The pathophysiological role of L-lactate in the normoxic brain

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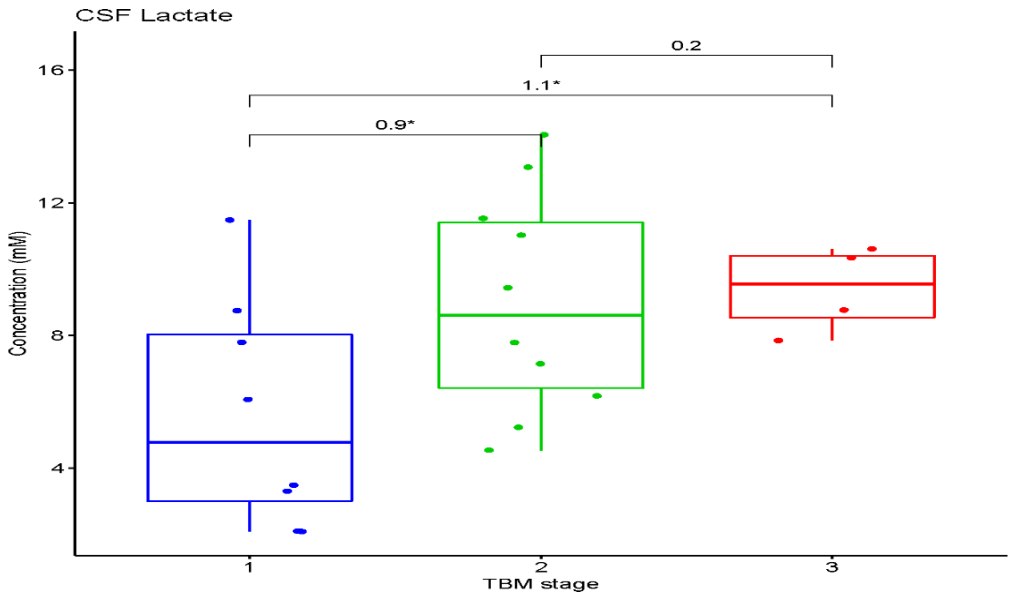
In biochemistry it is fundamentally known that under hypoxic conditions anaerobic respiration drives the production of lactate via lactate dehydrogenase: Pyruvate + NADH + H^+ => Lactate + NAD^+. But, there has been a paradigm shift – lactate is not simply a by-product, but an important component of neuroenergetics. Under normoxic conditions in the brain (homeostasis), it has been shown that the astrocyte-neuron lactate shuttle (ANLS)[i] is in effect – transport of glycolytic lactate from astrocytes to neurons to facilitate increased neural energy requirements. Under neuropathophysiological conditions of chronic neuroinflammation caused by invading infectious agents, it is postulated that the flow of lactate is redirected from neurons to the microglia (resident macrophages in the brain) to fight the infection. Neurons become inactivated to protect themselves (decreased consciousness) and excessive mitochondrial energy activity in the microglia leads to greater electron leakage and raised free radical production to fight the pathogen. The pathogen under investigation in this study is *Mycobacterium tuberculosis* in the brain, and the disease is tuberculous meningitis. Our observations are that cerebrospinal (CSF) lactate increases with severity of infections that cause chronic neuroinflammation, such as in tuberculous meningitis, driving the postulated astrocyte-microglia lactate shuttle (AMLS) – a derivative of the proven ANLS.



CSF lactate concentrations (mM) across TBM (*n*=22) stage. The effects size (Cohen's d-value) is shown as a number across the groups and * indicates statistical significance ($p<0.05$).

[i] ***Cerebral Cortex,* 6(1), 1996, doi.org/10.1093/cercor/6.1.50**