Title: Maple Syrup Urine Disease *GeneReview* – Pathophysiology of MSUD
Authors: Strauss KA, Puffenberger EG, Carson VJ
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Leucine and alpha-ketoisocaproic acid (aKIC) cause a complex neurochemical syndrome that disturbs brain protein accretion, neurotransmitter synthesis, cell volume regulation, neuron growth, and myelin synthesis (see Figure 1). The neurotoxicity of leucine stems in part from its ability to interfere with transport of other large neutral amino acids across the blood-brain barrier, reducing the brain's supply of tryptophan, methionine, tyrosine, phenylalanine, histidine, valine, and threonine [Gjedde & Crone 1983, Smith & Takasato 1986, Boado et al 1999, Killian & Chikhale 2001]. Cerebral amino acid deficiency has adverse consequences for brain growth and synthesis of neurotransmitter such as dopamine, serotonin, norepinephrine, and histamine [Kamei et al 1992, Araújo et al 2001, Zinnanti et al 2009].

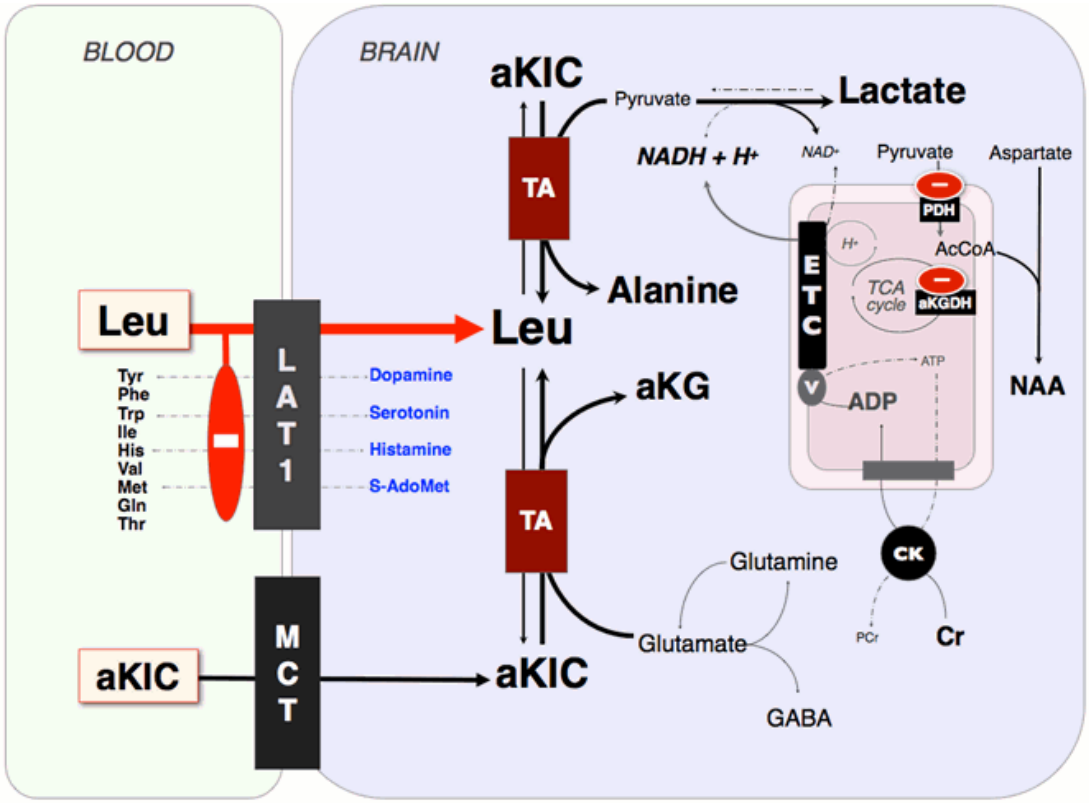

Figure 1. Theories of neurotoxic mechanisms from maple syrup urine disease. At the blood-brain barrier, leucine — which has a low K_m for large amino acid transporter 1 (LAT1) — saturates the transporter and blocks uptake of its competitors, tyrosine (Tyr), phenylalanine (Phe), tryptophan (Trp), isoleucine (Ile), histamine (His), valine (Val), methionine (Met), glutamine (Gln), and threonine (Thr). Among these are precursors for neurotransmitters (dopamine, norepinephrine, serotonin, and histamine) and S-adenosylmethionine (S-AdoMet), the brain's major methyl donor. Alpha-ketoisocaproic acid (aKIC) enters the brain via the monocarboxylate transporter (MCT) and reverses flux through cerebral transaminases (TA). This depletes brain glutamate, GABA, and glutamine while increasing production of leucine and

alpha-ketoglutarate (aKG). Glutamate and GABA are the most abundant excitatory and inhibitory neurotransmitters, respectively, in the human brain. MSUD encephalopathy may also block oxidative phosphorylation through an as-yet unknown mechanism; in vitro data have implicated aKIC-mediated inhibition of pyruvate dehydrogenase (PDH), alpha-ketoglutarate dehydrogenase (aKGDH), and components of the electron transport chain (ETC). Impaired mitochondrial function can interfere with the production of N-acetylaspartate (NAA), which therefore serves as a marker for neuronal energy production. Additionally, energy from ATP is sometimes transferred to the creatine (Cr)-phosphocreatine (PCr) system for later use.

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Alpha-ketoisocaproic acid and the other branched-chain alpha-ketoacids (BCKAs) may exert toxicity by interfering with transamination reactions in muscle and brain (see Figure 1). In tissue culture and perfused brain, extracellular aKIC concentrations greater than 60 µmol/L reverse astrocyte transamination reactions, causing a 50% depletion of glutamate and glutamine, and reduced aspartate and pyruvate [Yudkoff et al 2005, Zinnanti et al 2009]. Severe deficiencies of cerebral glutamate, GABA, and aspartate have been observed in brains of calves with naturally occurring branched-chain alpha-ketoacid dehydrogenase (BCKD) deficiency and in postmortem brain of a human infant with MSUD [Prensky & Moser 1966, Dodd et al 1992]. In a murine model of MSUD [Zinnanti et al 2009], leucine and aKIC accumulation in brain tissue is accompanied by depletion of glutamate, GABA, pyruvate, and dopamine, while alpha-ketoglutarate, alanine, and lactate increase. In humans with classic MSUD, quantitative proton magnetic resonance spectroscopy (MRS) reveals brain glutamate levels 69%-79% of normal that vary inversely with plasma leucine concentration and the calculated cerebral leucine uptake (see Figure 2) [Muelly et al 2013].

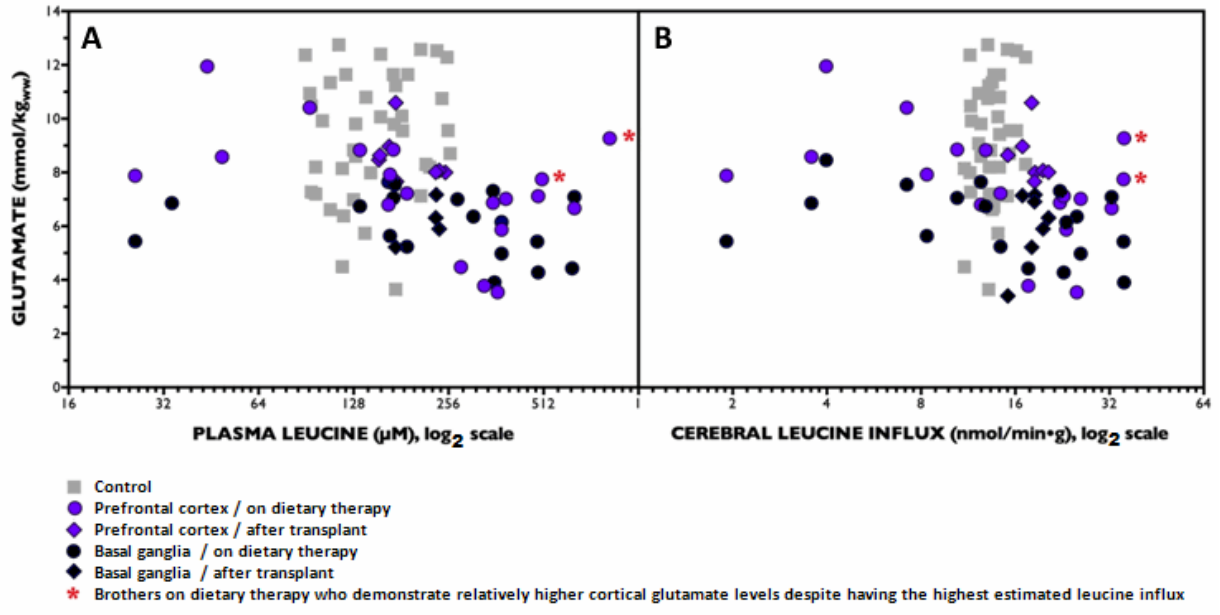

Figure 2. Cortical glutamate and plasma leucine levels. Glutamate (in mmol/kg wet weight, ww) in the prefrontal and anterior cingulate cortices (violet) and basal ganglia region (black) inversely correlated with ambient plasma leucine (A) and the calculated cerebral leucine influx (B) in affected individuals on the MSUD diet (circle) or after liver transplantation (diamond). Red asterisks indicate two patients (brothers)

on the MSUD diet who demonstrate relatively higher cortical glutamate levels despite having the highest estimated leucine influx.

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Cerebral lactate is elevated in humans with acute MSUD encephalopathy [Heindel et al 1995, Jan et al 2003] and may be related to reversible inhibition of the respiratory chain by elevated cerebral alpha-ketoisocaproic acid [Sgaravatti et al 2003]. In the mouse model, cerebral ATP and phosphocreatine are low and the ratio of lactate to pyruvate in tissue increases 40-fold, suggesting reduced electron flow through the respiratory chain as reducing equivalents accumulate in mitochondria and cytosol [Zinnanti et al 2009]. The cerebral lactic acidosis associated with MSUD encephalopathy resolves without permanent sequelae, and does not have the same prognostic significance as cerebral lactate accumulation caused by ischemia. Quantitative MRS of individuals with MSUD who are clinically and metabolically stable shows a statistically significant 10%-15% decrease of cerebral N-acetylasparate [Muelly et al 2013], indicating that the biochemical derangement caused by BCKD deficiency may chronically interfere with neuronal energy and/or neurotransmitter metabolism and not be fully corrected by liver transplantation [Strauss et al 2020].

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