SUMMARY AND CONCLUSION

GABA MEDIATED DESPAIR BEHAVIOUR: ROLE OF \( \text{GABA}_A \) AND \( \text{GABA}_B \) RECEPTOR SUBTYPES AND ANTIDEPRESSANT ACTION OF DRUGS

GABA and GABA agonists exhibited biphasic response on forced swimming-induced despair behaviour in mice; smaller doses, GABA (100 mg/kg), muscimol (0.05 and 1 mg/kg), baclofen (0.5 and 1 mg/kg), sodium valproate (100 mg/kg), piracetam (25 mg/kg) and fengabine (10 and 20 mg/kg) decreasing forced swimming-induced immobility period, while higher doses enhancing the immobility period. GABA, muscimol, and baclofen also reversed reserpine-induced prolongation of the forced swimming-induced immobility. When GABA was administered with antidepressant agents, it potentiated the effect of some classical antidepressants. Bicuculline and picrotoxin, the GABAergic antagonists, by themselves enhanced the forced swimming-induced immobility period, they had no significant effect on reserpine-induced prolongation of the immobility period. When animals were chronically exposed to forced swimming, there was a gradual increase of the immobility period which was reduced on treatment with GABAergic agents. Further, both (+) and (-) baclofen were found to attenuate the forced swimming-induced immobility in mice. Baclofen was effective in reversing the effect of isoprenaline which enhanced the forced
swimming-induced immolity period. The effect of baclofen was not only stereospecific but also bicuculline-insensitive. It potentiated the effect of both desipramine and propranolol. These observations suggest that GABA has a modulatory role in reversing forced swimming-induced despair and also in potentiating the effect of antidepressants.

**IN VolvEMENT OF GABA-ERGIC AGENTS AND CLONIDINE IN ATTENUATING FOOTSHOCK-INDUCED AGGRESSION IN MICE.**

GABA elicited a biphasic effect in modulating the footshock-induced aggressive behaviour in mice. A lower dose (200 mg/kg) of GABA enhanced the aggressive score, while at a higher dose (400 mg/kg) it attenuated the aggressive behaviour. The latter effect was reversed by both bicuculline and picrotoxin. Clonidine (0.5 and 1 mg/kg) enhanced the aggressive score, and the effect of clonidine was reversed by idazoxan. GABA (400 mg/kg) and clonidine (1 mg/kg) significantly reduced the aggressive score in reserpinized mice. Baclofen (5 mg/kg) showed no effect per se in either reserpinized or non-reserpinized mice. On concomitant administration of clonidine (0.5 mg/kg) with a subeffective dose of either GABA, baclofen, or diazepam, there was significant reduction in the aggressive score. A modulatory role of GABAergic and noradrenergic systems in footshock-induced aggression is speculated.
ROLE OF GABA-ERGIC AGENTS AND ALPHA$_2$ IN REVERSING CHEMO (ISONIAZID (INH)-INDUCED) CONVULSIONS IN MICE

GABAergic agents (GABA, baclofen, fengabine) and alpha$_2$ agonists (clonidine and BHT-920) produced significant protection against INH-induced convulsions and death. The protective effect of alpha$_2$ agonists were found to be sensitive to blockade by yohimbine or idazoxan. Concomitant administration of a subeffective dose of either an alpha$_2$ agonists or GABAergic agent with a subeffective dose of diazepam provided potentiation of the diazepam effect. It is suggested that alpha$_2$ agonists via GABAergic mechanism provide protection against INH-induced seizures in mice.

STUDIES ON GABA AND NOCICEPTION

GABA (200 and 400 mg/kg), muscimol (0.2 mg/kg) and baclofen (5 mg/kg) enhanced the reaction time to radiant heat as effect per se. Concomitant administration of these GABAergic agents with morphine potentiated the morphine-induced analgesic effect. The GABA antagonists bicuculline and picrotoxin failed to reverse the antinociceptive effect. Paradoxically, both these agents elicited antinociceptive effect per se and also enhanced the analgesic effect of morphine. In the production of analgesia, an interaction of GABAergic system with other neurotransmitters is speculated.
NEUROPSYCHOPHARMACOLOGICAL PROFILE OF FENGABINE: A GABA RECEPTOR AGONIST

On systemic administration, fengabine a benzylidene derivative was found to have modulatory effect on 1) forced swimming-induced immobility, 2) footshock-induced aggression, 3) maximal electro shock-induced convulsion, 4) radiant heat-induced nociception and 5) locomotor activity. However, it was found to have no effect on the muscle strength of the animal. The GABA_A receptor antagonists (bicuculline and picrotoxin) reversed its effects in forced swimming-induced immobility and footshock-induced aggression, implicating a GABAergic involvement in its mechanism of action. But these antagonists failed to reverse the potentiating effect on morphine-antinociception, suggesting a possible interaction of the drug with opioid receptors.

ALTERED RESPONSE TO GABA-ERGIC AGENTS FOLLOWING ELECTRO- AND CHEMO-CONVULSIONS

ECS was found to have varying effects on bicuculline and picrotoxin-induced convulsions in mice. The GABA agonists (baclofen, progabide and fengabine) were also found to differ in their modulatory effects on bicuculline and picrotoxin-induced convulsions. Similarly, acute and chronic ECS varied in their effects. These alterations in effect are suggested to be due to: i) variation in the site of action of the modulatory drug, ii) change in the mechanism
of action of oicuculline and picrotoxin in blocking the GABA gated Cl⁻ channel, iii) involvement of other neurotransmitter systems which might occur as result of acute and as well as chronic ECS, and iv) the supersensitivity or impairment that may occur in the neuronal system as a result of chronic ECS.

EFFECT OF CHRONIC Ro 15-1788 TREATMENT AND ITS WITHDRAWAL ON CORTICAL AND HIPPOCAMPAL EEG ACTIVITY

Chronic treatment with Ro 15-1788 and its withdrawal produced alterations in the EEG of cortical and hippocampal area. Further it was found to produce potentiation of the effects of pentobarbitone and picrotoxin, while it antagonised the effect of diazepam and FG7142, the agonist and inverse agonist at the benzodiazepine site, respectively. These observations indicate that Ro 15-1788 may have some intrinsic activity as indicated by the changes in the EEG pattern. Further, chronic treatment and its withdrawal may alter the sensitivity of various binding sites on the GABA/benzodiazepine receptor complex. The present findings along with the receptor binding studies that are reported in the literature may indicate the role of altered receptor sensitivity in the drug discontinuation syndrome due to benzodiazepines in man and animals.