

## **Evaluation of the endocannabinoid receptors and enzymes in the postmortem cerebellum of different SCA patients**

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### Research question and background

Cannabinoid compounds are a rare and unique class of substances that are capable of affording neuroprotection through the combination of different cellular and molecular mechanisms. Even, the early malfunctioning of the cannabinoid signaling system has been associated with the initiation and the progression of these disorders. Our group has contributed significantly during the last 15 years in the study of the function and therapeutical potential of the cannabinoid signaling system in Huntington's disease, Parkinson's disease and multiple sclerosis using *in vivo* and *in vitro* experimental models of these diseases. There is, however, no data on the neuroprotective potential of cannabinoids in spinocerebellar ataxias (SCAs), so we recently decided to study the issue in this class of genetic disorders starting by an evaluation of the status of the endocannabinoid signalling system in postmortem tissues from SCA patients.

### Methods and tissues used

We have conducted some analyses in postmortem tissue from patients with different types of SCAs received from NBB. We performed immunostaining for CB1 and CB2 receptors and endocannabinoid-degrading enzymes FAAH and MAGL in the cerebellum of patients compared with control subjects. We also conducted double-staining analyses in order to establish the cellular localization of those elements of the endocannabinoid system that appear altered in the cerebellum of patients.

### Results and conclusion

Our results show an increase in the immunoreactivity for the CB1 and CB2 receptor, FAAH and MAGL in the cerebellum of patients that was evident in granular and Purkinje layers but also in other parts of the cerebellum. The double-staining experiments showed that CB1 receptors are localized in Purkinje cells and also in astrocytes, reactive microglia and macrophages of the cerebellar white matter. CB2 receptor is localized in Purkinje cells, Bergmann glia, astrocytes and microglia of the cerebellar white matter. The identification of various elements of the endocannabinoid system in the Purkinje neurons, which are the main cells affected in SCAs, as well as the changes observed in these elements in SCA patients, suggest that alterations in this neuromodulatory system may be related to the pathogenesis of SCAs. This also supports the idea that the endocannabinoid system could be a potential therapeutic target for treating symptoms and, particularly, disease progression in SCAs, a fact that we are presently investigating in a model of SCA3 mutant mice.

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