AIMS AND OBJECTIVES
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The main aims and objectives of the present study were:
(i) to assess the role of the inhibitory neuro-transmitter, GABA in the expression of different behavioural patterns with special reference to an animal model of depression, (ii) to characterize GABA receptor subtypes in these responses, and (ii) to study the involvement of these receptor(s) in the action of certain psychotropic drugs.

To achieve these objectives, the following experimental approach was pursued, and the entire study is discussed under the titles described below: (i) GABA-mediated despair behaviour: Role of GABA_A and GABA_B receptor subtypes and antidepressant action of drugs, (ii) involvement of GABA-ergic agents and clonidine in attenuating footshock-induced aggression in mice, (iii) role of GABAergic agents and alpha_2 agonists in reversing chemo (isoniazid-induced) convulsions in mice, (iv) studies on GABA and nociception, (v) neuropsychopharmacological profile of fengabine- a new GABA- receptor agonist (vi) altered response to GABAergic agents following electro- and chemo-convulsions and (vii) effect of chronic Ro 15-1788 treatment and its withdrawal on cortical and hippocampal EEG activity.

GABA MEDIATED DESPAIR BEHAVIOUR: ROLE OF GABA_A AND GABA_B RECEPTOR SUBTYPES, AND ANTIDEPRESSANT ACTION OF DRUGS

The major biochemical hypothesis of depression and the
mechanism of action of antidepressants are centered around the cerebral monoamines, suggesting a functional deficiency of NE and 5-HT and an enhancement of cerebral monoaminergic activity by antidepressants (Post et al., 1973; Garelis et al., 1974). But during the past few years, new evidences have accumulated, making the catecholamine hypothesis inadequate in explaining the mechanism of action of antidepressants. Both clinical (Lloyd et al., 1983), and biochemical (Suzdak and Gianutsos 1985) findings suggest that GABA may play a major role in affective disorders such as depression.

Two types of GABA receptors are speculated, namely GABA_A, activation of which opens up Cl^- channels, and GABA_B, activation of which may diminish the entry of Ca^{2+} into cells (Bowery 1982). Chronic administration of antidepressants has been shown to alter the density of GABA_A (Suzdak and Gianutsos 1985), GABA_B (Lloyd et al., 1985), and BZ recognition sites (Barbaccia et al., 1986). While the mechanism responsible for these are unknown, it is possible that decreased sensitivity of GABA_A receptors could result due to increased GABA release (Korf and Venema 1983), and the increase in GABA_B binding may be the result of an interaction between NE and GABA on postsynaptic cAMP generating system. GABA agonists appear to potentiate NE-induced cAMP accumulation (Hill et al., 1984).

Baclofen, an analog of GABA is known to act at GABA_B receptors in both spinal cord and brain. It is shown to have activity
both presynaptically (Collins et al., 1982; Olpe et al., 1982) and postsynaptically (Inoue et al., 1985; Blaxter and Carlen 1985). An interaction between baclofen and the anticholinergic properties of the antidepressants is suggested to cause memory deficits in patients receiving the combination therapy (Sandyk and Gilman 1985).

Progabide, which has both GABA_A and GABA_B agonists activity is shown to have an antidepressant profile in animal models and in clinical trials as well (Sanger et al., 1986; Weiss et al., 1986). Hence, the present investigation was undertaken to investigate the role of GABA_A and GABA_B agonists alone and in combination with other pharmacological agents in the forced swimming-induced immobility (despair behaviour) in mice. Effect of baclofen on isoprenaline-induced despair behaviour was studied to elucidate the role of GABA_B receptors on β-adrenoceptor mediated action.

**INVolvement of GABA-Ergic Agents and Clonidine in Attenuating Footshock-Induced Aggression in Mice**

Neurochemical and pharmacological evidences are indicative of the involvement of GABAergic mechanism in the control of aggressive behaviour in mice and rats (De Paulis and Vergnes, 1983; Anden et al., 1976). BZs the widely prescribed anxiolytics are thought to produce their pharmacological actions via specific high affinity binding sites on a supramolecular complex composed of BZ and GABA
receptors coupled with a Cl\(^{-}\) channel (Cost et al., 1975). In intact
animals, GABA\(_A\) receptor activation is shown to be associated with
an anticonvulsant (Morselli et al., 1983) and anti-anxiety (Williams
1983) actions. GABA agonists are known to induce inhibition
of neuronal activity but the underlying ionic involvement is not clear
(Bowery 1983).

Quipazine, a non-specific 5-HT agonist, yohimbine, an
alpha\(_2\) antagonist, and FG7142 (N-methyl-\(\beta\)-carboline-3-carboxamide),
BZ inverse agonist are known to be anxiogenic, indicating the possible
involvement of other neurotransmitters in anxiety, and multiple sites
of action as well. Therefore, in this study, the effects of GABAergic
agents and clonidine were investigated in footshock-induced aggressive
behaviour in mice (normal and reserpinised animals). The effect
of these drugs were studied alone and as well as in combination.

**ROLE OF GABA-ERGIC AGENTS AND ALPHA\(_2\) AGONISTS IN REVERSING
CHEMO (ISONIAZID-INDUCED) CONVULSIONS IN MICE**

A critical role for GABA is demonstrated in the patho-
physiology of epilepsy, and agents which facilitate GABAergic trans-
mission are shown to be potent anticonvulsants (Meldrum 1975).
Despite the progress made in the development of new anticonvulsants,
the definite mechanisms of action of most antiepileptic drugs are
not totally clear as yet. Most of the observations suggest an interaction
of the anticonvulsant drugs with different components of GABA/BZ
receptor Cl⁻ ionophore complex, resulting in an enhancement of GABAergic transmission (Rastogi and Ticku 1986). However, the role of the two GABA receptors (GABA_A and GABA_B), in the anticonvulsant activity is debated. There are reports demonstrating the involvement (Mehta and Ticku 1986), as well as non-involvement (Ulloque et al., 1986) of GABA_A receptors in the anticonvulsant activity of barbiturates against maximal electroshock (MES)-induced seizures.

Catecholamine involvement has long been suggested in chemo- and electroshock-induced convulsions (Oishi et al., 1979; Stull et al., 1977). A reduction in monoamine content as in the case of reserpinised animals is reported to increase the susceptibility to seizures (Kulkarni 1981). But isoniazid, a potent MAO inhibitor, is known to induce convulsions (Pieri and Biry 1985). Earlier studies have demonstrated the anticonvulsant profile of clonidine and other related adrenoceptor agonists (Kulkarni 1981; Kulkarni and mehta, 1983). A recent study has demonstrated that clonidine stimulates the release of GABA in rat cerebral cortex synaptosomes (Pittaluga and Raiteri 1988). Therefore in the present study an attempt has been made to investigate the effects of GABAergic agents and alpha₂ agonists on INH-induced seizures in mice.

STUDIES ON GABA AND NOCICEPTION

It has been proposed that the antinociceptive output neurons in the midbrain periaquedctal grey (PAG) that trigger descending
inhibition are maximally active, when released from tonic GABAergic inhibition (Sandkuhler et al., 1989). Several other studies also indicate a role for GABA in analgesia (Buckett 1980; Ho et al., 1976). However, the results available are conflicting. For example, muscimol (Biggio et al., 1977), and AOAA (Yoneda et al., 1976) are reported to enhance the analgesic effect of morphine in mice, whereas, Christensen et al., 1978) have reported that an equi dose of muscimol is devoid of effect on morphine analgesia in the wire-grid test. Also AOAA is shown to have antagonised the morphine analgesia in mice (Ho et al., 1976). Further, muscimol is shown to antagonise the morphine-induced analgesia in mice, and the muscimol effect was shown to be reversed by bicuculline (Zonta et al., 1981. In the present study, an attempt was made to elucidate the role of GABA on radiant heat induced nociception in mice. The effects of GABA_A and GABA_B agonists separately and in combination with morphine or clonidine were investigated.

**NEUROPSYCHOPHARMACOLOGICAL PROFILE OF FENGBABINE, A NEW GABA RECEPTOR AGONIST**

Progabide and fengabine are two benzylidene derivatives, demonstrated to have antidepressant activity comparable to that of the tricyclic antidepressants (Musch and Garreau 1986). But they are devoid of any activity on monoamine uptake or MAO (Lloyd et al., 1987) Emergence of such atypical and promising antidepressants
demand further investigation to elucidate their mechanism of action and potential as therapeutic agents in other neuro-psychopharmacological disorders. Progabide is presently in clinical use. In the present study, the potential usefulness of fengabine in various behavioural disorders were investigated, and also the involvement of GABA receptors in its mechanism of action was assessed.

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

Electroconvulsive shock therapy has been extensively employed for many years to treat psychiatric illness. But the mechanism of its action still remain unidentified. Reports on the effects of ECS on biogenic amines of rat brain are contradictory both after single and multiple shocks (Essman 1973). Repeated, but not single ECS is shown to cause (i) an enhancement in catecholaminergic postsynaptic activity (Modigh 1975), (ii) an inhibition of \( \text{K}^+ \) evoked release of 5-HT and NE from cortical slices (Green et al., 1987), (iii) an increase in postsynaptic \( \text{5-HT}_2 \) receptor number (Kellar et al., 1981), (iv) an increase in GABA content in several brain regions (Green et al., 1978), and (v) an alteration in GABA\(_B\) receptor function in mouse frontal cortex (Lloyd et al., 1985; Gray and Green 1987).

A sudden decrease in abnormally elevated GABA levels is shown to generate epileptogenic processes (Brailowsky, et al.,
Further, changes in GABA$_B$ receptor function is shown to alter the 5-HT mediated behaviour in rats (Gray et al., 1986). Clonidine, an alpha$_2$ agonist is demonstrated to have anticonvulsant activity (Kulkarni 1981), and yohimbine an alpha$_2$ antagonist is shown to block the anticonvulsant action of intranigral muscimol in the ECS model (Kenneth et al., 1987). In the present study, alterations in the effect of GABAergic agents after acute and/or chronic ECS were investigated. Also have studied the effect of acute and/or chronic ECS on the convulsant and anticonvulsant effects of GABAergic agents with a view to assess the alteration in receptor sensitivity due to ECS treatment.

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

Ro 15-1788, an imidazodiazepine antagonises a wide spectrum of behavioural effects of BZs. It also antagonises the intrinsic effects of B-carbolines that are inverse agonists at the BZ binding sites (Nutt et al., 1982). In addition, Ro 15-1788 is shown to have intrinsic activity in several behavioural, neurological, electrophysiological and biochemical tests. At the BZ receptor, a continuum of effects ranging from agonists to inverse agonist is considered to be possible, depending on the ability of GABA to enhance or decrease the binding of compounds to BZ receptor (Braestrup et al., 1982). The interpretation that all the intrinsic actions of Ro 15-1788 is either agonist-
like or inverse agonist-like at the BZ receptor suggests that the intrinsic actions of this compound are mediated at BZ receptors. The agonist-like, inverse agonist-like and antagonistic actions of Ro 15-1788 is shown to have some dose dependence, but the results are not found to be consistent (Liljequist and Engel 1984; Jensen et al., 1984). Such inconsistent results also lead to the speculation that the compound may be acting at different sites of the GABA/BZ receptor complex or the involvement of other CNS systems. Moreover, unlike the BZ studies, very few reports are available regarding the chronic effect of Ro 15-1788. Some recent studies have demonstrated the upregulation of BZ sites in rat cerebral cortex (Meding et al., 1988) and other studies have revealed the upregulation of inverse agonistic sites also in the rat cerebral cortex and the hippocampus (Kulkarni and Ticku 1989). If the inverse agonistic sites are upregulated during the withdrawal period Ro 15-1788 one may expect both behavioural and electroencephalographic excitation in these brain areas. In the present study, therefore, effect of chronic treatment and its withdrawal due to Ro 15-1788 was studied on cortical and hippocampal EEG discharges in rat brain. The possible modification of the activities by agents acting at BZ site (agonist, diazepam), picrotoxin site (convulsants, anticonvulsants, picrotoxin, pentobarbitone) and inverse agonist site (FG7142) and GABA were investigated.