LETTER

High brain lactate is not caused by a shift in the lactate dehydrogenase A/B ratio

In their paper, Ross et al. (1) suggested that high brain lactate is a marker of aging and that this lactate accumulation is explained by a shift in the lactate dehydrogenase (LDH) isoenzyme pattern also found to be associated with aging. Although the brain lactate increase with age is highly interesting, the suggested explanation may be problematic.

LDH is a tetramere of two proteins M and H (products of the *Ldh-A* and *Ldh-B* genes, respectively). Therefore, the LDH enzyme presents with five isoenzymes: M_4, MH_3, M_2H_2, M_3H, and H_4. The M-dominated isoenzymes have different kinetic properties (K_m and V*max* values) than H-dominated forms. Ross et al. (1) and others (2, 3) interpret this fact as the cause of LDH isoenzymes composed primarily of M subunits to preferentially catalyze the reduction of pyruvate → lactate and conversely, isoenzymes composed primarily of H subunits predominantly should catalyze oxidation of lactate to pyruvate (1–3). However, despite changed kinetic constants, the equilibrium constant, K_{eq}, is the same for all isoenzymes, because it is the same chemical reaction being catalyzed. This is stated in the Haldane Equation relating K_{eq} with the kinetic constants of the forward and reverse reaction:

$$K_{eq} = (V_{max\,f}\ K_{mp})/(V_{max\,r}\ K_{ms}).$$

Therefore, if the LDH reaction can be assumed to be a dead-end near-equilibrium reaction and steady state conditions apply, as is probably the case in ref. 1, the isoenzyme pattern cannot have any influence on the equilibrium lactate concentration. Also, figure 5c in ref. 1 indicates increased total LDH activity with age, which, if anything, will contribute to a near-equilibrium state of the LDH reaction.

In the brain in vivo, the LDH reaction may actually not be a dead-end reaction, because there may be a concentration gradient from intra- to extracellular space with a possible lactate flux out of the cell. Such conditions of steady state non-equilibrium are analyzed in ref. 4, showing that total LDH activity rather than the isoenzyme pattern determines the steady state lactate concentration. Furthermore, the change in isoenzyme composition reported in ref. 1 would cause a fall, not an increase, in lactate concentration (4).

During nonsteady state, nonequilibrium conditions (e.g., large rapid changes in glycolytic vs. pyruvate dehydrogenase flux), there may be a temporary significant deviation from equilibrium of the LDH reaction. Under such conditions, it cannot be excluded that isoenzyme pattern may influence the time course of the lactate concentration. However, because the LDH activity is high, such transitions in net flux of the LDH reaction must be short-lived and are unlikely to explain the observations by Ross et al. (1).

All in all, the observed increase in brain lactate with age (1) is, in our opinion, unlikely to be explained by the isoenzyme pattern. Rather, it is a consequence of changed cytosolic redox state and/or a changed pyruvate steady state concentration.

In fact, in this respect, the LDH reaction is analogous to another dead-end reaction in energy metabolism, the creatine kinase reaction, where the [PCr] $[H^+]$/[Cr] ratio passively reports the ADP level (5).

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