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“THE GUT-BRAIN AXIS IN
SEIZURE SUSCEPTIBILITY:
A ROLE FOR MICROBIAL
METABOLITE S-EQUOL”



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ABSTRACT

Epilepsy is a complex, chronic neurological disorder with diverse underlying etiologies characterized by the spontaneous occurrence of seizures. In adults, the leading cause of epilepsy worldwide in central nervous system (CNS) infection, while in neonates the most common cause of seizures is hypoxic/ischemic encephalopathy (HIE). However, in both adults and neonates, current antiepileptic drugs (AEDs) are ineffective in 30-50% of patients, despite the availability of over 20 FDA approved AEDs with diverse molecular targets. This disparity highlights a critical need for novel therapeutics in seizure-susceptibility and epilepsy. The microbes that inhabit gut mucosal surfaces, termed the gut microbiota, have been increasingly implicated in the pathology of neurological diseases including epilepsy. In this dissertation, we evaluate gut microbiome alterations in the Theiler's murine encephalomyelitis virus (TMEV) adult mouse model of CNS infection-induced seizures and find decreases in S-equol-producing bacteria in the gut microbiomes of TMEV-infected mice with seizure phenotypes. We additionally characterize entorhinal cortex (ECTX) pyramidal neuronal hyperexcitability, and demonstrate the ability of exogenous S-equol to ameliorate CNS-infection-induced ECTX neuronal hyperexcitability ex vivo. Finally, we demonstrate that perinatal and postnatal exposure to antibiotics alters the gut microbiome and increases seizure-susceptibility following HIE exposure in p9/p10 mice, potentially via sex-specific alterations in neuronal function. Together, this dissertation evaluates the gut-brain axis in pediatric and adult mouse models of seizure-susceptibility and identifies the gut metabolite S-equol as a potential target for the treatment of seizures.