Targeting mitochondrial transporters to treat metabolic and neurodegenerative disease

Clinical markers consistently link Alzheimer's Disease (AD) with dysregulated glucose metabolism, and this association is reinforced by epidemiological data showing type 2 diabetes is a significant risk factor for cognitive impairment. As such, several anti-diabetic therapies are currently under evaluation for the treatment of AD and other neurodegenerative diseases. These repurposing efforts include intranasal insulin delivery, incretin analogs, and thiazolidinediones (TZDs). In addition to being PPARγ agonists, we discovered that TZDs also inhibit the mitochondrial pyruvate carrier (MPC) at clinically relevant concentrations. The MPC is an inner membrane transporter that facilitates pyruvate uptake from the cytoplasm into mitochondria, and is a crucial regulatory branch point in cellular energy metabolism.

Reductions in mitochondrial pyruvate uptake do not compromise ATP production, but rather rewire mitochondrial metabolism to rely more on amino acids and fatty acids to fuel energetic and biosynthetic needs. In primary cortical neurons, MPC inhibition selectively increases oxidation of the amino acid glutamate, the dominant excitatory neurotransmitter in the brain. This protects neurons from glutamate excitotoxicity by reducing the size of the glutamate pool released upon depolarization, thus limiting the positive-feedback cascade of excitotoxic neuronal injury. The results establish mitochondrial pyruvate transport as a surprising and novel therapeutic avenue to treat neurodegenerative diseases characterized by excessive synaptic glutamate accumulation, which include epilepsy, stroke, traumatic brain injury, and AD.