Role of epinephrine and Na^+/K^+ pump activity in abnormal glycolysis in subacute sepsis

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Introduction:
Septic patients exhibit abnormal carbohydrate metabolism and increased circulating epinephrine (Epi) and lactic acid. Traditionally, increased lactate is attributed to tissue hypoxia and *anaerobic* glycolysis. However, Epi-stimulated Na^+/K^+ pump activity leads to increased glycolysis and lactate production in well-oxygenated tissues. Understanding whether increased blood lactate in sepsis results from hypoxia, increased Epi or other causes is important for understanding metabolic derangements in sepsis and guiding treatment.

Hypothesis:
Increased blood lactate in sepsis reflects increased *aerobic* glycolysis in skeletal muscle secondary to Epi-stimulated Na^+/K^+ pump activity.

Methods:
Subacute sepsis was induced in male Sprague-Dawley rats (100-130 g) by subcutaneous *E. coli* injection; control animals received saline. At 4, 8 and 24 hours after injection, blood was drawn and extensor digitorum longus and soleus muscles were dissected. Lactate, glucose, glycogen, and glucose-6-phosphate were measured fluorometrically. Epi, norepinephrine, phosphocreatine (PCr), and ATP were assayed by HPLC. Muscle Na^+ and K^+ were measured using atomic absorption spectrometry. Statistical analysis employed ANOVA and post-hoc tests.

Results:
In septic rats, plasma Epi and lactate were significantly higher than in controls (Table 1), as was muscle lactate (Table 2). Muscle Na^+/K^+ ratio was significantly lower in sepsis (Table 2), indicating higher Na^+, K^+-ATPase activity. ATP and PCr were unchanged in sepsis, suggesting adequate tissue oxygenation. Results are expressed as mean ± SEM for *n*=5-8.

TABLE 1	**Plasma Epinephrine (pmol/ml)**		**Plasma Lactate (mM)**	
Time after injection (hr)	**Septic***	**Control**	**Septic***	**Control**
4	1.95 ± 0.19	1.72 ± 0.07	1.9 ± 0.8	1.3 ± 0.2
8	1.39 ± 0.24	1.04 ± 0.49	1.9 ± 0.4	1.1 ± 0.2
24	2.41 ± 0.49	1.47 ± 0.64	1.9 ± 0.4	1.2 ± 0.4

*, Significantly different from Control by ANOVA.

TABLE 2	**Soleus Lactate (μmol/g)**		**Soleus Na^+/K^+ ratio (mol/mol)**	
Time after injection (hr)	**Septic**	**Control**	**Septic**	**Control**
4	1.11 ± 0.10*	0.67 ± 0.05	0.136±0.004*	0.159±0.008
8	1.02 ± 0.12*	0.73 ± 0.06	0.138±0.004*	0.158±0.004
24	1.16 ± 0.04*	0.69 ± 0.04	0.137±0.005*	0.181±0.007

*, Significantly different from Control by ANOVA and post-hoc test.

Conclusions and Significance:
These results correlate, for the first time, increased muscle lactate production and Na^+/K^+ pump activity with increased plasma lactate and Epi in sepsis, consistent with our hypothesis. Inferring hypoxia from elevated lactate in sepsis may be erroneous. Hence, aggressive therapy aimed at improving tissue O_2 delivery in sepsis may be unwarranted.