The Diabetic Brain During Hypoglycemia

In the Midst of Plenty of Lactate

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Many factors impact the fluctuating rates of glucose flux and clearance in one's daily life (meal size and composition, gastric emptying rate, physical activity, etc.). With this constantly changing need for circulating insulin abundance, it is challenging for the treatment strategy to be entirely successful in individuals with type 1 diabetes (T1D), and transient periods of hypoglycemia occur. Humans have evolved metabolic strategies to cope with hypoglycemia, and these include counter-regulatory endocrine responses to increase hepatic glucose production as well as selection of alternative fuels for mitochondrial respiration. The central nervous system can use glycolytic end products that were produced by other tissues (circulating lactate) as well as ketones to some extent. The ability to take up and oxidize these alternative fuels is likely critical for tolerance of and survival through hypoglycemia.

The traditional view was that glycolysis makes pyruvate and that only under anaerobic conditions would lactate be generated. It is now recognized that glycolysis makes lactate even under fully aerobic conditions because of the intrinsic kinetic properties of lactate dehydrogenase, which rapidly interconverts pyruvate and lactate and favors lactate on a mass basis. Thus, lactate can be considered the major product of glycolysis even when the fate of glycolytic carbon is primarily mitochondrial oxidation. The basal lactate concentration in tissues and arterial circulation is at least 10 times greater than pyruvate and even higher under stresses that increase the glycolytic rate (1,2), so lactate is the primary shuttling form of glycolytic end products through the cytoplasm and through the circulation from one organ to another. The liver releases glucose to share its carbohydrate fuel depot with other tissues. However, through lactate release, nonhepatic tissues, such as skeletal muscle, can also transfer carbohydrate potential energy to other organs. This mechanism of carbohydrate exchange through lactate flux has been referred to as the cell-cell lactate shuttle concept (3). Once taken up, lactate can then be used as a fuel, requiring lactate dehydrogenase and monocarboxylate transport into mitochondria, via an intracellular lactate shuttle process (4). Although glucose has been considered the sole fuel for the brain in the past, it is now known that the brain can take up lactate from circulation and oxidize it as fuel, which can spare blood glucose (5). Molecular machinery has been demonstrated for neuronal lactate utilization involving monocarboxylate transporters (6,7) but still few studies have assessed lactate metabolism in the intact brain.

In the current issue of *Diabetes*, De Feyter et al. (8) investigated brain lactate metabolism in humans in vivo. Concentration of lactate in the brain and its use as fuel was assessed during hypoglycemia using a stable isotope tracer methodology with magnetic resonance spectroscopy (MRS).

With isotope tracer technology and MRS, the same group previously observed increased brain acetate concentration and increased oxidation of acetate in T1D brain versus control individuals during hypoglycemia (9). They inferred that the rate of acetate uptake from circulation was higher in T1D and that other monocarboxylates (such as lactate) might also be transported and oxidized in diabetic brains during hypoglycemia at accentuated rates. In their current work (8), they used a [^{13}C]lactate tracer to further test monocarboxylate metabolism in vivo. The investigators recruited healthy people and individuals with T1D and induced a steady-state hypoglycemia while continuously infusing [3-^{13}C]lactate. MRS was used to assess labeling of brain glutamate and glutamine as surrogate indices of tricarboxylic acid cycle labeling to detect the oxidation rate of circulating lactate, and the concentration of lactate in the brain was also measured, which required the assumption that lactate isotopic enrichment (IE) on carbon 3 was equal to IE of glutamate on carbon 4; this assumption (further addressed below) requires that lactate and pyruvate pools are homogeneous and fully equilibrated with one another in the brain. The authors discovered that during hypoglycemia, the brain lactate concentration is more than five times higher in diabetic patients than control subjects. Furthermore, they observed that the brain lactate oxidation rate was not different between groups, despite the differences in lactate concentration.

It is possible that enhanced capacity for lactate uptake is an adaptation to habitual exposure to hypoglycemic episodes in T1D in order to allow the central nervous system to substantially use lactate as an alternative fuel when glucose supply is low. This interpretation is reasonable but would be even more convincing if the increased concentration of lactate in T1D had been accompanied by a proportional increase in its oxidation. It is worth noting that increased uptake rate of circulating lactate is only one of at least four possible explanations for the large brain lactate pool size in T1D (Fig. 1). Reduced export of lactate is also a possible explanation, although monocarboxylate transporters are bidirectional rather than selectively capable of modulating lactate release. An additional explanation for increased brain lactate concentration would be increased glycolytic rate within the brain. Finally, as the authors observed a reduced ratio between lactate oxidation

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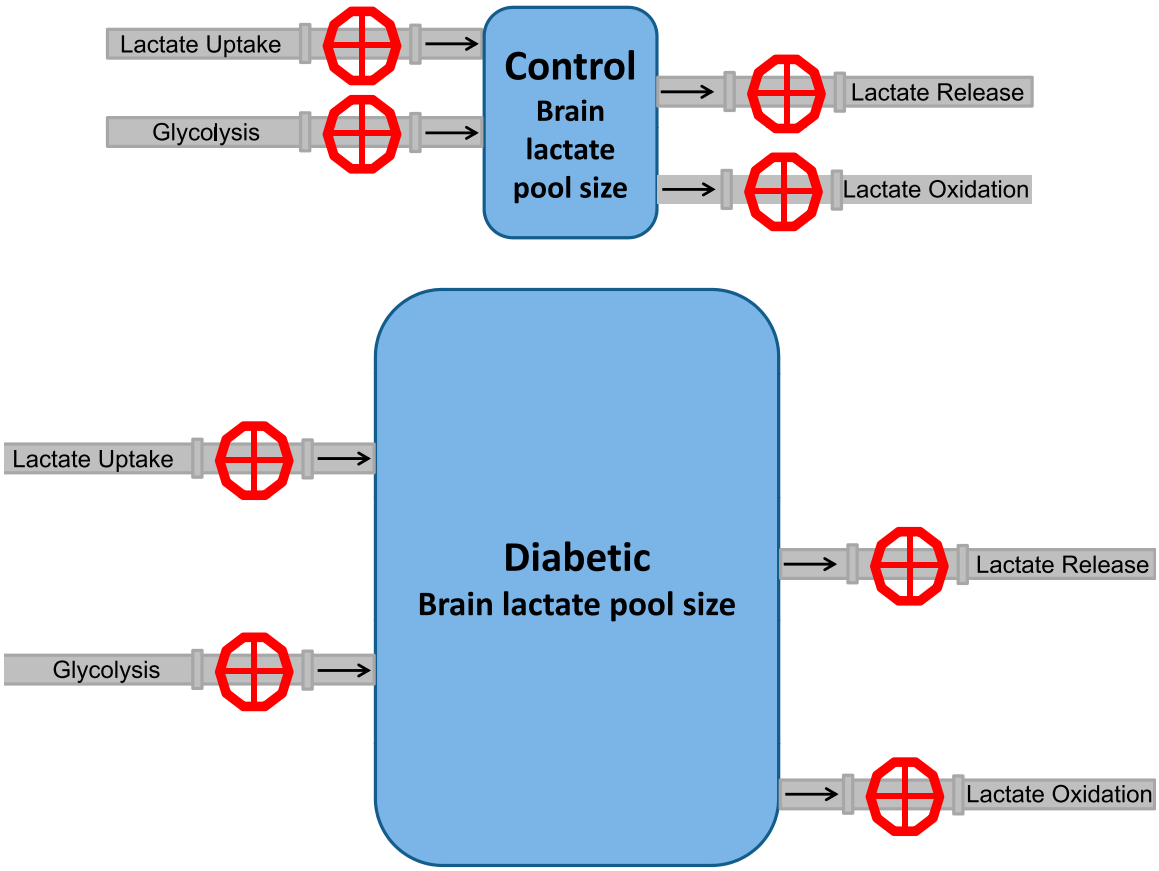

FIG. 1. Brain lactate concentration during hypoglycemia. The pool size (concentration) of lactate in the brain depends upon the rates of uptake from circulation, release into circulation, glycolysis (i.e., lactate production) within neural tissue, and mitochondrial oxidation of lactate. Additionally, flow restrictions (reduced clearance) at specific sites of transport and metabolism can alter the brain lactate pool size independently of the rates at each step by creating a need for a higher concentration gradient to drive a certain rate of transport or metabolism. De Feyter et al. (8) discovered different lactate pool sizes without differences in lactate oxidation rates between control subjects and T1D patients. Glycolytic rate, lactate uptake, lactate release, and efficiency of transfer of monocarboxylates into the mitochondria are factors that could have played roles in determining the lactate pool sizes.

and lactate concentration in T1D, it is plausible that flow of lactate into mitochondrial respiration is restricted during hypoglycemia in T1D, requiring a higher intracellular lactate concentration to achieve a similar lactate oxidation rate as control subjects. Future work with stable isotopes as well as continued molecular work on the lactate oxidation complex of mitochondria (6) may shed light on the meaning of the elevated lactate concentration in the brain of individuals with T1D during hypoglycemia.

As the authors compared groups for lactate metabolism solely under hypoglycemic conditions, conclusions about lactate metabolism cannot be drawn regarding differences between normoglycemic versus hypoglycemic states. An additional remaining gap in knowledge is whether IEs of lactate, pyruvate, and the tricarboxylic acid cycle (glutamate) are similar to one another in the brain. This was a critical assumption in the model of De Feyter et al. (8). This assumption of lactate/pyruvate pool homogeneity and equilibration would fail in heart tissue (10,11) and likely skeletal muscle (1), but it is possible that in brain the assumption is sufficiently accurate for mathematical modeling of the MRS data. This issue can be addressed with alternative physiological models and complementary analytical techniques to further address this modeling issue in the future.

Despite some remaining questions, the study contributes novel and important information to the literature. The authors used a highly sophisticated analytical approach and a clinically relevant study design. By using a combination of gas chromatography/mass spectrometry to monitor IE of blood lactate and MRS to monitor labeling of the brain tricarboxylic acid cycle, conclusions about intermediary metabolism could be drawn for a question that few laboratories would be capable of addressing. In line with current concepts and emerging ideas in lactate metabolism, a valuable attribute of the authors' contribution is their interpretation of the study results, in viewing lactate as a substrate for mitochondrial respiration as well as a possible signaling molecule. The authors have contributed to an ongoing elaboration of lactate shuttle concepts (3,4,12) that may ultimately be critical for the understanding and treatment of metabolic disorders.

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