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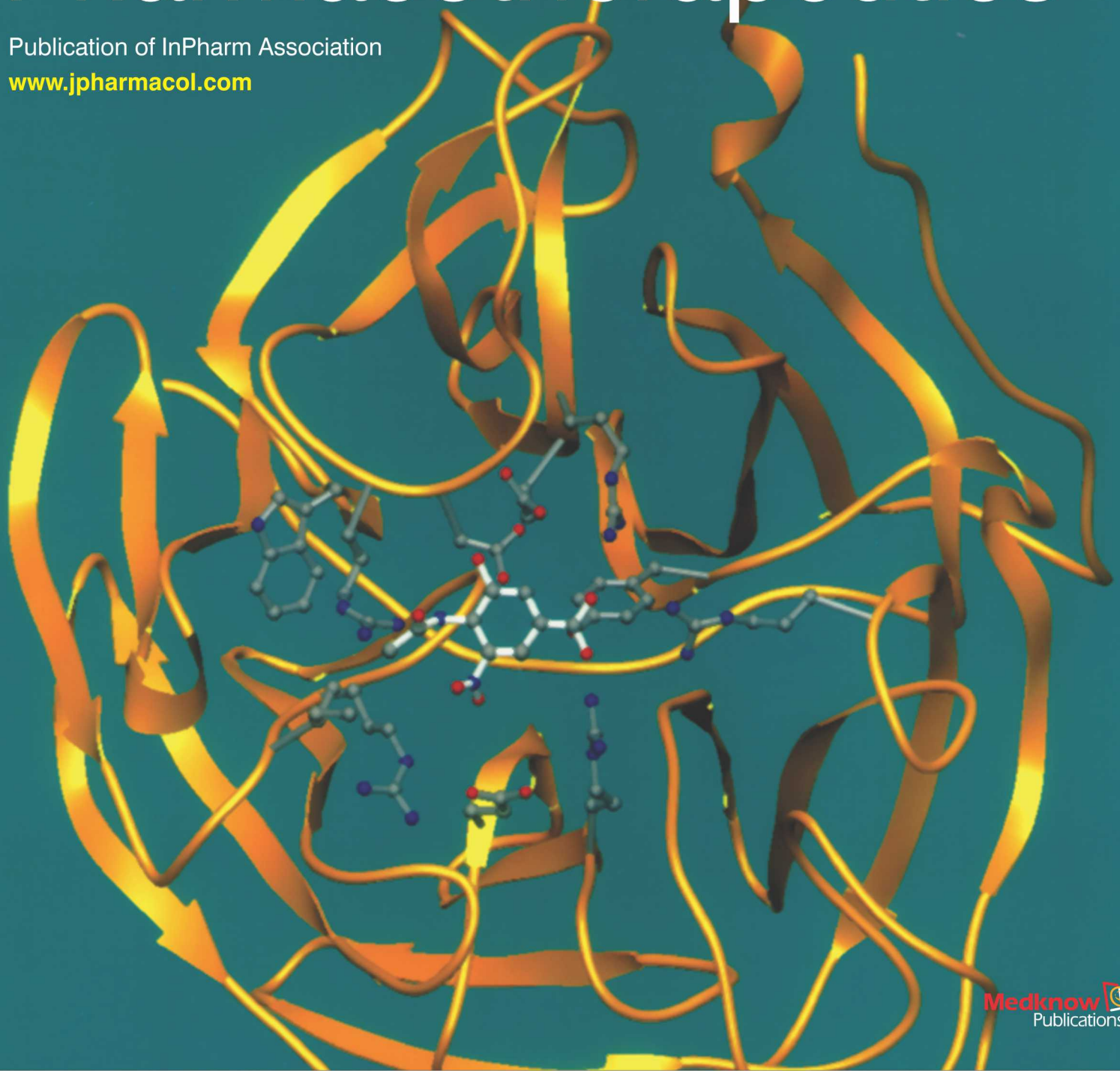

Medknow Publications

Evaluation of role of noradrenergic system in the antidepressant activity of tramadol using tail suspension test in Albino mice

Sir,

Opioid peptides and their receptors are potential candidates for the development of novel antidepressant treatment. Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. It is a central analgesic with a low affinity for opioid receptors. Experimental and clinical data suggest that tramadol may also exert its analgesic effect through direct modulation of central monoaminergic pathways. The action of tramadol on the monoaminergic reuptake is similar to that of antidepressant drugs.[1-3] Several studies have suggested that tramadol could play a role in mood improvement. This study was undertaken to evaluate the role of noradrenergic system in the antidepressant activity of tramadol in a test predictive of antidepressant activity in mice.

The study was conducted after getting approval from the Institutional Animal Ethical Committee. Adult Albino mice (Swiss Strain) of either sex weighing 20–25 g inbred in the central animal house of Kasturba Medical College were used for this study. Mice were housed in clean polypropylene cages, six mice in each cage, in a controlled environment (26°-28°C) with a 12-h light and dark cycle. They were fed with commercial pelleted chow (supplied by VRK Nutritional solutions, Sangli) and water *ad libitum*. The mice were allowed to acclimatize for these conditions for 1 week. Experiments were performed during the light phase of the cycle.

Drugs used in the experiment were tramadol (Urgendol Winmedicare), imipramine (Torrent pharmaceuticals), propranolol (Sigma), and phentolamine (Sigma). All drugs were administered intraperitoneally in a volume of 10 ml/kg body weight. Initially to confirm the antidepressant-like activity of tramadol, the animals were divided into five groups with six mice in each group.

Group 1: Control group receved 10 ml/kg normal saline
Group 2: Tramadol 10 mg/kg
Group 3: Tramadol 20 mg/kg
Group 4: Tramadol 40 mg/kg
Group 5: Imipramine 10 mg/kg

To test the hypothesis that the antidepressant-like effect of tramadol is mediated through an interaction with noradrenergic system, animals were divided into six groups with six mice in each group.

Group 1: Control group receved 10 ml/kg normal saline
Group 2: Tramadol 40 mg/kg
Group 3: Propranolol 5 mg/kg
Group 4: Tramadol 40 mg/kg + propranolol 5 mg/kg
Group 5: Pretreated with phentolamine 10 mg/kg
Group 6: Pretreated with phentolamine 10 mg/kg + tramadol 40 mg/kg

For acute experiment, drugs were given as single dose 15 min before the experiment, and the pretreatment period was 15 min. For chronic study, drugs were given daily for 10 days, and the pretreatment period was 15 min on the 10th day of drug administration. The duration of immobility in mice was measured by tail suspension test. Mice were suspended on the metal rod stand 50–75 cm above the table top by the adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was recorded during 8-min period. Animal was considered to be immobile when it did not show any movement of body and hanged passively. A decrease in the immobility period is indicative of antidepressant-like activity.[4]

The decrease in immobility period in the group pretreated with tramadol 10 mg when compared with control was significant for acute treatment (P=0.03) and it was also significant for tramadol 20 mg (acute) versus normal saline (P=0.02) and for tramadol 40 mg (acute) versus normal saline (P=0.04). Duration of immobility was significantly less in tramadol 40 mg/kg group when compared with tramadol 10 and 20 mg/kg group on acute administration (P=0.005) [Figure 1].

Phentolamine countered the immobility duration reducing action of tramadol to a greater extent than propranolol. Both these drugs when given alone have did not affect the immobility duration when compared with control animals [Figure 2]. This study conclusively shows that tramadol has significant antidepressant activity which was comparable with standard antidepressant drug imipramine as observed in earlier studies.[1-3]

In order to investigate the possible involvement of noradrenergic system in the antidepressant-like effect of tramadol, phentolamine (alfa-blocker) and propranolol

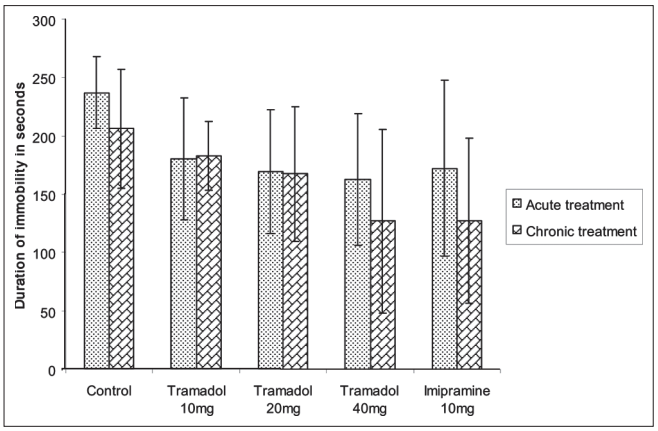

Figure 1: The effect of acute and chronic treatment of tramadol and imipramine on duration of immobility in tail suspension test. The values are mean ± SD; *n*=6

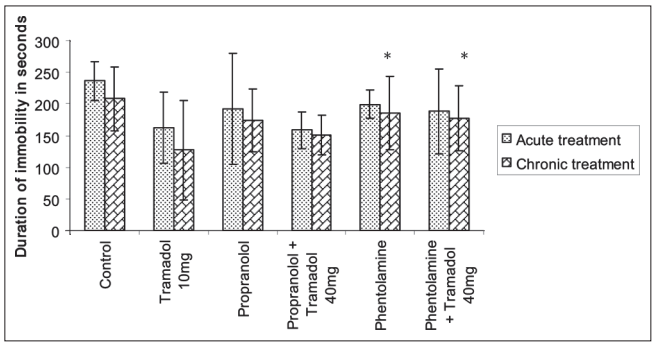

Figure 2: The effect of acute and chronic treatment of tramadol in combination with adrenergic blockers on duration of immobility in tail suspension test. The values are mean ± SD; *n*=6. **P*<0.05 when compared with acute treatment

(beta-blocker) were used. Phentolamine countered the immobility duration reducing action of tramadol to a greater extent than propranolol. Thus the antidepressant activity of tramadol may be mediated through its interactions with the noradrenergic system as evidenced by the results of our study. Similar observations were noted in the earlier literature.[5] Although the antidepressant-like effect of tramadol is explained by its ability to modulate opioid receptors and noradrenergic system, the serotenergic system and the dopaminergic system might also account for its action as these are also substrates for monoaminergic transporter.[5,6] Role of these monoaminergic systems was not evaluated in this study which needs to be investigated in future studies.

In conclusion, the results of this study indicate that antidepressant activity of tramadol is mediated through interaction with the noradrenergic system and may increase the levels of noradrenaline.

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