance of intracellular pH to cellular function, the decrease in pH activates several mechanisms designed to return pH to baseline.[6]

One of the mechanisms used by the cell to stabilize pH is activation of sodium-dependent proton-base transporters, particularly NHE1. Recent studies of myocardial and other cells suggest that activation of this and other sodium-dependent transporters might secondarily increase intracellular calcium ion levels and contribute to cellular dysfunction and injury.[21]

RECENT ADVANCES

Cellular pH Regulation

Baseline intracellular pH in most cells varies from 7.1-7.3.[6] Stabilization of intracellular pH around this range is necessary for optimal function of most enzymes, optimal DNA and RNA synthesis, and function of several other proteins.[6,7] Cellular pH homeostasis after a cellular acid load is accomplished by binding of protons by buffers in the cell as the first line of defense.[22] In addition, the decrease in intracellular pH will activate cellular proton-base transporters designed to return pH to baseline.

In the myocardium, a critical organ affecting the clinical response to lactic acidosis, transporters are located in the sarcolemma of myocytes and include NHE1; the sodium-bicarbonate cotransporter (NBC) isoforms NBCe1, NBCe2, and NBCn1 (encoded by the *SLC4A4*, *SLC4A5*, and *SLC4A7*); a proton-translocating adenosine triphosphatase pump (H^+-ATPase)[23]; and MCT, the monocarboxylate transporter, which mediates transport of protons and the lactate anion.[24,25] Quantitative studies of proton base flux with acid loading of myocytes have shown that the proton extrusion rate through NHE1 is almost 7-fold greater than base entry through the NBC (40 vs ~6 mM/min). The combined action of both sodium-dependent proton-base transporters accounts for removal of 60% of the acid load. Residual protons are removed through the MCTs.

The Cellular Ionic Environment

Activation of sodium-dependent proton-base transporters not only increases proton exit or base entry, but also augments sodium ion entry into the cell. If the increased sodium influx cannot be removed through the ATPase sodium-potassium pump (Na^+-K^+-ATPase) because the quantity of sodium entering the cell is extremely large or activity of this enzyme is constrained by decreased ATP concentrations due to hypoxia,[20] an increase in intracellular sodium concentration will result. The increase in cellular sodium can slow the activity or reverse the sodium-calcium exchanger, causing an increase in cellular calcium.[24,26] The increase in intracellular sodium can cause cell swelling, whereas the increase in calcium can