Ortho-hydroxy phenyl boronic acids rescue mice from lactic acidosis by increasing lactate metabolism

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Statement of Purpose: There is a great need for the development of strategies that can reduce blood lactate levels in patients suffering from acidosis. The current therapy for lactic acidosis is bicarbonate treatment, which is ineffective because of its toxic side effects and because it only normalizes blood pH, and does not address the numerous pathologies that elevated lactate itself triggers, such as altering blood pressure, triggering apoptosis and decreasing intracellular pH levels. Removing lactate from the blood during acidosis is challenging because it is membrane impermeable and can only be metabolized intracellularly via conversion to pyruvate. Although, lactate can be transported intracellularly by the monocarboxylate transporter (MCT), its capacity for removing extracellular lactate is limited because it uses the hydronium ion as a counter ion, causing cellular acidification. In addition the MCT transporter is predominantly expressed in the liver and kidneys, which are frequently dysfunctional in acidosis patients, and therefore acidosis patients cannot metabolize elevated blood lactate via MCT driven transport.

Methods: The ability of ABA to bind lactate was determined by boron NMR. Jurkat T-cells were utilized to verify if the ABA-lactate complex is cell membrane permeable. C57Bl6/j mice were utilized to determine if ABA decreases lactate levels in vivo and rescues mice from lactic acidosis.

Results: 1. ABA binds lactate in serum. Ortho-hydroxy phenyl boronic acids (ABA) is designed to bind lactate in the blood and increase its membrane permeability (Figure 1). ABA does not bind any of the metabolites normally present in serum and DMEM, in particular glucose, due to the presence of the ortho hydroxyl group, which makes it specific for lactate at pH 7.4. We demonstrate that the dissociation constant of ABA with lactate is 0.002, which suggests that it will efficiently bind lactate in vivo, but will also have an off-rate on the timescale of milliseconds, allowing for the release of free lactate and its intracellular metabolism (Figure 2). 2. ABA enhances the membrane permeability and metabolism of lactate. The ability of ABA to enhance the membrane permeability of lactate was investigated in T-cells, a cell type that does not generally metabolize lactate. Figure 2 demonstrates that the ABA-lactate complex increases pyruvate production by 2 fold suggesting that ABA can catalyze the detoxification of extracellular lactate via transporting it within cells. 3. ABA rescues mice from metformin induced lactic acidosis. Lactic acidosis was induced in mice by an intraperitoneal injection of 400 mg/kg of metformin, and blood lactate levels were monitored. After the lactate levels reached 10 mM, these mice were injected with either 100 mg/kg of ABA in PBS or PBS, and after 30 min the blood pH, lactate and glutamate levels were analyzed. Figure 3 demonstrates that ABA can rescue mice from metformin induced lactic acidosis.

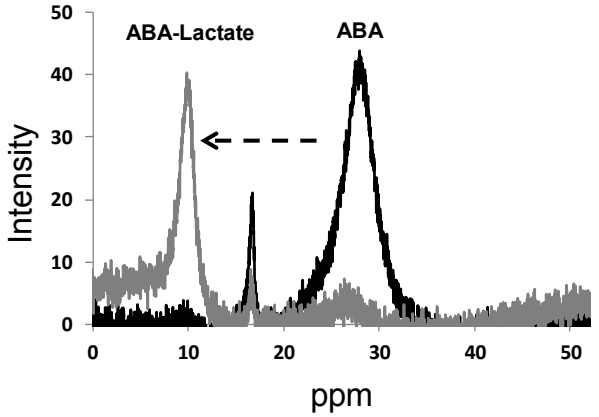

Figure 1. ABA binds sodium lactate in the presence of 10% serum as determined by boron NMR. Free ABA in serum has a boron peak at $\delta = 29$, which shifts to $\delta = 9$ in the presence of equimolar lactate.

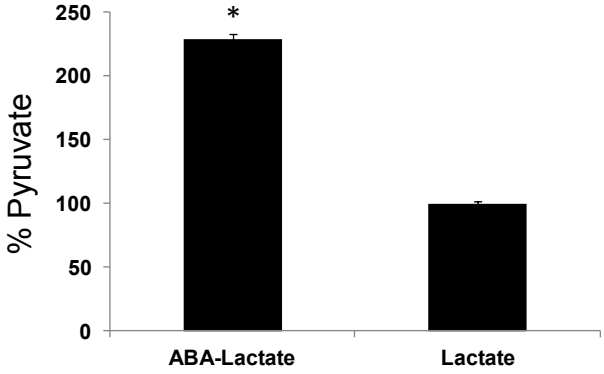

Figure 2. ABA increases lactate metabolism into pyruvate.

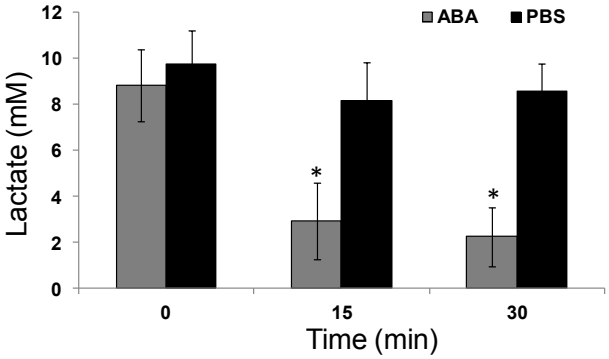

Figure 3. ABA normalizes blood lactate levels in mice suffering from lactic acidosis.

Conclusions: A new biomaterial that can modulate lactate levels was designed and utilized to rescue mice from lactic acidosis. Notably, this is a new class of molecules that can be utilized to modulate lactate metabolism in vivo and utilized in diseases such as cancer.

References: 1) Acharya et.al. *Under Review* Nat. Commn. 2) Peters N Crit Care 2008.