THE PROTECTIVE EFFECTS OF FERROSTATIN-1 (FER-1) IN RESPONSE TO EXCITOTOXICITY IN MOUSE HIPPOCAMPAL SLICES

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Dedication

Dedicated to my mother Mireya Mendez Legarreta

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Abstract

The development of different neurological disorders has been associated with the accumulation of reactive oxygen species (ROS). Elevated ROS levels can disrupt the neuronal electrical activity. This phenomenon has been seen during epilepsy and neurodegenerative diseases like Parkinson's disease. Furthermore, the excess of ROS and development of such disorders have been linked to neuronal cell death partly due to excessive, non-physiological glutamate release. Ferroptosis is a recently defined iron-dependent cell death mechanism. Inducible by a small molecule called erastin, ferroptosis was first described in cancer cells. Erastin-induced ferroptosis differs from apoptosis, necrosis and autophagy, since it leads to different biochemical and morphological changes, compared to the other cell death mechanisms. It is characterized by the accumulation of iron-dependent lethal ROS. Interestingly, both ferroptosis and glutamate excitotoxicity are associated with an increase in ROS levels. Moreover, both erastin-induced ferroptosis in cancer cells and glutamate-induced cell death in neurons can be inhibited by Ferrostatin-1 (Fer-1), a small molecule bearing antioxidant properties. This suggest that both cell death mechanisms share a similar lethal pathway that can be rescued by Fer-1. To better understand the neuroprotective properties of Fer-1, the morphological and electrophysiological changes induced by glutamate excitotoxicity and erastin were examined and compared to conditions where Fer-1 is present. The proposed project employed cell cultures, immunostaining and *in vitro* electrophysiological experiments in hippocampal slices from mice.

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