PERSPECTIVE

Lactate oxidation for brain energy metabolism: To exercise or not, that is the question

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Handling Editors: Harold Schultz & Sophie Møller

The peer review history is available in the Supporting Information section of this article (https://doi.org/10.1113/JP290102#support-information-section).

The brain's metabolic needs are normally fuelled by oxidizing glucose extracted from circulating blood. But when glucose becomes restricted, other substrates become necessary. Lactate is a glucose-sparing molecule. In this issue of *The Journal of Physiology*, Koep et al. (2025) show that the brain is agnostic when it comes to oxidizing lactate removed from circulation, because the brain does not discriminate when lactate is created endogenously (exercise) *versus* introduced exogenously (infusion). Lactate is clearly a stakeholder of energy metabolism because it serves multiple crucial roles (e.g. fuel, signalling, plasticity). Given benefits to brain function with lactate generated by exercise, are 'lactate pills' the next brain health supplement?

Normally, the brain's principal fuel is glucose extracted from circulating blood, which is metabolized to serve both biosynthetic and energetic needs (Yu et al., 2023). The classical view of lactate, synthesized from incomplete glucose oxidation (aerobic glycolysis), as a metabolic waste has now been debunked as lactate is also oxidized in the brain (Boumezbeur et al., 2010). Given the incessant energy demands of brain function, alternative fuels (e.g. ketones, fats, glycogen, acetate, lactate) are necessary should glucose become scarce (e.g. fasting, starvation, exercise, sleep, ageing, injury, disease). Hence, mechanisms by which glucose can be spared are critical (Rothman et al., 2022).

Glucose is metabolized in neurons and astrocytes, but acetate is specifically oxidized in astrocytes. Glycogen metabolism in astrocytes can handle transient glucose limitations. Lactate is generated from metabolism of glucose and glycogen, but not acetate. Since lactate can be imported into cells and exported out of cells, lactate can efflux out (for pH regulation) and/or exchange between cells (to handle glucose shortages). While normal function relies on glucose oxidation, ketones and/or fats are mobilized during fasting and starvation. Alternative fuels become critical for sleep, ageing, injury and pathologies because glucose oxidation usually declines.

To determine how much glucose is spared when circulating lactate is produced in muscles and circulated body-wide or when lactate is simply injected into the bloodstream, Koep et al. (2025) measured cerebral blood flow (CBF) by ultrasound and metabolic rates of utilization for oxygen (CMR_{O_2}), glucose (CMR_{glc}) and lactate (CMR_{lac}) from substrates (oxygen, glucose, lactate) in brain artery and vein (Fig. 1*A*). During both situations, CMR_{O_2} remained unchanged regardless of lactate concentration, but with increasing lactate as CMR_{glc} decreased, CMR_{lac} increased (Fig. 1*B*). Regardless of how lactate is exposed to the brain, its circulation leads to preferential lactate oxidation during reduced glucose oxidation. Koep et al. also observed higher CBF with infusion compared to exercise (Fig. 1*B*), indicating lactate's capacity as a signalling molecule thanks to lactate receptor-enabling modulation of cellular or vascular activity (Liu & Zhou 2024).

But what is the extra lactate for? There are two considerations: lactate is either lost as waste via the perivascular space or lactate is used as an energy fuel while sparing glucose. Even if lactate is wasted, the lymphatic clearance is quite slow (Koep et al., 2025) and unlikely to change within the experimental duration. The lactate as glucose-sparing view is likely because lactate is used to repair myelinated axons (lipid or protein synthesis) and boost antioxidant defence (nucleotide synthesis), but lactate can also be oxidized to produce high-yield energy similar to glucose (Rothman et al., 2022).

Oligodendrocytes need lactate to repair myelinated axons (Liu & Zhou 2024). While the pentose phosphate pathway (for antioxidant synthesis) is also quite slow (Koep et al., 2025), lactate can spare some glucose if this shunt is active. Neurons and astrocytes use lactate as an energy fuel because of its mobility into cells and out of cells according to the astrocyte-to-neuron lactate shuttle (ANLS) and glucose-sparing by glycogenolysis (GSG) models (Rothman et al., 2022). The ANLS model suggests glutamate released by neurons is taken up by astrocytes to trigger glycolysis, generating lactate which is reallocated to neurons for oxidation. Owing to astrocytic compartmentation of glycogenesis and glycogenolysis, the GSG model stipulates that stimulation-induced glycogenolysis enables additional neuronal glucose uptake to ease glucose craving by astrocytes. Thus, lactate supplementation from the blood can spare glucose uptake in both models.

In summary, Koep et al. (2025) suggest lactate metabolism is impartial. Be it endogenously generated lactate or exogenously introduced lactate, the way glucose is spared in both scenarios is nearly identical. Since exercise-generated lactate is implicated in synaptic plasticity through brain-derived neurotrophic factor (Liu & Zhou 2024), lactate has already been considered as an 'exercise pill' to improve brain health. Is it possible then that the results of Koep et al. (2025) usher an era of 'lactate pills'? While some charlatans may indeed commercialize this discovery without vetting, it is ever more crucial to explore the diverse and often paradoxical roles of lactate in health and disease.

DOI: 10.1113/JP290102

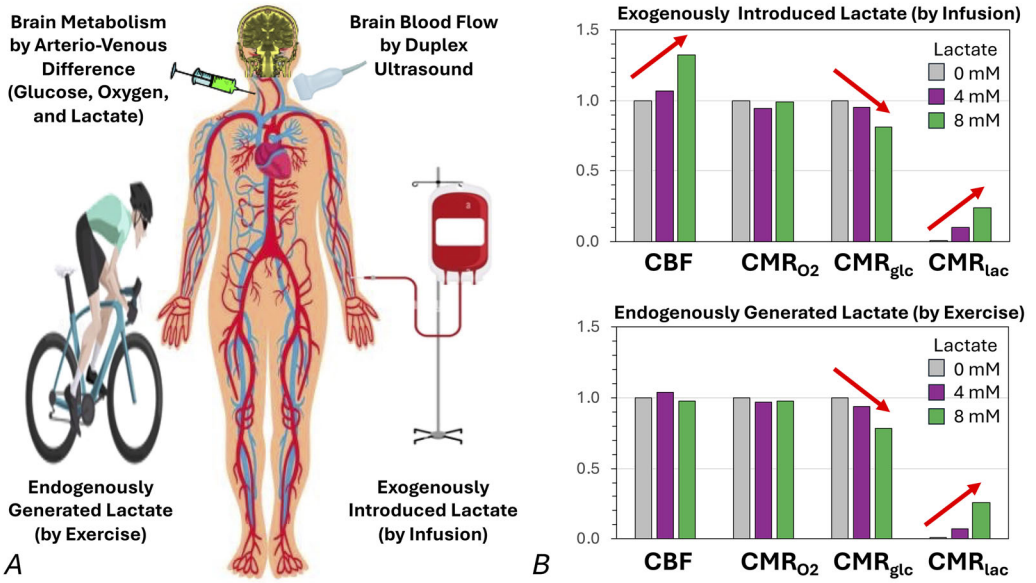

Figure 1. Koep et al. (2025) asked if brain discriminates when lactate is created endogenously (exercise) or introduced exogenously (infusion)
A, experimental design to create different levels of lactate exposed to the brain. Cartoons from internet. *B*, measures of CBF, CMR_{O_2}, CMR_{glc}, and CMR_{lac} were used to determine the glucose-sparing capacity of lactate.

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Additional information

Competing interests

F.H. is the founder of InnovaCyclics.

Author contributions

Sole author.

Funding

The author is supported by NIH Grants (R01 AG-084681, R01 MH-129371, R01 CA-280871).

Acknowledgements

Thanks to Yale colleagues for insightful comments.

Keywords

acetate, astrocyte, fats, glycogen, glycolysis, ketones, neuron, oxygen, shuttle

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Peer Review History