Nonlinear Kinetics of Lactate Uptake across Blood-Brain Barrier

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The paper by Young et al. [1] contains material inaccuracies in the quantitative interpretation of data which we believe should be brought to the attention of the scientific community. The authors explicitly state on page 47:

‘The rate of entry of lactate across the blood-brain barrier was modelled using:

$$\frac{dC_{br}}{dt} = k[C_{art} - C_{br}]$$

The authors further allege on page 49:

‘A constant of proportionality (k), relating the blood-brain lactate gradient and the rate of change of brain lactate, was calculated using serial in vivo NMR spectra and simultaneous blood determinations made during the initial portion [sic] of the experiment ...’

Implicit in the foregoing allegation is the author’s erroneous presumption of kinetic linearity in which there is assumed a direct proportionality of blood-brain transfer rates of lactate to concentration or concentration differences. The data presented by the authors in figure 2 can be demonstrated to fail the fundamental tests of kinetic linearity.

A Cartesian plot derived from figure 2(1) of dC_{br}/dt vs. $(C_{art} - C_{br})$ over the 30-min infusion period gives a curved line which approaches an asymptote ($dc/dt \rightarrow V_{max}$ as $C_{art} - C_{br} \rightarrow \text{infinity}$) in conformity with the equation of Michaelis and Menten [2]. The asymptotic nature of the curve is a consequence of the finite mass of brain tissue which imposes a saturation limit in the dosage range used, for the amount of metabolite taken up by the tissue. Nonlinear compartment models have been used successfully in the neonatal rat to estimate in vivo the maximal velocity of lactate influx from blood to brain [3] and the rate of transport of lactate from blood to brain in the physiological steady-state condition [4].

The differential equation used by the authors is a restatement of Fick’s law for unidi-mensional molecular diffusion. Their reliance on Osmotic effects’ as the primary mechanism for transport of lactate from blood to brain is not supported by their data [see fig. 2 of ref. 1]. A Cartesian plot of the brain lactate concentration versus the corresponding arterial lactate concentration during the 30-min infusion period generates a nonlinear function which cannot be forced through the origin within experimental error. This graphical result does not conform to the constant (straight line) concentration gradient which is expected for transport by molecular diffusion.

An additional patent defect in the model promulgated by the authors [1] is the failure

Letter to the Editor

of their differential equation to account for all of the metabolic forces determining the rate of change of brain lactate concentration ($dC_{t,r}/dt$). For example, their model fails to distinguish between lactate efflux from brain and the oxidation of lactate within the tissue. Such a distinction may be of paramount significance in tissue such as the brain which is comprised of a heterogeneous cell population. It has been suggested [5] that the rate of change of tissue metabolite amount depends on the passage between blood and tissue a bothway process, and the rate of tissue oxidation of the metabolite. It is advisable therefore that the authors [1] use a different model to achieve a better fit to their data in accordance with the foregoing recommendations.

References

- Young RSK, Petroff O, Chen B, Aquila W, Gore J: Preferential utilization of lactate in neonatal dog brain: In vivo proton NMR study. *Biol Neo-nate* 1991;59:46-53.
- Michaelis L, Menten M: *Biochem Z* 1913;49:333-369.
- Cremer J, Cunningham V, Pardridge W, Braun L, Oldendorf W: *J Neurochem* 1979;33:439-445.
- Mehler H: *Lactic Acid Metabolism*. Los Angeles, Mehler Publishing Co. 1988.
- Teorell T: *Arch Int Pharmacodyn* 1937;57:205-240.