

Monocarboxylate Transport Matters

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The liver makes ketone bodies (3-hydroxybutyrate, acetoacetate, and acetone, the breakdown product of acetoacetate) from fat when intracellular glucose is in short supply — for example, in starvation or unregulated diabetes. The generated 3-hydroxybutyrate and acetoacetate serve as alternative energy sources for the cells. However, when the production of ketone bodies greatly exceeds cellular consumption, the potentially lethal condition of ketoacidosis can occur. How do ketone bodies get out of hepatocytes and into cells in other parts of the body to be metabolized?

Ketone bodies and other monocarboxylates, such as lactate and pyruvate, are transported out of and into cells by monocarboxylate transporters (MCTs), which are encoded by members of the solute carrier 16 (SLC16) gene family.¹ The proton and the monocarboxylate anion are transported together in the same direction, which means that the acid equivalents produced in ketogenesis follow the anion. The driving force is the combined concentration gradients of the monocarboxylate and proton that result from the difference between monocarboxylate production and consumption.¹

In this issue of the *Journal*, van Hasselt et al.² describe several defects in the gene encoding monocarboxylate transporter 1 (MCT1, or SLC16A1) as causes of inherited forms of ketoacidosis. Among 96 patients with ketoacidosis of unknown cause, the authors identified eight different mutations in MCT1, with corresponding loss of MCT1 function. The most severely affected patients were homozygous for the mutant allele. In these persons, intermittent stressors, such as infections or low energy intake, precipitated profound metabolic acidosis and massive excretion of 3-hydroxybutyrate and acetoacetate in the urine. In all patients, intravenous treatment with bicarbonate and glucose rapidly cleared the ketoacidosis.

All patients presented with episodic ketoacidosis, precipitated by fasting or infections during infancy. The age at diagnosis was 3 to 23 months for homozygous patients and 18 months to 6 years for patients with heterozygous variants. The symptoms subsided before 17 years of age,

which suggested the presence of adaptive mechanisms, such as adaptive expression of alternative MCT isoforms (although this remains to be demonstrated).

Heterozygous family members of patients with homozygous MCT1 mutations and MCT1 deficiency were often asymptomatic, which indicated that low-level MCT1 deficiency can go undetected or may cause symptoms only under conditions of clinically significant stress, such as prolonged fasting. Therefore, MCT1 deficiencies may be more prevalent than is currently apparent, and additional MCT1 mutations may be identified in the future.

A loss of MCT1 function could also occur as a result of other mechanisms, such as changes in basigin (also known as CD147), which modulates MCT1 function, or possibly by autoantibodies directed against external domains of these proteins.¹

MCT1 is the most widely distributed MCT isoform and, with its affinity intermediate between MCT2 and MCT4, is suitable for export as well as import of monocarboxylates.¹ MCT1 is expressed in hepatocytes (where ketogenesis takes place), as well as in tissue cells where ketolysis can occur, primarily in skeletal muscle, heart, and brain, including in brain capillary endothelium — that is, at the blood–brain barrier.³ The localization of MCT1 at the luminal and abluminal surfaces of the brain vascular endothelial cells,⁴ which are connected by tight junctions, controls the entry of ketone bodies into the brain.

The proportion of MCT1 present at the endothelial cell surface is regulated through cAMP-dependent mechanisms,⁵ which implies that there is regulation of the tissue entry and exit of monocarboxylates. The 3-hydroxybutyrate receptor HCAR2 (also known as nicotinic acid receptor, GPR109A) down-regulates cAMP.⁶ HCAR2 has vascular effects,⁷ and its congener, the lactate receptor HCAR1 (GPR81), is found on brain capillaries⁸; therefore, these receptors may be involved in regulating the large capacity of the brain for consumption of ketone bodies and in controlling the cerebral effects of ketoacidosis. Of note, MCT1 is also expressed in erythrocytes,⁹

where it increases the capacity of blood for carrying ketone bodies between organs.

Some of the patients with *MCT1* mutations had signs and symptoms of central nervous system (CNS) disorders, such as microcephaly, migraine, and epilepsy. Patients with homozygous mutations also had moderate intellectual disability. A link between *MCT1* dysfunction and CNS disorders is plausible. Humans with medically intractable focal epilepsy and animal models thereof have marked alterations in the density and distribution of *MCT1* in the seizure focus,⁴ which suggests a role for *MCT1* in seizure regulation, possibly by regulating extracellular brain lactate concentrations, which are increased in the seizure focus.¹⁰

Van Hasselt et al.² have shown that *MCT1* is important for the transfer of ketone bodies to tissue cells that can use them. Thus, *MCT1* mutations have an important and newly discovered role in the causation of ketoacidosis. The findings call for further studies of *MCT* mutations in human health and disease.

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

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