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Topic: AS03 Stem Cells, Organoids, Neural Injury Neurotoxicity and Repair

DIFFERENT NEUROPROTECTIVE STRATEGIES WITH NEUROTROPHIC FACTORS FOR DEALING WITH SELECTIVE NEURONAL LOSS

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The Purkinje Cell Degeneration (PCD) mouse suffers the postnatal death of cerebellar Purkinje neurons and mitral cells of the olfactory bulb (OB). Moreover, PCD mice are defective in IGF1, but little is known about other neurotrophic factors. Besides, neurotrophic factors have a well-known neuroprotective effect, which can be employed to develop refined and effective therapies. First, the expression of different neurotrophic factors (IGF1, BDNF, VEGF-A and VEGF-B) around cerebellar and bulbar degenerations was analyzed by qPCR and ELISA. Then, we applied two different therapeutic approaches depending on the affected region of PCD mice. 1. Since a transplant of healthy bone marrow can slow down the degeneration of mitral cells, we refined this methodology for dealing with OB degeneration. PCD mice were transplanted with 7.5 million healthy bone marrow stem cells, supplemented with genetically modified hematopoietic cells for overexpressing the *Igf1* gene. At P150, animals were sacrificed and their olfactory bulbs were analyzed by immunofluorescence and quantitative PCR. 2. Concerning cerebellar degeneration, recombinant human IGF-1 (rhIGF-1) or recombinant human VEGF-B (rhVEGF-B) were administered in PCD mice following a schedule based on the variations on their expression around Purkinje cell loss. After motor test, cerebella were analyzed at either P25 or P30 by immunofluorescence. Results showed that only IGF1 and VEGF-B presented variations around the neurodegenerative processes of PCD mice. Concerning OB, the transplantation of a genetically modified healthy bone marrow stopped the mitral cell loss of PCD mice. IGF1-enriched transplants changed the inflammatory pattern and prevented DNA damage. Regarding cerebellar degeneration, we observed an improvement in both motor coordination and Purkinje cells survival in PCD mice administered with rhVEGF-B. qPCR analyses revealed an inhibition of the intrinsic pathway of the apoptotic process. In conclusion, neurotrophic factors are very suitable candidates to develop different neuroprotective therapies. Support: MICINN (PID2019-106943RB-I00), JCyL (SA129P20), USAL

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IMPACT OF DIFFERENT FORMULATIONS OF PHARMACEUTICAL CANNABIS-BASED EXTRACTS ON THE NEUROPROTECTIVE EFFECT IN CEREBELLAR GRANULE CELL CULTURES

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Preclinical research supports the benefits of pharmaceutical cannabis-based extracts for treating different medical conditions (e.g., epilepsy); however, their neuroprotective potential has not been widely investigated. In addition, there is still controversy about the impact of other factors in the beneficial effect of these extracts (e.g., the entourage effect, and oil formulations). We evaluated the neuroprotective activity of Epifractan (EPI), a cannabis-based medicinal extract containing a high level of cannabidiol (CBD), components like terpenoids and flavonoids, and trace levels of Δ9-tetrahydrocannabinol and the acid form of CBD. Using primary cultures of cerebellar granule cells, we determined the ability of EPI to counteract the rotenone-induced neurotoxicity by analyzing cell viability and morphology of neurons and astrocytes by immunocytochemical assays. The effect of EPI was compared with XALEX, a plant-derived and highly purified CBD formulation (XAL), and pure CBD crystals (CBD). The results revealed that EPI induced a significant reduction in the rotenone-induced neurotoxicity in a wide range of concentrations without causing neurotoxicity per se. EPI showed a similar effect to XAL suggesting that no additive or synergistic interactions (i.e., entourage effect) between individual substances present in EPI occurred. In contrast, CBD crystals did show a different profile to EPI and XAL since a neurotoxic effect per se was observed at the higher concentrations assayed. Medium-chain triglyceride oil used in EPI formulation could explain this difference. Our data support a neuroprotective effect of EPI which may provide neuroprotection in different neurodegenerative processes. The results highlight the role of CBD as the active component of EPI but also support the need for an appropriate formulation to dilute pharmaceutical cannabis-based products, which could be critical to avoid neurotoxicity at very high doses.

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