

## Morphological effects of chronic excitotoxicity depend on autophagy activation failure

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It is well known that exposure to excitatory amino acid in specific experimental conditions might produce a defect in the autophagy pathway. Such an effect was observed in motor neurons exposed chronically to glutamate agonists. In particular, it is well known that glutamate induces motor neuron death and this is supposed to play a key role in the pathophysiology of motor neuron loss in amyotrophic lateral sclerosis (ALS). Similarly, a defective recruitment of autophagy was recently documented in ALS.

In the present study, we used primary motor neuron cultures to analyze whether AMPA receptor stimulation via kainic acid produces activation of autophagy and whether this is defective compared with what it is required to rescue motor neurons. In particular we found that exposure of motor neurons to kainic acid produces intracellular alterations associated with defective autophagy.

The ultrastructural alterations consist of increased motor neurons size, damaged mitochondria, protein accumulation, large cytoplasmic vacuoles placed in perinuclear positions. These cellular alterations are reminiscent of ALS, which in turn is characterized by a defective autophagy.

Once we confirmed that excitotoxicity recruits autophagy, which remains defective to clear altered proteins and organelles, we provided a pharmacological stimulation of such a pathway in order to ameliorate motor neuron survival.

In these experimental conditions, we observe that pharmacological activation of the autophagy machinery is able to counteract kainic acid-mediated motor neuron damage.

Keywords: Kainic acid; excitotoxicity, lithium; motor neuron; amyotrophic lateral sclerosis.