Neuroprotective or neurotoxic effects of 4-aminopyridine mediated by KChIP1 regulation in primary hippocampal cells.

María Teresa Frejo[1], Paula Moyano[2], María Jesús Díaz[1], Gloria Gomez[2], María José Anadón[2], Margarita Lobo[1], Jimena García[3], Miguel Andrés Capo[1], Jose Manuel Garcia[2] and Javier del Pino[1]

[1]Complutense University, School of Veterinary Medicine, Madrid 28040, Spain.
[2]Complutense University, Medical School, Madrid 28040, Spain.
[3]Alfonso X University, Health Sciences School, Madrid 28691, Spain.

INTRODUCTION

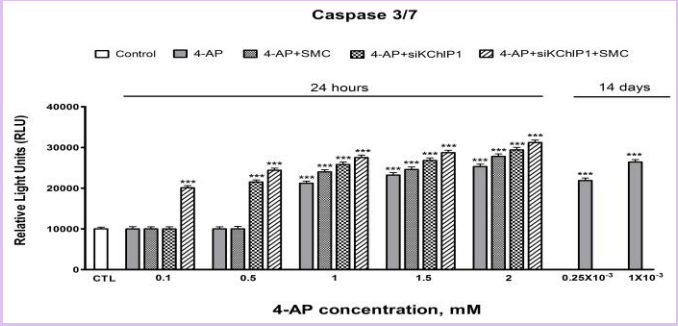
4-Aminopyridine (4-AP) is a potassium channel blocker used for the treatment of neuromuscular disorders. Otherwise, it has been described to produce a large number of adverse effects among them cell death mediated mainly by blockage of K+ channels. Specifically, 4-AP has been reported to produce cell death in central nervous system on hippocampal cells. However, a protective effect against cell death has also been described. On the other hand, Kv channel interacting protein 1 (KChIP1) is a neuronal calcium sensor protein that is predominantly expressed at GABAergic synapses and it has been related with modulation of K+ channels, GABAergic transmission and cell death. According to this KChIP1 could play a key role in the protective or toxic effects induced by 4-AP.

METHODS

We evaluated, in wild type and KChIP1 silenced (siKChIP1) primary hippocampal neurons, the effect of 4-AP (0.25 mM to 2 mM) with or without semicarbazide (SMC, 0.3 M) co-treatment after 24 h and after 14 days 4-AP alone exposure on cell viability.

RESULTS

4-AP induced cell death after 24 h (from 1 mM) and after 14 days treatment, which was modulated by KChIP1 through GABAergic transmission.



CONCLUSIONS

These data might help to explain protective and toxic effects observed after overdose and long term exposure.