under aerobic conditions, whereas livers of monkeys, and males of all species tested, produced more aminonitrotoluenes after nitrogen flush. In addition, the livers of monkeys produced more metabolites which remained at the origin after nitrogen flush.

In summary, the present study demonstrates that 2,4-DNT is metabolized in the liver by a postmitochondrial supernatant. The pattern of metabolites produced is altered by pretreating male rats with phenobarbital or SKF 525-A and by varying incubation conditions in all the species examined. In addition, the metabolic profile of 2,4-DNT was characterized in several species. A comparison of species' differences in toxicity[2,3] and the corresponding metabolic profile does not clearly indicate what role metabolism plays in toxicity.

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Modification by levo-propranolol of tremors induced by harmine in mice

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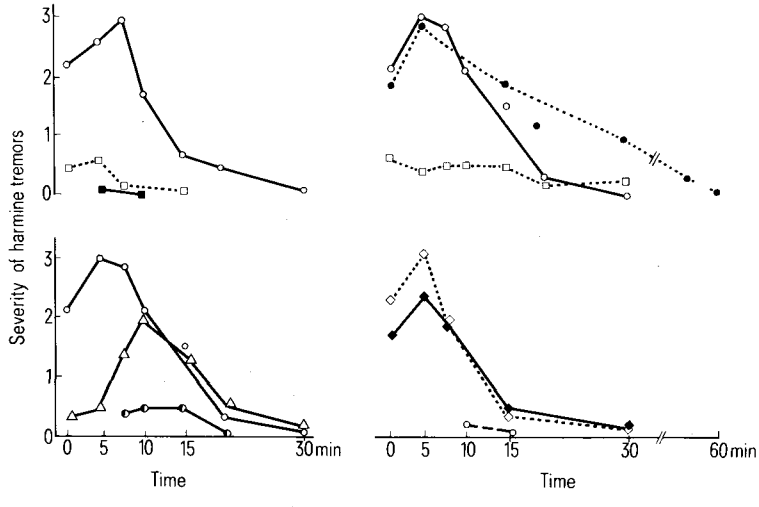
Summary. It has been recently reported that the levo isomer of propranolol possesses anti-serotonin properties in animals. Since harmine-induced behavioural changes in mice are reported to be mediated through central serotonergic receptors, an attempt was made to test whether l-propranolol would also modify harmine-induced responses by virtue of its anti-serotonergic or anti-adrenergic property. The results indicated that l- and dl-propranolol inhibited central serotonin receptor mediated responses to harmine in mice, a finding that is analogous to other recent observations.

Harmine-induced tremors in animals are believed to be serotonergic in origin because of its structural similarity to serotonin[1,2]. The recent observations that dl-propranolol had beneficial effects in schizophrenia[3] and that l-propranolol inhibited the behavioural responses of rats to increased serotonin levels in the central nervous system[4] prompted us to test whether l-propranolol would also have similar effects on the harmine-induced (serotonergic receptor mediated) responses in mice.

Quipazine, 2-1(1-piperazinyl)-quinoline, has been reported to stimulate serotonin receptors both in the central and peripheral nervous systems[5,6]. The behavioural responses to quipazine are antagonized by methysergide, BOL 148 and cyproheptadine[5]. Since quipazine and harmine possibly act by the same mechanism, namely the stimulation of serotonergic receptors, in the present study, we also investigated the effects of quipazine on harmine-induced responses and their modification by propranolol.

Male albino Swiss-Webster mice (25–30 g) maintained on a 12-h light and dark cycle and ad libitum food and water were used. All drugs were dissolved in distilled water or saline in concentrations such that the i.p. injection volume 1 ml/100 g of mice was kept constant. Each group consisted of 8–10 animals.



Modification by levo-propanolol of harmine (H) and quipazine (Q) effects in mice. ○——○, harmine (15 mg/kg); □····□, levo-propranolol (20 mg/kg)+H; ■——■, levo-propranolol (40 mg/kg)+H; ●····●, H+Q (20 mg/kg); □····□, levo-propranolol (20 mg/kg)+H+Q; ◐——◐, cyproheptadine (0.5 mg/kg)+H; △——△, cyproheptadine+H+Q; ◇····◇, practolol (20 mg/kg)+H; ◆——◆, phenoxybenzamine (15 mg/kg)+H; ○- - - -○, dl-propranolol (20 mg/kg)+H.

Resting tremors were induced in mice with harmine (15 mg/kg). The severity of tremors were scored as intensive, severe, moderate or simple presence designated by 4, 3, 2 and 1 pluses, respectively. The tremors were scored at 5, 7, 15, 20, 30, 45 and 60 min after harmine administration. The cumulative scores of tremors were plotted against time. Levo-propranolol (20 and 40 mg/kg), dl-propranolol (20 mg/kg) were administered to mice 30 min prior to i.p. injections of harmine alone or in combination with quipazine (20 mg/kg). To verify that harmine does indeed act through 5-HT receptors, cyproheptadine (0.5 mg/kg) was used. To show whether propranolol exerts its effects on the harmine-induced tremors as a result of its anti-serotonergic or anti-adrenergic activity, another beta-blocker, practolol (20 mg/kg) and an alpha-blocker, phenoxybenzamine (15 mg/kg) were employed. Any change in animal behaviour such as stereotypic cage biting response and vocalization, brought about by harmine, quipazine or their combination were noted.

Harmine-induced tremors were noticeable within minutes of its administration. The peak effect was apparent in 5–7 min and lasted up to 15–20 min. Quipazine prolonged the duration of harmine-induced tremors. These animals showed severe head and body movements, repetitive vocalization, and stereotypic cage biting behaviour. The peak effect, i.e. maximum intensity of tremors appeared much faster in combination treatment (figure). Both l- and dl-propranolol significantly antagonized harmine effects, the higher dose showing complete inhibition of tremors. Quipazine-induced prolongation of the harmine effect was also blocked by prior treatment of mice with l-propranolol (figure). Cyproheptadine significantly blocked the effects of harmine. Similarly, it also reduced the severity and the duration of tremors that induced by combined treatment of harmine and quipazine. However, phenoxybenzamine and practolol did not modify the harmine-induced tremors (figure).

The structural similarities between harmine and serotonin would suggest that a modification of serotonin function in the central nervous system may be involved in eliciting the pharmacologic effects of harmine[2]. Moreover, cyproheptadine, a 5-HT antagonist, blocked the effects of harmine. The exaggerated effects of harmine in quipazine-pretreated mice could very well be explained on the basis of their common site of pharmacologic action, namely, the serotonergic receptors.

There is convincing evidence in the literature supporting the idea that l-propranolol competitively antagonizes the effects of 5-HT on smooth muscles. These effects are demonstrated to be independent of the general membrane stabilizing properties of beta-adrenergic blocking agents[7]. Green and Grahame-Smith[4] using 5-HT precursors have recently demonstrated that l- and dl-propranolol in intact animals inhibited central serotonin function. It is also known that propranolol abolishes the stimulant effects of 5-HT on transmission in the cat superior cervical ganglion[7]. The present observations that l-propranolol significantly antagonized the harmine-induced tremors in mice could, therefore, be attributed to its anti-serotonergic property. Furthermore, neither practolol, a relatively specific beta-blocker, nor phenoxybenzamine had any effect on harmine-induced behavioural changes in mice.

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Modification of radiation-induced spleen weight changes in mice by 2-mercaptopropionylglycine

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Summary. It was found that the MPG partially protects the spleen against weight loss due to radiation, and exaggerates the compensatory reaction in the tissue during recovery. It is also concluded that MPG protects the stem cells in the spleen, which helps to restore the peripheral blood by extramedullary erythropoiesis.

2-Mercaptopropionylglycine[1] (MPG), an artifically synthesized thiol compound is effectively radioprotective at a very low optimum dose as compared to other radioprotectors[2-3]. Recently MPG was tested on various tissues of Swiss albino mice after external irradiation in this laboratory[4-9].

Material and methods. Male Swiss albino mice of 6–9 weeks with an average weight of 24 g were selected from an inbred colony maintained on Standard mice feed (procured from the Hindustan Lever Ltd, Delhi) and water ad libitum. 3 doses of gamma rays were used for the experiment. Each dose was given to an experimental (MPG treated) and a control (untreated) group with an equal number of animals. MPG (2-mercaptopropionylglycine, received from Santen Pharmaceutical, Osaka, Japan, was dissolved in distilled water so as to give a concentration of 1 mg/ml and pH was adjusted at 6.4 with 0.1 NaoH) was injected i.p. with 20 mg/kg b.wt. in the experimental animals and control groups were given an equal volume of distilled water in the same manner. After 15–30 min of this treatment, the animals were exposed to 500, 1000 and 1500 R at the dose rate of 24 R/min.

Animals were sacrificed by cervical dislocation at 12, 24, 72 h and 5, 7, 14, 21 and 28 days after irradiation. At least 4 animals were used at each interval and the wet weight of the spleen from each animal was determined separately. The results were calculated as the mean tissue weight ± SE and were plotted against autopsy interval on a linear graph.

Results. Control. The pattern of weight changes is similar in all the control groups up to 7 days after irradiation. But reduction in weight is dose dependent, i.e. the higher the dose (1500 R) the greater is the weight loss (table, figure). The maximum weight loss is observed at 7 days. The spleen in 1000 R group becomes more than 3 times heavier than that of the 500 R group at 21 days after exposure. After 21 days weight decreases but does not return to the normal level by 28 days. However, in the 500 R group the weight gain is slow and does not reach normal value even at 28 days. Supralethally (1500 R) irradiated