THE UNIVERSITY OF ARIZONA
COLLEGE OF MEDICINE TUCSON
Pharmacology

Seminar Series
Presents

"Modulating CRMP2 in a mouse model of multiple sclerosis: Effects on neurons and oligodendrocytes"

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Abstract: LKE (lanthionine ketimine ethyl ester) is a derivative of lanthionine ketimine, a cyclized metabolite of the amino acid lanthionine. In vitro LKE has neuroprotective and neuritogenic actions, and reduces inflammatory activation of microglial cells. In vivo, LKE provides benefit in mouse models of neurological diseases including ischemia, AD, and spinal cord injury. We examined effects of LKE in a mouse model of MS called EAE. We found that LKE given to already ill mice reduced disease severity, and using EM found that LKE reduced neuronal damage and increased myelin thickness. To examine mechanisms, using primary neurons and find that LKE directly reduces neurotoxicity due to glutamate, and increases neurite numbers and length. We also tested effects on primary cultures of oligodendrocytes (OLG) and find that LKE increases the number of OLG progenitor cells (OPCs) and induces their maturation. One of the major targets of LKE is CRMP2 (collapsing response mediator protein 2), whose activity is regulated by multiple phosphorylation events. To determine if CRMP2 mediates LKE actions, we generated mice with conditional knockout of CRMP2 from neurons. Surprisingly, this led to less severe EAE disease. In contrast, replacement of a key serine residue (S522) with alanine to render it non-phosphorylatable led to protection, as seen in other models. Overall, our studies suggest that CRMP2 modulators such as LKE could be of benefit in demyelinating diseases; and begin to shed light on which proteins and mechanisms underlie those actions.

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