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LETTER TO THE EDITOR

EFFECT OF α-MPT ON IMIPRAMINE INDUCED ANTINOCICEPTION IN RATS

Sir,

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Neurophysiological and pharmacological evidence have demonstrated that the main neurotransmitters implicated in descending pain control are serotonin (5HT), noradrenaline (NA) and the endogenous opioids, although others may also play a role. Involvement of serotonergic and noradrenergic mechanism have been implicated in morphine (1) and nicotine (2) induced antinociception. Imipramine, a tricyclic antidepressant, is shown to produce antinociception in animal experiments (3). It inhibits 5HT and NA uptake. Our previous study (unpublished data) has shown that both ondansetron ($5HT_3$ antagonist) and serotonin biosynthesis inhibitor parachlorophenylalanine (PCPA) pretreatment inhibits the antinociceptive action of imipramine. In the present study, we have investigated the effect of α-methyl-para-tyrosine (α-MPT), an inhibitor of NA synthesis, on imipramine induced antinociception, to ascertain the role of noradrenergic mechanism.

Healthy male albino rats of wistar strain (200-250 gms) were divided into five groups. Animals were kept under standard laboratory conditions. Group 1 received normal saline (1 ml/kg, I.P.). Group 2–4 received imipramine 2 mg, 5 mg and 10 mg/kg I.P., respectively. Imipramine 10 mg/kg was chosen for subsequent experiments. Group 5 animals received α-MPT in a dose of 250 mg/kg twice 12 hours apart (4). Imipramine 10 mg/kg was administrated two hours after the last dose of α-MPT. All the drugs were dissolved in normal saline. The time course effect of imipramine alone and pretreatment of α-MPT on the latency of tail flick response was studied. In the tail flick test (thermal nociception), the rat was placed on tail flick apparatus (Techno), radiant heat was applied to a portion of the tail (about 5 cm from the tip) (5) and the latency of tail flick response (TFL) was noted for each rat at 0 (pre drug), 15, 30, 60, 90 and 120 minutes after drug administration. The cut off point was 20 seconds and six rats were used for each dose response. The area under the curve (AUC, sec) of the tail flick latency was determined by using traphezoidal rule. Results are expressed as mean ± SE and unpaired 't' test was applied for comparison between groups. $P<0.05$ was considered statistically significant. In the present study, imipramine caused a dose related increase in the tail flick latency in rats (Fig. 1). AUC of imipramine 2 mg/kg was 558 ± 21.3; imipramine 5 mg/kg was 653.8 ± 26.7 and imipramine 10 mg/kg was 732.8 ± 39.6. AUC of control was 551.9 ± 22.63. Prior administration of α-MPT to rats decreased the AUC of imipramine (10 mg/kg) from 732.8±39.6 to 418.05 ± 49.06 ($P<0.05$) (Fig. 1). α-MPT alone did not modify tail flick latency.

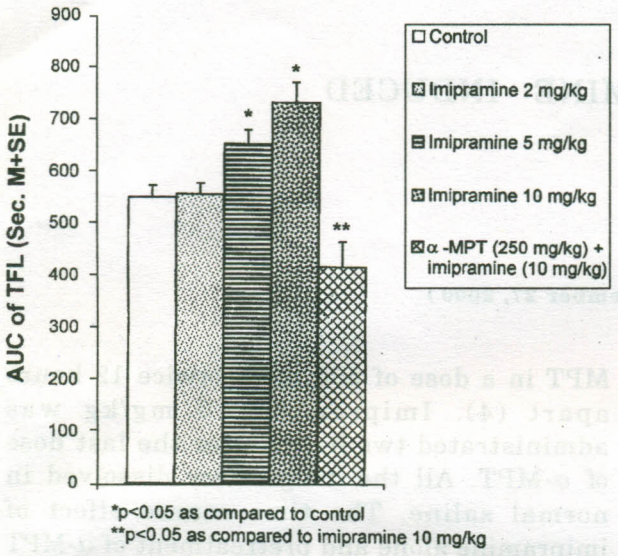

Fig. 1: Modification by α-MPT of anti-nociceptive response of imipramine (AUC, M ± SE) on tail flick latency (TFL) in rats.

Imipramine is a tricyclic antidepressant. It's antidepressant action is believed to be as a result of blockade of reuptake of 5HT and NA. In animal experiments imipramine is shown to produce antinociception (3). Studies have shown that the descending inhibitory systems in the pain pathways are in part noradrenergic and serotonergic (6–8). Our previous study (unpublished data) has shown the involvement of serotonergic mechanism in imipramine induced antinociception. The present study was conducted to ascertain if noradrenergic mechanisms are involved in the imipramine induced antinociception. In the present study, pretreatment with α-MPT decreased the antinociceptive effect of imipramine, suggesting that at least a part of imipramine antinociceptive effect may be mediated through noradrenergic mechanism.

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