

## INVOLVEMENT OF CANNABINOID SYSTEM IN PROLIFERATION OF CEREBELLAR NEURAL PROGENITOR CELLS

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The recent discovery of neural progenitor/stem cells in the adult brain has provided strong support for the existence of neurogenesis (*i.e.*, generation of new neurons). The cannabinoid system has been recently shown to promote neurogenesis in the adult hippocampus (1), although the intracellular molecular mechanisms underlying this effect have not been fully understood. Cannabinoids and endocannabinoids exert their actions in the brain through activation of two types of metabotropic receptors, CB1 and CB2, and affect a large number of physiological processes, including learning, memory, emotion, pain perception, immune and inflammatory responses, cardiovascular function, and reproduction.

To elucidate the cellular and molecular mechanisms underlying cannabinoid neurogenic action, we used neural progenitor cells isolated from post-natal cerebellum, as an *in vitro* model of neural cell proliferation. Phenotypical and genotypical characterization of these cells by immunocytochemistry and RT-PCR, respectively, has shown that they were immunoreactive for several immature neuronal markers and possess both cannabinoid receptors, CB1 and CB2. Furthermore, isolated cerebellar progenitor cells could be induced to differentiate into mature neuronal and glial cells by withdrawing the mitogen growth factors. Twenty four-hour treatment of cerebellar neural progenitor cells at 10 days in vitro (DIV) with increasing concentrations (1-1000 nM) of the non-selective synthetic cannabinoid agonists, CP-55,940 and WIN-55,212-2, increased cell proliferation, evaluated as [<sup>3</sup>H]thymidine incorporation, by  $20.2 \pm 7.9\%$  and  $35.3 \pm 9.5\%$ , respectively. The proliferative response induced by either CP-55,940 or WIN-55,212-2 was completely abolished by the selective CB1 receptor antagonist AM251 (0.1-1  $\mu$ M), thus suggesting an involvement of CB1 receptor activation. In addition, preliminary results showed that both cannabinoid agonists increased mRNA levels for cyclin D1, which is known to play a critical role in the progression of cell cycle. Research are in progress to define the intracellular transduction pathways leading from CB1 receptor activation to the increase in cyclin D1 expression.

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2. Zusso M., Debetto P., Guidolin D., and Giusti P. (2004) Crit. Rev. Neurobiol. 16(1-2): 59-65.