KTX 0101: A Potential Metabolic Approach to Cytoprotection in Major Surgery and Neurological Disorders

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ABSTRACT

KTX 0101 is the sodium salt of the physiological ketone, D-β-hydroxybutyrate (βOHB). This neuroprotectant, which has recently successfully completed clinical Phase IA evaluation, is being developed as an intravenous infusion fluid to prevent the cognitive deficits caused by ischemic foci in the brain during cardiopulmonary bypass (CPB) surgery. KTX 0101 maintains cellular viability under conditions of physiological stress by acting as a “superfuel” for efficient ATP production in the brain and peripheral tissues. Unlike glucose, this ketone does not require phosphorylation before entering the TCA cycle, thereby sparing vital ATP stores. Although no reliable models of CPB-induced ischemia exist, KTX 0101 is powerfully cytoprotective under the more severe ischemic conditions of global and focal cerebral ischemia, cardiac ischemia and lung hemorrhage. Neuroprotection has been demonstrated by reductions in infarct volume, edema, markers of apoptosis and functional impairment. One significant difference between KTX 0101 and other potential neuroprotectants in development is that βOHB is a component of human metabolic physiology which exploits the body’s own neuroprotective mechanisms. KTX 0101 also protects hippocampal organotypic cultures against early and delayed cell death in an in vitro model of status epilepticus, indicating that acute KTX 0101 intervention in this condition could help prevent the development of epileptiform foci, a key mechanism in the etiology of intractable epilepsy. In models of chronic neurodegenerative disorders, KTX 0101 protects neurons against damage caused by dopaminergic neurotoxins and by the fragment of β-amyloid, Aβ1–42, implying possible therapeutic applica-
tions for ketogenic strategies in treating Parkinson’s and Alzheimer’s diseases. Major obstacles to the use of KTX 0101 for long term therapy in chronic disorders, e.g., Parkinson’s and Alzheimer’s diseases, are the sodium loading problem and the need to administer it in relatively large amounts because of its rapid mitochondrial metabolism. These issues are being addressed by designing and synthesizing orally bioavailable multimers of βOHβ with improved pharmacokinetics.