CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Inhibition of Lactate Dehydrogenase to Treat Epilepsy

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Epilepsy is a highly prevalent neurologic condition that is characterized by spontaneous recurrent seizures and occurs at all ages in approximately 1% of the world's population. Although antiseizure drugs are efficacious in controlling spontaneous recurrent seizures in the majority of patients (albeit with potentially major side effects), a third of patients do not have a response to current therapies[1] and continue to have debilitating epilepsy-associated medical conditions, including cognitive impairment and depression. Despite decades of research into the neurobiology of epilepsy and advances in clinical and experimental therapeutics, the proportion of patients with unremitting seizure activity has remained essentially unchanged.

The reasons for this sobering scenario are manifold and underscore the complexity and heterogeneity of the epileptic brain. One possible explanation for this perplexing situation is that the screening process for investigational compounds has focused largely on aberrant neuronal firing mediated by plasma membrane–bound ion channels and transporters. Such screening has ignored glial cells, in addition to the enzymes and substrates responsible for normal cellular metabolism and homeostasis. In the broad context of brain metabolism, there has been growing experimental interest in metabolism-based treatments, such as the ketogenic diet, a high-fat and low-carbohydrate therapy that has been used for nearly a century to treat medically intractable epilepsy[2] and whose hallmark feature is the production of ketone bodies by the liver. Although the mechanisms of the ketogenic diet have yet to be fully delineated, there is intriguing evidence that metabolic substrates (and by extension, perhaps enzymes) may underlie its clinical benefits.[3,4]

To both clinicians and scientists alike, lactate dehydrogenase (LDH) is a ubiquitous enzyme that is best known as a marker of disease and tissue injury. Lactate dehydrogenase catalyzes the interconversion of lactate and pyruvate; the latter is the final product of glycolysis. Lactate is used as fuel by diverse tissues under fully aerobic conditions: it provides the oxidative and gluconeogenic substrates required for cellular homeostasis. In the brain, lactate is a major source of fuel for brain metabolism and is supplied locally from aerobic glycolysis or through the peripheral circulation. A major concept in brain metabolism is the astrocyte-to-neuron lactate-shuttle hypothesis, which posits that astrocytes synthesize lactate that is then transported into adjacent neurons as a metabolic substrate under physiologic or pathologic conditions. In this context, Sada and colleagues[5] recently reported that seizures and epileptiform activity can be suppressed by inhibiting the activity of LDH, thus invoking a key metabolic pathway in the control of epilepsy.

Probing into the seminal biochemical shift from glycolysis to fatty acid oxidation effected by the ketogenic diet (which results in systemic ketosis), Sada et al. observed marked hyperpolarization of neurons in rodent brain slices from the subthalamic nucleus and the substantia nigra (two subcortical structures that regulate seizure activity) when the bathing medium was switched from glucose to ketones. Realizing that the astrocyte-to-neuron lactate shuttle links glycolysis to oxidative metabolism and is also involved in diverse physiologic functions in the brain, such as synaptic transmission, Sada et al. asked whether manipulation of this metabolic pathway could explain the physiologic effects observed (Fig. 1). They found that the neuronal hyperpolarization was completely reversed by the addition of lactate and showed that the inhibition of LDH with oxamate — a structural analogue of pyruvate that stereoselectively blocks LDH and disrupts the gluconeogenic pathway — mirrored the hy-

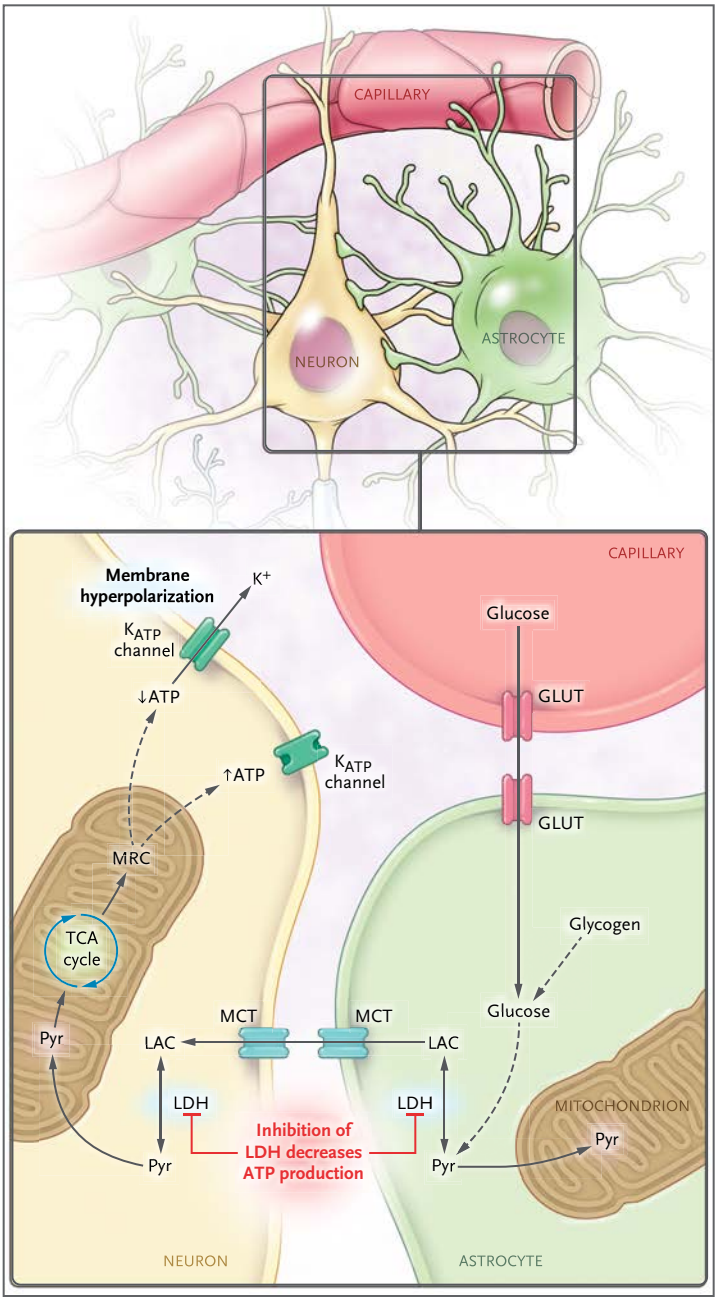

Figure 1. Blocking Seizure Activity through the Inhibition of Lactate Dehydrogenase.

Shown are the pathways through which neuronal excitability can be dampened by interference with the astrocyte-to-neuron lactate shuttle. Glucose is provided to astrocytes either endogenously through the breakdown of glycogen or from the peripheral circulation (which requires the activity of glucose transporters [GLUTs]). Pyruvate (Pyr), the end product of glycolysis, is then converted to lactate (LAC) through the action of lactate dehydrogenase (LDH). In turn, lactate is shuttled from astrocytes to neurons by means of monocarboxylic acid transporters (MCTs). Once inside the neuron, lactate is converted again by LDH to Pyr, which then enters the mitochondrion to feed into the tricarboxylic acid (TCA) cycle. Through oxidative phosphorylation within the mitochondrial respiratory chain (MRC), adenosine triphosphate (ATP) is produced and released into the cytosolic compartment. High levels of ATP inhibit ATP-sensitive potassium (K_{ATP}) channels on the plasma membrane, whereas low concentrations of ATP activate these channels and lead to efflux of positively charged potassium ions, thereby hyperpolarizing the neuronal-cell membrane and thus inhibiting neuronal discharge. Within this pathway, the inhibition of LDH prevents the activation of K_{ATP} channels by ultimately decreasing ATP production, rendering the neuron less excitable.

perpolarizing effects of the glucose-to-ketone switch. The effects of oxamate were seen not only in the basal ganglia but also in pyramidal cells in the hippocampus, an intensely studied brain structure, given its seizure-prone disposition and pathophysiological linkage with commonly encountered forms of temporal-lobe epilepsy. Further evidence of the pivotal role of LDH in seizure control was provided through knockdown experiments in which the expression of LDHA (a subunit of LDH) was diminished through direct intrahippocampal injection of an antisense oligodeoxynucleotide. Sada et al. found that the inhibition of LDH was cell-type specific, in that only principal cells but not inhibitory interneurons were affected. Moreover, they found that the hyperpolarization induced by LDH blockade was reversed by ATP-sensitive potassium-channel blockers.

They went on to show that LDH inhibition suppresses spontaneous recurrent seizures in two different animal models of temporal-lobe epilepsy (i.e., the pilocarpine and kainate models) and found that the ketogenic diet led to lower hippocampal levels of lactate. These intriguing findings led the investigators to explore whether any of the existing antiseizure drugs might work in part through LDH inhibition. They discovered that stiripentol, an agent that is used in the treatment of Dravet's syndrome (also called severe myoclonic epilepsy of infancy), a rare epileptic condition that is also responsive to a ketogenic diet, was only 1 of 20 antiseizure drugs that had a substantial inhibitory effect on LDH. Furthermore, in the quest to identify compounds similar to stiripentol, they discovered that isosafrole (an analogue lack-

ing the hydroxyl and tertiary-butyl groups) was also a potent LDH inhibitor and had similar antiseizure effects in their models. Collectively, their data identify an important metabolic enzyme that mirrors key aspects of the ketogenic diet.

For epilepsy therapeutics and our understanding of the neurobiology of epilepsy, the implications of these findings are enormous. First and foremost, the study by Sada et al. challenges the traditional view that epilepsy is principally a neuronal disease and does not critically involve other brain structures, such as glia or the vascular network. There is growing evidence that epilepsy, in a broad sense, may indeed be a metabolic disease. Second, the targeting of substrates and enzymes that are involved in cellular bioenergetics to counter metabolic abnormalities may prove to be at least as efficacious as existing treatments, since the ketogenic diet improves seizure control in the majority of patients who do not have a response to antiseizure drugs. Third, although the study by Sada et al. provides important mechanistic information about stiripentol and its structural analogues, it is conceivable that other antiseizure drugs might work in part by affecting differential aspects of cellular metabolism, potentially highlighting additional unique molecular targets for therapeutic development.

However, despite the scientific appeal of the study by Sada et al., there are important caveats. Several different isozymes of LDH are differentially localized in multiple cell types throughout the body (including in both neurons and glia), and it is not clear whether broad or selective inhibition of this enzyme family underlies modulation of seizure activity. Furthermore, since lactate is an important fuel under physiologic conditions, interfering with its conversion to pyruvate may result in untoward effects. Finally, the pathologically altered epileptic brain is bound to be vastly different from the normal one from a metabolic standpoint and undergoes widespread biochemical fluxes between interictal and ictal states. Notwithstanding such considerations, the study by Sada et al. will spark further debate regarding the relevance of neurons versus glia. It pragmatically highlights a new therapeutic target for the treatment of epilepsy and extends the profile of an enzyme that has long been perceived as a harbinger of illness and injury.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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DOI: 10.1056/NEJMcibr1503558