

NEUROGENIC RESPONSE INDUCED BY FLUOXETINE CHRONIC TREATMENT IN NEURAL PROGENITOR CELLS ISOLATED FROM RAT POSTNATAL CEREBELLUM

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In a previous study (1), we demonstrated that primary cultures of granule cells obtained from rat postnatal cerebellum contain a cell population, named *round cells*, responsible for the increase in cell proliferation and differentiation induced by chronic treatment with the selective serotonin-reuptake inhibitor (SSRI) fluoxetine. In the present work, we phenotypically and functionally characterized *round cells* as neural progenitor cells, upon isolation and expansion in culture, based on their expression of several immature neuronal markers and their lack of immunoreactivity to mature neural markers. Isolated *round cells* could proliferate for extended periods, but displayed only a limited self-renewal capacity. After removal of growth factors from the medium, *round cells* spontaneously differentiated into neuronal and glial phenotype, thus proving their multipotency. Chronic treatment of *round cells* with 1 μ M fluoxetine induced a significant increase in both cell proliferation and differentiation, that was completely abolished by the selective antagonist at 5-HT_{1A} serotonin receptor, N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride maleate (WAY-100635). The genotypic characterization of *round cells*, by means of RT-PCR and Western blotting, revealed the expression of either tryptophan hydroxylase (TPH) or serotonin and the presence of mRNA for serotonin transporter (SERT) and several serotonergic receptor subtypes. Furthermore, fluoxetine chronic treatment of *round cells* activated cAMP-response element-binding protein (CREB) and extracellular signal-regulated protein kinase (ERK1/2) by increasing their phosphorylation state, and increased the expression of cyclin D1. All these effects were completely counteracted by WAY-100635. These findings show that rat postnatal cerebellum contains neural progenitor cells able to proliferate and differentiate *in vitro* in response to fluoxetine chronic treatment, possibly through activation of 5-HT_{1A} receptor leading to CREB activation.

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