EFFECTS OF COMBINED TREATMENT WITH IMIPRAMINE AND METYRAPONE IN THE FORCED SWIMMING TEST IN RATS. BEHAVIORAL AND PHARMACOKINETIC STUDIES

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In the present study, we examined the effects of imipramine (IMI) and metyrapone (MET) given alone or in combination of IMI and MET in the forced swimming test in rats. We also measured pharmacokinetic parameters: the level of IMI and its metabolite, desipramine (DMI), in the rat plasma and brain (1 h after the forced swimming test). The present studies indicate that MET (50 mg/kg) reduced immobility time. Combined treatment with MET (50 mg/kg) and IMI (5 or 10 mg/kg) produced stronger antidepressant-like effect than either of drugs given alone. Sulpiride (dopamine D2/3 antagonist), or WAY 100635 (5-HT1A antagonist) but not prazosin, (α1-adrenergic antagonist), at doses ineffective in the forced swimming test, inhibited an antidepressant-like effect induced by co-administration of IMI with MET. The active behaviors in that test did not reflect an increase in general activity, since combined administration of IMI and MET failed to alter the locomotor activity of rats, measured in the open field test. MET elevated the concentrations of IMI and DMI in plasma, and the total drug concentration (IMI + DMI) was doubled by MET treatment. MET elevated the concentrations of IMI and DMI in brain, and the total drug concentration (IMI + DMI) was not changed significantly by MET treatment. The obtained results suggest that dopamine D2/3 and 5-HT1A receptors may contribute to the mechanism of synergistic action of IMI and MET in the forced swimming test in rats, and that pharmacokinetic interaction should not have a substantial impact on the MET-induced potentiation of IMI effect, observed in vivo. These findings may be of particular importance to pharmacotherapy of drug-resistant depression.

Key words: imipramine, metyrapone, behavioral and pharmacokinetic studies, rats

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