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Original article

Repeated co-treatment with antidepressants and risperidone increases BDNF mRNA and protein levels in rats

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ABSTRACT

Background: Recently, several clinical studies have suggested a beneficial effect of a combination of antidepressants (ADs) with antipsychotic drugs in drug-resistant depression. Moreover, preclinical and clinical studies indicated a role of brain-derived neurotrophic factor (BDNF) in the pathology of depression, as well as in the mechanism of action of ADs.
Methods: In the present study, we investigated the effect of repeated administration of ADs, escitalopram, fluoxetine or mirtazapine and a low dose of risperidone (an atypical antipsychotic drug) given separately or in combination, on the mRNA and protein levels of BDNF or cAMP response element binding (p-CREB) in the hippocampus and frontal cortex of male Wistar rats. ADs were given repeatedly (once daily for 14 days), separately or in combination with a low dose of risperidone. The tissue for biochemical assays was dissected 24 h after the last dose of ADs.
Results: The obtained results showed that repeated co-treatment with an inactive dose of risperidone and escitalopram or mirtazapine but not fluoxetine increased the BDNF mRNA expression in the hippocampus and frontal cortex. Moreover, combined treatment with an inactive dose risperidone and escitalopram elevated the protein levels of p-CREB in the frontal cortex. While, co-treatment with risperidone and fluoxetine or mirtazapine increased the protein levels of BDNF and p-CREB in both examined regions of the brain.
Conclusions: Our present findings suggest that enhancement levels of BDNF may be essential for the therapeutic effect of co-treatment with ADs and a low dose risperidone in patients with drug-resistant depression.

Introduction

Recent preclinical and clinical studies indicated an important role of brain-derived neurotrophic factor (BDNF) in the pathology of depression as well as in the mechanism of action of antidepressant drugs (ADs) [*e.g.* [1–3]]. It was shown that stress decreased the expression of BDNF in the hippocampus [4], which is the region of the brain important in emotional cognition and memory processing [5], and this effect might contribute to the observed atrophy of stress-vulnerable neurons in this region of the brain [1,6,7]. The prefrontal cortex is also essential to emotional processing, and in patients with major depressive disorder (MDD) this region was also shown to decrease in volume, what correlated with the reduction BDNF levels [2,3]. The above data suggested that both stress and MDD affected BDNF expression in limbic brain regions. Furthermore, studies using a postmortem human brain tissue demonstrated an increase in the hippocampal BDNF immunoreactivity in patients treated with ADs compared to untreated subjects [8]. In addition, some earlier clinical studies have shown that serum BDNF levels are reduced in depressed patients and it can be normalized by successful treatment with ADs [2,9].

Moreover, behavioral studies showed that local infusion of BDNF into the midbrain and hippocampus evoked antidepressant-

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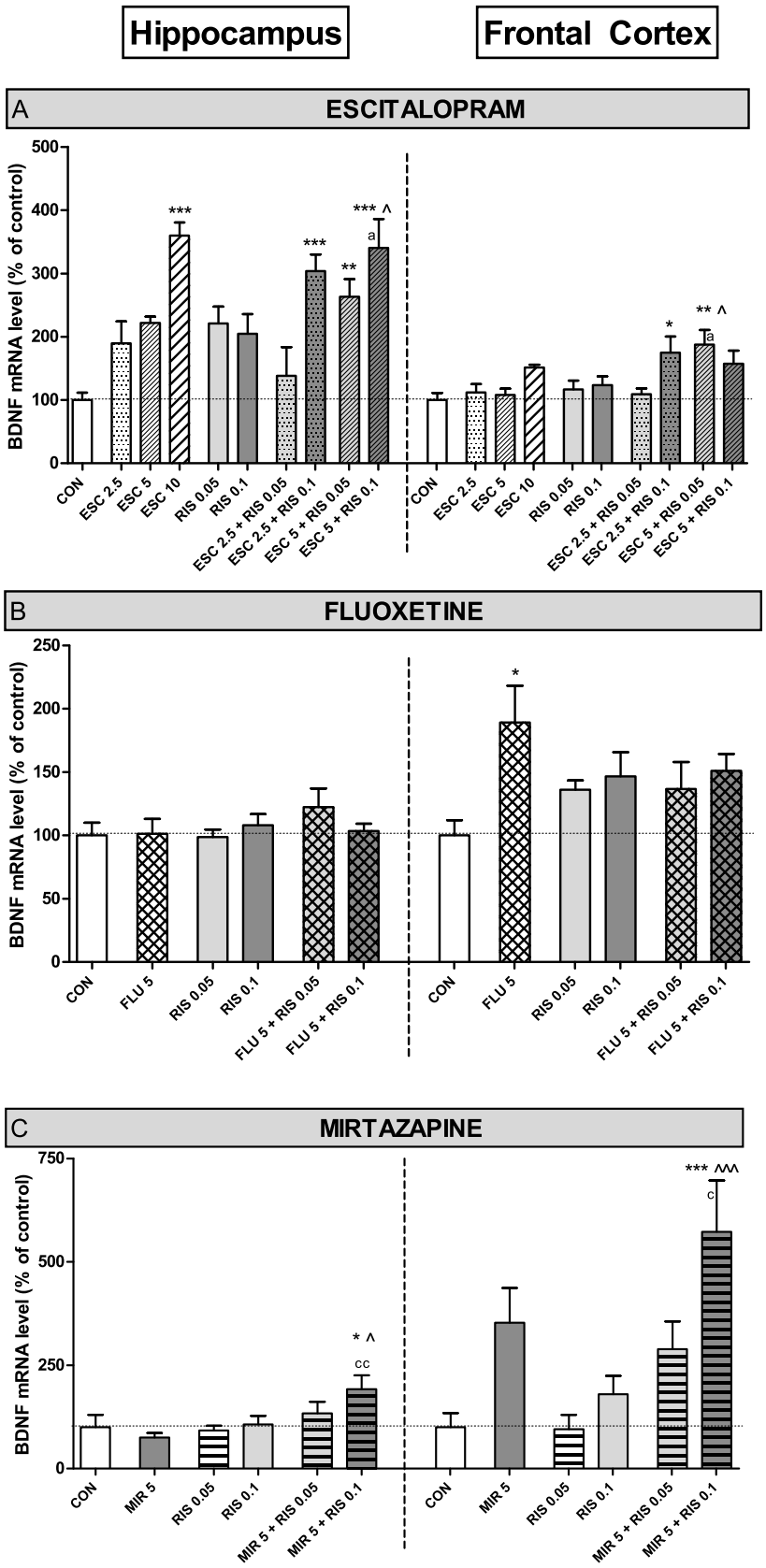

Fig. 1. The effect of repeated treatment with escitalopram (ESC; 2.5, 5 or 10 mg/kg) (A), fluoxetine (FLU; 5 mg/kg) (B), mirtazapine (MIR; 5 mg/kg) (C) and risperidone (RIS; 0.05 or 0.1 mg/kg) administered separately or in combination, on the BDNF mRNA levels in the hippocampus and frontal cortex. The results are presented as the mean ± SEM of 7–8 animals/group. Statistical significance was evaluated using a two-way ANOVA followed by the Newman Keuls test. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ *vs.* CON-treated group; $^{\wedge}p < 0.05$, $^{\wedge\wedge\wedge}p < 0.001$ *vs.* RIS 0.1; $^{a}p < 0.05$ *vs.* ESC 5; $^{c}p < 0.05$, $^{cc}p < 0.01$ *vs.* MIR 5.