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# Can Ringer's Lactate be a Mood Stabilizer?

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## ABSTRACT

The exploration of the lactate shuttle has led to the understanding that lactate is a metabolic fuel, including in the central nervous system. In addition to being an intercellular messenger, it also plays a role in gene expression. Bipolar disorder, specifically, exhibits features of a biphasic energy dysregulation. Cognitive impairment is observed even during remission periods. Mitochondrial dysfunction is a current and important area of research in the etiology of this neuroprogressive disorder. In our studies, we demonstrated a band-specific metabolic/oxidative coupling between electrophysiological brain dynamics, quantified by Entropy Doubling and Ruzsa Distance derived from EEG data and serum lactate levels in patients diagnosed with bipolar disorder. We suggest that band-specific metabolic coupling is different between patients with mania predominant polarity and those with depression predominant polarity. This article asks whether Ringer's lactate may be a mood stabilizer.

**Keywords:** Bipolar disorder, mitochondrial dysfunction, EEG, band specific metabolic/oxidative coupling, lactat, mood stabilizer

## Introduction

The exploration of the lactate shuttle has led to the understanding that lactate is a metabolic fuel, including in the central nervous system.[1-4] Lactate is transported from the bloodstream, astrocytes and oligodendrocytes, and activated microglia to neurons. At this point, whether the transported lactate is a primary source of pyruvate is an important question, as the amount is considerably greater than that produced by neuronal glucose metabolism.

The metabolism of one glucose molecule provides 30 ATP through oxidative phosphorylation, while two lactate molecules are used for the same task. Lactate is a three-carbon monosaccharide that can be produced and released by many cells, including immune cells. The high-energy activity of the brain requires the use of six-carbon glucose, which is then provided by glycolysis.

Lactate synthesis is linked to oxidative phosphorylation in the mitochondria of the consuming cell. Cellular oxygen consumption increases linearly with complete lactate oxidation because the recycling of lactate to pyruvate by the bidirectional redox enzyme lactate dehydrogenase (LDH) is mediated by the tricarboxylic acid cycle (TCA) and molecular oxygen, which serves as the final electron acceptor in the respiratory chain.

It is crucial to understand the relationship between lactate oxidation and cortical functions and its role in fueling neuronal excitability and signal transmission. This exciting topic has been studied ex vivo in hippocampal slice preparations using electrical stimulation, optogenetic tools, and receptor-ligand applications.[5-7] In the absence of glucose, only lactate has been shown to disrupt gamma and theta-gamma oscillations, which require high energy requirements, during which time the cerebral oxygen metabolic rate is fully regulated. This disruption, characterized by moderate hyperexcitability, has been attributed to excitation-inhibition dysregulation. It has been demonstrated that this dysregulation is suppressed by increasing the glucose fraction of the energy substrate. In contrast, lactate alone preserves the lower-energy, intermittent sharp wave activity when the cerebral oxygen metabolic rate is around 65%. Similarly, lactate has been observed to slow neurotransmission in pyramidal cells and fast-firing GABAergic interneurons by simply reducing neurotransmitter release from presynaptic terminals, while simultaneously regulating the generation and propagation of action potentials in the axon. In addition to being an intercellular messenger, lactate also plays a role in gene expression.[3]

## Lactate in Bipolar Disorder

Bipolar disorder exhibits the characteristics of a biphasic energy disorder.[8-14] It is characterized by depressive and manic episodes, with mood swings that alternate between depressed and elevated, and psychomotor activity that decreases and increases. Furthermore, cognitive impairment is observed even during periods of remission in these patients. Mitochondrial dysfunction is a current and important area of research in the etiology of this neuroprogressive disorder.

In bipolar patients, lactate was found to be elevated in the brain using Magnetic Resonance Spectroscopy (MRS) in six studies and in the cerebrospinal fluid (CSF) in two studies.[15] Peripheral measurements yielded two positive and two negative results. Guo et al.[16] reported that elevated serum lactate was associated with a depressive episode. Vieira et al.[17] demonstrated that this elevation was reversible with lithium. Serum lactate levels were found to be higher in 105 bipolar adolescents than in healthy controls, while cct-mtDNA levels, another suggested biomarker for mitochondrial dysfunction, were not different.[18] However, it was found to correlate with lactate and negatively correlate with depressive symptoms in bipolar patients but not in healthy controls.

Animal studies demonstrating elevated lactate levels in the brain have suggested that this may serve as a transdiagnostic endophenotype characterized by cognitive impairment in bipolar disorder, as well as in schizophrenia, autism, epilepsy, and Alzheimer's disease.[19] A common feature of the 5 studies with 2294 animals is the association between high lactate levels and poor working memory performance.

In our studies, we investigated the relationship between electrophysiological brain dynamics measured using the Entropy Ruzsa Distance and Entropy Doubling methods obtained from EEG signals and peripheral lactate levels in patients diagnosed with bipolar disorder in remission. Entropic Rusza Distance is the additive combinatorial entropy on the electrodes. Analytical signals for each EEG channel were processed using the Hilbert-based Entropy Doubling method. All EEG data were processed with a sampling frequency of 125 Hz. Metabolic syndrome was an exclusion criterion because, according to multivariate regression analyses, lactate levels were correlated with triglycerides, blood glucose, and systolic and diastolic blood pressure.[20] Mitochondrial markers were also measured differently in patients with metabolic syndrome, where lactate levels were normal and elevated. Another exclusion criterion was the use of typical antipsychotics, because a possible elevation in creatine kinase could affect lactate levels.[21]

## A band-specific metabolic/oxidative stress in electrophysiological brain dynamics

In electrophysiological brain dynamics, a band-specific metabolic/oxidative stress was observed. The energy dysregulation, related to lactate, involved the theta and gamma frequency bands.[22] We found linear correlations with lactate levels in the F7 theta band and negative correlations with lactate levels in the O1, Fz, and Cz gamma bands. Ki was significantly higher in the Fz and Cz electrodes.

Functional MRI studies have consistently shown that lactate levels increase during intense neural activation, and that EEG high-frequency power generally covary with extracellular lactate dynamics.[23] The strong correlations we observed between lactate and entropy at central electrodes may reflect changes in neuronal oxidative capacity and energy traffic driven by lactate-mediated metabolism. Gamma oscillations are also observed enveloped within theta oscillations, as has been demonstrated optogenetically in ex vivo experiments.[24]

Gamma oscillations occur in many cortical areas during perception, psychomotor activity, and memory formation.[25] They are a dialogue between glutamatergic pyramidal cells and GABAergic interneurons. Several hippocampal and neocortical GABAergic interneuron subtypes exert rhythmic perisomatic inhibition on pyramidal cells via GABA release. Rhythmic perisomatic inhibition is commonly produced by fast-spiking interneurons, such as parvalbumin-positive GABAergic basket cells. Fast-spiking interneurons possess unique electrophysiological properties, including extensive axon arborization and high-frequency presynaptic GABA release.[26] It has been suggested that the impairment of gamma oscillations during metabolic/oxidative stress originates primarily from fast-spiking interneurons rather than pyramidal cells.[27] This corresponds to an increase in theta activity.

In our study, we found a linear relationship between serum lactate levels and theta oscillations, which bears traces of theta-gamma coupling, suggesting a band-specific metabolic/oxidative coupling. High lactate levels and associated metabolic acidosis have been associated with EEG slowing.[28] This finding is consistent with meta-analyses showing that theta-beta power is associated with lactate clearance during sleep and cortical activation.[29]

When we evaluated euthymic bipolar patients with mania predominant polarity, we found a linear relationship between high beta amplitude entropy at electrodes F7 and O2 and high beta phase entropy at electrode T5.[30] This very specific and stable relationship reflects high beta-specific lactate activity. Accordingly, we suggest that band-specific metabolic coupling is different between patients with mania predominant polarity and those with depression predominant polarity.

## Discussion

Impairment of lactate-induced gamma and theta-gamma oscillations is associated with i) decreased neuronal excitability, ii) decreased neurotransmitter release, and iii) altered postsynaptic glutamatergic and GABAergic receptor activation. This may result in i) ATP deficiency resulting from decreased glycolysis and limited lactate oxidation, ii) partial inhibition of mitochondrial respiration by neuronal NO synthesis, iii) intracellular acidification mediated by ATP hydrolysis and H-linked neuronal MCTs, iv) shifts in the cytosolic NAD/NADH ratio, v) lactate-mediated HCAR1 activation, and vi) activation of purinergic and adenosine receptors.[31]

ATP synthesis by aerobic glycolysis, or aerobic glycolysis itself, appears to be essential at excitatory and inhibitory synapses. On the other hand, lactate is less effective than glucose. Its long-term use during high-energy-cost neural network rhythms can even be potentially harmful after a certain point.

Administration of a low-affinity, competitive AMPA receptor antagonist reduced the amplitude of postsynaptic transmission in pyramidal cells in the presence of glucose, with this effect being greater with lactate alone. Administration of a low-affinity, competitive GABA-A receptor antagonist reduced the amplitude of inhibitory postsynaptic transmission in pyramidal cells in the presence of glucose. This effect was greater with lactate alone.

The decrease in lactate-induced neurotransmitter release may differ in glutamatergic and GABAergic neurons during gamma oscillations of pyramidal and fast-spiking interneurons. During neuronal excitation, glycolysis can be reregulated by increasing glucose supply.

Physical exercise can increase lactate concentration in the blood severalfold. This exogenous lactate can be taken up and utilized by the brain in the ways described above. However, during intense physical exercise, it may not allow glucose utilization. Lactate also serves as an important supplementary fuel in hypoglycemia. In healthy subjects, lactate infusion during insulin-induced hypoglycemia has been shown to improve cognitive function, reduce autonomic symptoms, and regulate the release of stress hormones. However, in severe forms of hypoglycemia, glucose infusion reversed these symptoms, while lactate infusion was insufficient.

## Can Ringer Lactate be a mood stabilizer?

Neuroinflammation creates a shift from oxidative phosphorylation to glycolysis. This leads to NO release. Ex vivo studies have shown that this condition causes severe metabolic and oxidative stress in pyramidal cells and interneurons. It has been shown that network oscillations are slowed, resulting in neurodegeneration.[31]

During low-energy network activity, lactate is an adequate substitute for glucose.[32] Gamma activity, however, is attenuated at low glucose concentrations. Lactate can only be a supplementary fuel in this rhythm. Only moderate hyperexcitability, superimposed on gamma oscillations by lactate utilization, was observed. This state, reflecting a type of excitation-inhibition imbalance, is suppressed by glucose utilization. However, the impairment in gamma oscillations that occurs at low glucose concentrations is not accompanied by hyperexcitability. At this point, it is thought that the neural excitation-inhibition balance can be maintained as long as the rate of decrease in glucose concentration is not too rapid.

Given lactate's dual role as a fuel and signaling molecule involved in neuroplasticity and gene regulation, EEG-metabolite relationships may reflect integrated neuroenergetic and neuroprotective processes potentially related to stress sensitivity and neurodegenerative risk. Lactate consumption alone does not affect the threshold for generation or the number of action potentials. This finding supports the notion that axons may be nourished by lactate transported from myelinating oligodendrocytes and Schwann cells, including during action potential generation and propagation.

Lactate can be taken up or released depending on supply. Repeated findings have shown that it significantly supports synaptic plasticity.[3] High lactate levels are present in conditions such as ischemic and traumatic brain injury, and sepsis. The interactions discussed thus far

support the necessity of therapeutic infusion of exogenous lactate in cases of ischemic and traumatic brain injury, and sepsis.

Any mood episode is an ischemic and/or neuroinflammatory event.[33] The energy dysregulation associated with a mood episode can be likened to the relationship between lactate and glucose utilization/ oxidative phosphorylation and glycolysis, or even a Warburg effect as in cancer. At this point, the question of whether Ringer's lactate may be a mood stabilizer can be considered a valid and necessary one.

The ideal balance appears to be that adding a small amount of glucose to the lactate supply (10-16 mM vs. 2-5 mM) can improve gamma oscillations, with lactate contributing up to 60% to oxidative energy metabolism, with glucose providing the remainder. Replacing glucose with lactate as a supplementary fuel option to this extent may be beneficial and neuroprotective in some physiological and pathophysiological situations.

## Conclusion

In conclusion, the effects of high lactate/glucose ratios on mood and cognition appear to depend on the pathophysiological context. These exciting fundamental concepts and their clinical implications require future comprehensive collaborative studies involving morphology, biochemistry, electrophysiology, and neuroimaging. Our current limitation is that correlation does not necessarily confirm causation.

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