

#### **4<sup>th</sup> EUROPEAN GLUT1 CONFERENCE – July 15-16, 2023**

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*“How Does the Diet Work? Ketogenic Dietary Effects and Mechanisms in Brain Metabolism”*

#### **ABSTRACT**

At the turn of the first century of ketogenic diet (KD) use for medically intractable epilepsy, investigators have uncovered a multiplicity of potential mechanisms that may underlie the clinical effects of this metabolism-based treatment. In the process, there have emerged important insights into the biochemical and metabolic bases of epilepsy, and novel approaches and targets that can be exploited for experimental and clinical therapeutics. Historically, metabolic changes thought to mediate the KD's anti-seizure effects have included – but are not limited to – ketosis, glycolytic restriction, increased purinergic and GABAergic neurotransmission, fatty acid modulation of ion channels, improved cellular and mitochondrial bioenergetics, as well as a reduction in oxidative stress. More recently, it has been shown that the KD and its variants, such as the medium chain triglyceride diet, may induce anti-inflammatory, neuroprotective, epigenetic, and even anti-epileptogenic effects. Finally, the gut microbiome has been linked to enhanced central inhibitory-excitatory balance through changes in the blood metabolome. As dietary treatments have been increasingly shown to evoke a wide array of metabolic, physiologic and hormonal effects, future research will undoubtedly reveal an even more complex mechanistic framework for KD action, but one which should enable the development of improved dietary formulations, or simplified treatments based on the biology of specific biochemical substrates and enzymes, not only for epilepsy but also potentially for a broader range of neurological disorders.