Endocannabonoids and Stroke: a new therapeutically approach

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Background

Stroke is one of the leading causes of disability and death all over the world. The endocannabinoid system (ECS) is up-regulated in several neurological diseases including stroke or neurodegenerative disorders, and may represent a neuroprotective tool. The mechanism of neuroprotective effects is still unclear. Endocannabinoids (eCB) (anandamide, 2-arachidonoylglycerol) are lipid mediators synthesized "on demand" that inhibit neurotransmitter (glutamate and GABA) release and modulate neuroinflammation by activating specific receptors CB1 and CB2 (both highly expressed in the central nervous system and peripheral ones). ECB-related molecules like palmitoylethanolamide (PEA), have been showed also to exert neuroprotective effects in different neurological diseases.

Data analysis and personal experience

Previous animal and in vivo studies demonstrated increased expression of the CB1R in the penumbra area surrounding the central ischemic core. Moreover, CB1 agonist administration was associated with a decrease of infarct volume and improvement of clinical symptoms in stroke treated mice. ECS involvement include: modulation of immune responses and the release of inflammatory mediators; modulation of synaptic plasticity and excitatory glutamatergic transmissions; activation of cytoprotective signalling pathways; modulation of calcium homoeostasis and excitability; central hypothermia; antioxidant properties.

In one autoptic study we evaluated the cerebral expression of CB1R in the ischemic brain areas of 9 patients died after a first acute cerebral infarction in the middle cerebral artery territory. In the cerebral autoptic tissue, collected for each subject within 48 hrs since death, ischemic and contralateral normal appearing areas were identified. Through immunohistochemistry procedure brain tissue was incubated with the specific primary CB1R antibodies and total cell number and total CB1R-positive cells were counted. A significant increase of total CB1R staining was found in the ischemic regions in comparison to contralateral normal appearing areas, mainly due to a significant increase of CB1R-positive non-neuronal cells. According with previous data, we found an increase of CB1R expression in the ischemic region (due to neuronal and non-neuronal cells) that may reflect the inflammatory reaction to the ischemic insult. Whether such response might mediate neuroprotective actions or excitotoxicity-related detrimental effects is still unclear.

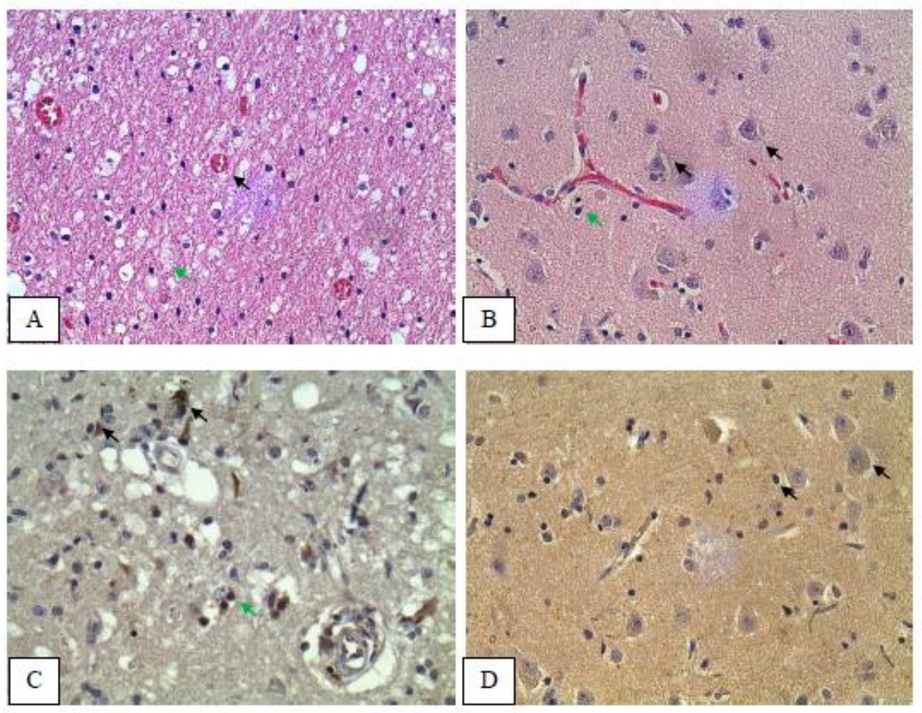

Figure 1*: (A-B) Hematoxylin-eosin tissue coloration showing at 40X lesional, ischemic sample (A) oedematous (green), with important neuronal cells loss and alterated vessel's wall (black), and healthy tissue (B), with neuronal cells (black) and glia (green). (C-D) IHC sample, (C) lesional CB1 reactivity in neurons (black) and non-neronal cells (green). (D) CB1 reactivity in "healthy" controlateral tissue (black).*

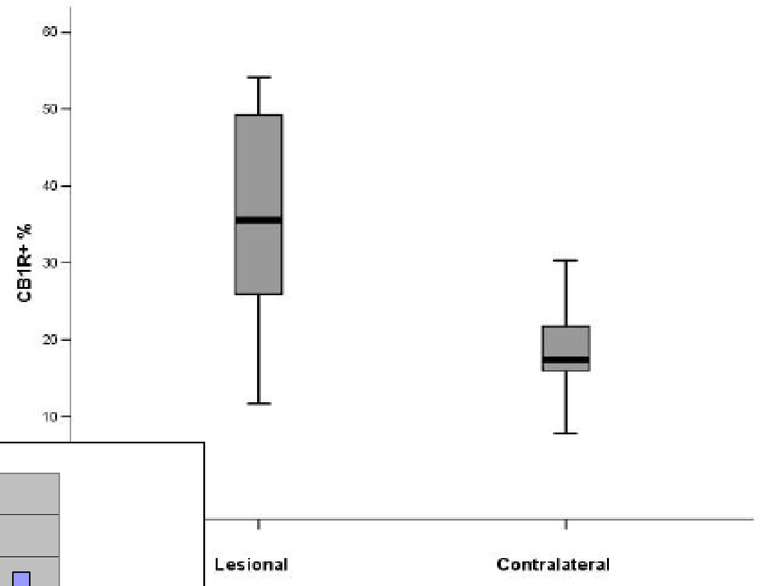

Figure 2*: Expression of CB1-positive elements in the Lesional region vs Controlateral tissue, for each subject. (CB1R+L=CB1R staining percentage in the Lesional area; CB1R+C= CB1R staining percentge in the Contaralateral ("healthy") region. Neuron: staining percentage for Neurons; Non-neuron: staining percentage for non neuronal cells). Box Plot of CB1 reactivity in Lesional and Controlateral area (p=0.00089).*

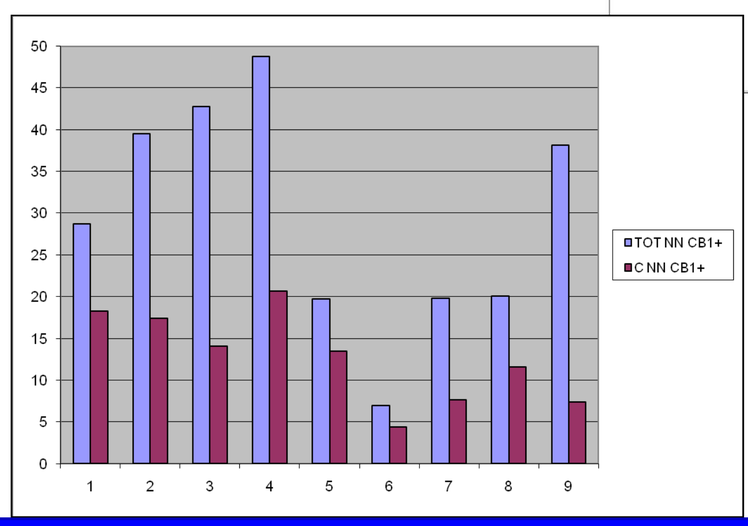

Figure 3: *CB1 positive non-neuronal cells in Lesional region vs Controlateral tissue, for each subject (p=0.0017).*

Conclusion and future perspective

Considering possible new therapeutics approach for stroke injury the potential neuroprotective role of the ECs and particularly of PEA should be investigated. Further studies are required to assess the efficacy of PEA administration in terms of functional recovery, reduction of incidence of cerebral or systemic embolism, radiological evolution of the ischemic region and safety.

References

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