

**BEHAVIORAL EFFECTS OF THE  $\beta_3$  ADRENOCEPTOR AGONIST SR58611A: IS IT THE PROTOTYPE OF A NEW CLASS OF ANTIDEPRESSANT/ANXIOLYTIC DRUGS?**

Gian Marco Leggio, Daniele Consoli, Carmen Mazzola, Vincenzo Micale, Filippo Drago

Department of Experimental and Clinic Pharmacology, Faculty of Medicine, University of Catania, Italy

A large body of evidence corroborates the notion that deficiencies of serotonergic system are likely involved in the pathogenesis of both depression and anxiety. Activation of  $\beta_3$ -adrenoceptors ( $\beta_3$ -ARs) has been shown to increase brain tryptophan (TRP) content suggesting an elevation of brain serotonin (5HT) synthesis. SR58611A is a selective  $\beta_3$  adrenergic agent possessing a profile of antidepressant activity in routine rodents' experimental models of depression. The present study was undertaken to evaluate in rodents the antidepressant properties of SR58611A and to assess its putative anxiolytic value in experimental models of depression and anxiety. Compared to the control group, SR58611A (0.1, 1, 5 or 10 mg/kg) caused a dose-dependent reduction in immobility of Wistar male rats in the forced swim test (FST). The maximum dose appeared to be equivalent to an effective dose of clomipramine (50 mg/kg). In addition, acute injection of SR58611A induced in rats a dose-dependent decrease in grooming response to a novel environment (novelty-induced grooming test, NGT). For any dose, the effect was lower than that of diazepam (1 mg/kg).

Chronic treatment with SR58611A resulted also in an increased social interaction time in the social interaction test (SIT) without affecting motor activity of rats. Furthermore, similarly to diazepam a chronic treatment with the highest doses of SR58611A was followed by increased exploratory behavior in Swiss male mice exposed to the elevated plus maze test (EPM). These effects are mediated by  $\beta_3$ -ARs since i.p. pretreatment with the selective  $\beta_3$ -ARs antagonist SR59230A (5 mg/kg) blocked the effects of SR58611A. Finally, also the 5HT antagonist methysergide (2 mg/kg) prevented the antidepressant and anxiolytic-like activity of SR58611A indicating that 5HT transmission is strictly involved in its action. If confirmed in human SR58611A may be a therapeutic tool for depression and anxiety.