



## Effects of co-administration of fluoxetine or tianeptine with metyrapone on immobility time and plasma corticosterone concentration in rats subjected to the forced swim test

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### Abstract:

Major depression is frequently associated with hyperactivity of the hypothalamic-pituitary-adrenocortical axis, and glucocorticoid synthesis inhibitors have been shown to exert antidepressant action. The aim of the present study was to examine the effect of co-administration of fluoxetine or tianeptine with metyrapone on immobility time and plasma corticosterone concentration in male Wistar rats subjected to the forced swim test. Metyrapone alone (50 mg/kg, but not 25 mg/kg) reduced the immobility time of rats in the forced swim test; moreover, both doses tested (25 and 50 mg/kg), dose-dependently decreased the stress-induced plasma corticosterone concentration. Joint administration of fluoxetine or tianeptine (10 mg/kg) and metyrapone (25 mg/kg – a dose inactive *per se*) exhibited antidepressant-like activity in the forced swim test in rats. WAY 100636 (a 5-HT<sub>1A</sub> antagonist), but not prazosin (an  $\alpha_1$ -adrenergic antagonist), used in doses ineffective in the forced swim test, inhibited the antidepressant-like effect induced by co-administration of fluoxetine or tianeptine with metyrapone (25 mg/kg). Combined treatment of fluoxetine or tianeptine and metyrapone inhibited stress-induced corticosterone secretion to a similar extent as metyrapone alone. The obtained results indicate that metyrapone potentiates the antidepressant-like activity of fluoxetine or tianeptine and that, among other mechanisms, 5-HT<sub>1A</sub> receptors may play some role in this effect. Moreover, metyrapone exerts a beneficial effect on the stress-induced increase in plasma corticosterone concentration. These findings suggest that the co-administration of metyrapone and an antidepressant drug may be useful for the treatment of drug-resistant depression and/or depression associated with a high cortisol level.

### Key words:

fluoxetine, tianeptine, metyrapone, forced swim test, corticosterone, rats

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