GROUP-II METABOTROPIC GLUTAMATE RECEPTOR LIGANDS AS ADJUNCTIVE DRUGS IN THE TREATMENT OF DEPRESSION: A NEW STRATEGY TO SHORTEN THE LATENCY OF ANTIDEPRESSANT MEDICATION?

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Introduction. Antidepressant drugs have a clinical latency that correlates with development of neuroadaptive changes. We found that low doses of LY379268 (a systemically active mGlu2/3 receptor agonist) shorten the latency of imipramine in down-regulating hippocampal ß-adrenergic receptors from 21 to 14 days (1). A recent study shows that fluoxetine enhances cell proliferation of cerebellar granule cell neuroprecursors in a new *in vitro* model of antidepressant-induced neurogenesis (2). Here, we examined whether pharmacological activation of mGlu2/3 receptors influences the ability of classical antidepressants to stimulate cell proliferation and differentiation of cultured cerebellar neuroprecursors, and to relieve depressive symptoms in genetically selected Flinders Sensitive Line (FSL) rats, which show an increased immobility time in the forced swim test and are known to respond to chronic, but not subchronic, antidepressant treatment. **Materials and Methods** Cerebellar neuroprecursors cells of 7- day-old rat pups were isolated and grown as described previously (3). Western Blot analysis of mGlu receptors was performed as previously described (1). Cell proliferation and differentiation were evaluated after 72 hours of treatment with fluoxetine and/or LY379268 by assaying the incorporation of bromodeoxyuridine and the immunoreactivity for neuronal markers (Tuj1 and NF) respectively. Signal transduction of mGlu2/3 receptors was assessed by measuring the inhibition of cAMP formation using a commercial RIA kit. *In vivo* experiments were carried out treating FSL rats i.p. with saline, chlorimipramine, LY379268, or the two drugs in combination. A standard 5-min Forced Swimming Test was performed 24 hours after the last injection. **Results** Neuroprecursors cells express mGlu2/3 and mGlu5 receptor protein, as shown by Western blot analysis. Co-administration of fluoxetine and low concentration of LY379268 (1 nM) increased both cell proliferation and the percentage of TuJ-1^{+} cells to a greater extent than that produced by each drug alone. Only few cells were positive for the glial marker GFAP. We also found a synergism between fluoxetine and LY379268 in inhibiting forskolin-stimulated cAMP formation. *In vivo*, we found that a co-treatment of FSL rats with chlorimipramine and LY379268 substantially reduced the immobility time after only 3 days, whereas both drugs alone were inactive. **Conclusions** Our data show that mGlu2/3 receptor ligands markedly potentiate the effects of antidepressant medication both *in vitro* and *in vivo* studies. We speculate that mGlu2/3 receptor agonists may be used as adjunctive drugs to shorten the time required for the relief of depressive symptoms.

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