Combined treatment with imipramine and metyrapone induces hippocampal and cortical brain-derived neurotrophic factor gene expression in rats

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Abstract:
The problem of drug-resistant depression indicates a strong need for alternative antidepressant therapies. Recently it was shown that joint administration of imipramine (IMI) and metyrapone (MET), an inhibitor of glucocorticoid synthesis, produced a more potent "antidepressant" effect in the forced swimming test than did treatment with either drug alone. Our studies also showed that co-administration of IMI and MET to drug-resistant, unipolar depressed patients effected a clinical improvement. In addition, recent studies indicated a role of the brain-derived neurotrophic factor (BDNF) in the mechanism of action of antidepressant drugs (ADs). Since the most potent effect of ADs on BDNF gene expression was found after prolonged treatment, in the present research we investigated the influence of repeated treatment with IMI (5 or 10 mg/kg) and MET (50 mg/kg), given separately or jointly (twice daily for 14 days), on the BDNF mRNA level (the Northern blot) in the hippocampus and cerebral cortex. The experiment was carried out on male Wistar rats. The tissue for biochemical assays was collected 24 h after the last dose of IMI and MET. The obtained results showed that in the hippocampus IMI (10 mg/kg) and cerebral cortex IMI (5 mg/kg) and MET (50 mg/kg) significantly elevated the BDNF mRNA level. Joint administration of IMI (10 mg/kg) and MET (50 mg/kg) induced a more potent increase BDNF gene expression in both the examined brain regions (compared to the treatment with either drug alone). Moreover, the obtained results suggested that BDNF may be involved in the mechanism of the synergistic antidepressant effect of IMI and MET in drug-resistant depressed patients.

Key words:
repeated treatment, imipramine, metyrapone, mRNA BDNF, rats