DISCUSSION
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The evidence that neurons using GABA as an inhibitory transmitter exists in the mammalian brain is no longer disputed. The first evidence that GABA is inhibitory on mammalian neurons came with the development of the micro-ionophoretic technique for applying drugs locally while recording from a single neuron. In both central and peripheral neurons of vertebrates the opening of ion channels for Cl\(^-\) appears to be the primary event in the widespread inhibitory actions of GABA that are sensitive to the antagonist bicuculline (Adams and Brown 1975; Barker and Ransom 1978). A major exception to this generalisation surfaced with the discovery of another inhibitory action of GABA that is pharmacologically distinct and appears to involve Ca\(^{2+}\) channels and not Cl\(^-\) channels (Dunlap 1981). Thus the GABA receptors and the associated mechanisms were shown to differ from those in responses characterized as bicuculline sensitive. Hill and Bowery (1981) termed the bicuculline-sensitive receptor of vertebrate neurons GABA\(_A\) and the novel receptor GABA\(_B\). Now we are able to distinguish these two classes of receptors, according to their transduction mechanisms and the properties of the transmitter recognition site (Figure - 63). The GABA\(_A\) receptor class gate the influx of Cl\(^-\) ions into postsynaptic cells and the recognition site for GABA\(_A\) is always located on the subunits of the integral protein that forms the anionic channel. But GABA\(_B\) receptor uses
at least two ionotropic (K⁺ and Ca²⁺) transduction mechanisms as well as one metabotropic mechanism. Accordingly, GABA_B receptor activation is suggested to decrease transmitter release (Szekely et al., 1987; Wojcik 1986).

The agonist selectivities of the GABA receptors in the cat spinal cord and cerebral cortex are shown to be dissimilar (Curtis et al., 1971) and the GABA receptors in the rat substantia nigra and the cat spinal cord are considered to have different agonist/antagonist specificities (Krogsgaard-Larsen et al., 1982). While muscimol, isoguvacine and GABA are bicuculline-sensitive agonists with a decreasing order of potency in the cat spinal cord, baclofen is a bicuculline-insensitive depressant of neuronal firing (De Feudis 1981). Inhibitory effects are mediated by both GABA_A and GABA_B receptors. GABA_A receptor activation can, in some situation, result in direct excitation, or facilitation of excitation by another transmitter (Levy 1977). The existence of both hyperpolarising and depolarising response to GABA in the same neurons has been reported to cultured mouse spinal cord neurons (Barker and Ranson 1978) and on CA1 pyramidal cells in slices of rat hippocampus (Alger and Nicoll 1982).

The properties of the GABA_A receptor make it an excellent model for studying how ion channels operate and how ionotropic receptor function is modulated by polytypic signalling (Figure-- 64).
Drugs influence GABAergic function by interaction at many different sites. The properties of GABA receptors have been demonstrated in terms of the drugs that directly interact with it. Evidences obtained from a series of studies (Allan et al., 1987) suggest that in the rat spinal cord, synaptic GABA receptors may have different spectrum of sensitivity from extrasynaptic receptors. In recent years the classical $GABA_A$ receptor with its integrated $Cl^-$ channel has been the subject of many studies. Two subunits, 'α' and 'β' of $GABA_A$ receptor have been deduced from cloned complementary DNAs. Further, subunits of $GABA_A$ have been isolated which are named as $GABA_{Aα1}$, $GABA_{Aα2}$, and $GABA_{Aα3}$. Coexpression of these units in heterogenous systems, generates receptors which display much of the pharmacology of their 'neural counter-parts including potentiation by barbiturates (for details see review).

Besides, picrotoxin, the GABA receptor $Cl^-$ channel ionophore complex contains regulatory sites for benzodiazepines and barbiturates which affect the GABA receptor function by increasing the frequency of the $Cl^-$ channel opening or by increasing the life time of the opened channel respectively (Study and Barker 1981). Barbiturates and benzodiazepines both enhance responses to GABA and mutually oppose the GABA antagonist action of picrotoxin, although they differ in the balance of their effects. Depending upon the consequences of $Cl^-$ ionophore opening, these drugs are reported
to influence both GABA mediated inhibition and GABA mediated facilitation. Muscimol and THIP are shown to be high affinity agonists for GABA$_A$ receptors while baclofen is of moderate affinity for GABA$_B$ receptors (Bowery 1982). The postsynaptic hyperpolarising action of two (-) baclofen is considered to account for its clinical potency as an antispasticity agent (Allerton et al., 1989). Progabide is of moderate low affinity for the GABA$_A$ and GABA$_B$ receptors; while SL 75-102 is shown to be less active than GABA for both GABA$_A$ and GABA$_B$ receptors (Lloyd et al., 1982). Thus, agonists with action on both GABA$_A$ and GABA$_B$ receptors have been demonstrated to be of value in various neurological and psychiatric disorders like parkinsonism, Huntington's chorea, epilepsy, schizophrenia, depression. Some of the GABA mimetics (progabide) are already in clinical use as therapeutic agents. With the subclassification of GABA receptor types and its cloning, it is expected that the coming decade would see more specific involvement of this inhibitory neurotransmitter in disease processes of the brain as well as development of specific therapeutic agent that modulate GABA synaptic pharmacology.

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

The therapeutic efficacy of antidepressants is traditionally ascribed to changes in monoaminergic transmission (Schildkraut, 1975).
used a higher dose (2 mg/kg), and/or due to the difference in animal species used, i.e., rats vs mice. Although convulsive threshold of picrotoxin have been reported to be different in male and female rats (Pericic et al., 1985), the possibility of oestrous cycle influencing the responses is less likely. The observations in male and female control groups in our study indicated that sex differences do not influence despair behavior in mice. There are several reports which demonstrate opposing effect of GABA regardless of whether the animals used belonged to the same sex or were different (Borsini and meli, 1988). For instance, GABAergic agents are both cataleptogenic and antica­taleptic against perphenazine (Shukla et al., 1985) and meperidine-induced catalepsy (Aley and Kulkarni, 1987).

The present findings that GABA potentiates the effect of antidepressants opens up further vistas for considering the modulatory role of GABA in the mechanism of action of other neurotransmitters. The reports demonstrating the coexistence of carriers for dopamine and GABA uptake on the same nerve terminal (Bonanno and Raiteri, 1987) focuses on the possibility of GABAergic interactions with dopamine and as well with other neurotransmitters. Although Porsolt et al. (1979) reported enhancement of immobility duration with Ro 4-1284, a reserpine like drug, but not with reserpine, we have consistently
However, recent findings have demonstrated the role of GABA agonists in animal models of depression (Sanger et al., 1986) as well as in clinical studies (Lloyd et al., 1983). GABA levels in the lumbar CSF of depressed patients is reported to be significantly lower as compared to the neurologic control group (Gold et al., 1980). These reports suggest that an endogenous deficit in the GABAergic mechanisms might play a role in the pathogenesis of depression. Therefore, reestablishment of the GABAergic tone could be considered to be an effective way of alleviating depression.

The results of the present study such as (1) attenuation of the forced swimming-induced immobility by all the GABA agonists tested, (2) reversal of the effect of GABA agonists by GABA antagonists (bicuculline and picrotoxin), (3) potentiation of the effect of antidepressants, and (4) attenuation of reserpine-induced immobility by GABAergic agents demonstrate that GABA has a definite role in the pathogenesis of depression. All GABA agonists tested reduced the forced swimming-induced immobility period at lower dose levels. This common effect is, therefore, unlikely to be secondary to an action at monoaminergic neurons and hence, can be considered to be GABA specific. More recently, Teruel et al. (1988) have demonstrated that sodium valproate, when given acutely, subacutely, or chronically, reduces immobility in rats in despair test, an effect, like the present study, sensitive to blockade by bicuculline or...
picrotoxin. Up-regulation of $GABA_B$ binding sites in rat frontal cortex by different classes of antidepressant drugs has also been reported (Lloyd et al., 1985). Further supporting the present observations. The functional consequences induced by GABA mimetics may be similar to that induced by conventional antidepressants. This speculation is supported by the synergism between GABA and tricyclic antidepressants with respect to the reduction of immobility period in forced swimming. From this, one may further speculate that there is an increase in cerebral noradrenergic transmission which ultimately may be responsible for bringing about the antidepressant activity. However, GABA and GABAergic agents at higher concentrations do not exhibit their antidepressant effect in this model. At this dose, the specificity or the locus of drug action may be different.

Nagatani et al. (1984) have reported that muscimol (0.25, 0.5 and 1 mg/kg) enhanced forced swimming-induced immobility in mice. At these dose levels of muscimol (0.2 and 1 mg/kg), the result of our study is in agreement with their finding. But at smaller dose levels of muscimol (0.05 and 0.1 mg/kg), we found that it has an opposite effect. The GABA antagonists bicuculline and picrotoxin reversed the effect of GABA (100 mg/kg) and muscimol (0.05 mg/kg). This finding is not in full agreement with the observations as reported by Borsini et al., (1986). This discrepancy could be due to the difference in the dose of muscimol as the earlier workers
observed that in our model, reserpine (2 mg/kg) given 4 or 24 hr before testing, produces significant immobility in mice (Kulkarni and Mehta, 1985; Parale and Kulkarni, 1986; Parale et al., 1987). Nagatani et al. (1984) failed to observe such an effect because, perhaps they did not allow complete depletion of monoamines following reserpinization, as animals were tested one hour after reserpine administration. It is well known that at least 4 hr are required for observable depletion of monoamines and, moreover, Porsolt et al. (1979) argue that serotonergic component of reserpine may be masking its effect on despair behaviour. But recent studies implicate serotonergic involvement in the despair and anti-despair action of drugs (Borsini and Meli, 1988; Malinge et al., 1988). Reduction in the reserpine-induced prolongation of the forced swimming-induced immobility period by GABAergic agents also points out towards this conclusion. Because of the widespread distribution of GABA in the CNS, it might induce a cascade of effects on the functions of other neurotransmitters. Recent studies suggest that GABA is an essential modulator of dopamine related functions within the striatal and limbic system (DiChiara and Gessa, 1981). Furthermore, the reversal of the GABAergic effect by bicuculline and picrotoxin confirms the involvement of GABA receptors in eliciting this effect (Teruel et al., 1988).

Results of the locomotor activity test have indicated that locus in the brain area that influences locomotion and behavioral
depression may be different as bicuculline and picrotoxin increased the forced swimming-induced immobility, but had no significant effect on locomotor activity at the dose investigated. This speculation is further confirmed by the finding that the doses of GABA (100 mg/kg) and muscimol (0.1 mg/kg) which reduced the immobility period of forced swimming-induced immobility have reduced the locomotor activity of the animals. Biswas and Carlsson (1978) reported that GABA in high dose (2 g/kg) or when given in combination with GABA-transaminase inhibitor decreases spontaneous motor activity per se or reduces the hypermotility of other drugs. In the doses investigated, none of the GABAergic agents had any effect on muscular tone. These observations taken together suggest that GABAergic drugs, both GABA_A and GABA_B agonists decrease immobility period in mice, and these receptor systems are implicated in the action of antidepressant drugs.

Further in the present study, both (+) and (-) baclofen were found to attenuate the forced swimming-induced immobility in mice. Baclofen was effective in reversing the effect of isoprenaline in enhancing the forced swimming-induced immobility period. The effect of baclofen was not only stereospecific but also bicuculline-insensitive and potentiated by both desipramine and propranolol. These results are suggestive of a definite role for GABA_B receptors (baclofen sensitive) in the effect of antidepressant drugs.
Lloyd et al. (1985) have shown that repeated administration of antidepressants and electroshock upregulate GABA<sub>B</sub> binding sites in the cerebral cortex of rat. The present observations not only tend to support the above observations but give direct evidence of GABA<sub>B</sub> (baclofen-sensitive) receptor mediation in despair behaviour in mice and also in the action of desipramine.

**IN VolVEMENT OF GABA-ERGIC AGENTS AND CLONICINE IN ATTENUATING FOOTSHOCK-INDUCED AGGRESSION IN MICE**

At a lower dose GABA enhanced the aggressive score while at a higher dose it attenuated the aggressive behaviour in mice. Such opposing results with variation in the dose of GABA agonists have been observed also in the depressive behaviour model in mice. Reversal of the effect of GABA by both bicuculline and picrotoxin indicate the involvement of GABA<sub>A</sub> receptors in the anxiolytic effect of GABA which is in agreement with earlier reports (Williams 1983). Baclofen (5 mg/kg) did not apparently make any alteration in the aggressive behaviour induced by footshock either in the reserpinised or non-reserpinised mice. But on concomitant administration of it with 0.5 mg/kg of clonidine to reserpinised mice, there was significant reduction in the aggressive score. But the mechanism involved in this effect is not clear. Perhaps, there is an interaction of these two (GABA and adrenergic) neurotransmitters which ultimately
brings about the result. Further investigation is needed to establish this possibility. However, activation of GABA_B receptor is reported to be associated with anxiolytic activity (Ketelaars et al., 1988). Hence an interaction between GABA_B and adrenergic receptors may be considered to be a remote possibility in reducing the footshock-induced aggressive behaviour in mice.

As per se effect, clonidine enhanced the aggressive behaviour in mice. At higher doses (e.g., 100 ng/kg), clonidine is reported to affect the alpha_1 noradrenergic (Anden et al., 1976), dopaminergic (Morpurgo 1968), cholinergic (Delbarre and Schmidt 1971), serotonergic (Svensson et al., 1975), and histaminergic (Sastry and Phillips 1977) systems. Further locus coeruleus, the major aggregate of noradrenergic neurons in the CNS are reported to have projection to GABAergic, cholinergic and serotonergic components (Redman 1977). The enhancement of the aggressive behaviour of mice by clonidine may be related to some nonselective interaction of it with any of these systems which might also explain the reason for the failure of yohimbine an alpha_2 agonist (Anden and Strombom 1974) to reverse it. For making this speculation of any value, the effect of idazoxan on clonidine action warrants clarification. Idazoxan, the specific alpha_2 antagonist (Freedman and Aghajanian 1984) is reported to have the ability to act on a number of differently located alpha_2 adrenoceptors such as somatodendritic receptors in...
the noradrenergic cell region and presynaptic receptors on noradrenergic nerve terminal (Langer 1981). Hence the reversal of the effect of clonidine on footshock-induced aggression may be due to its wider spectrum of activity on the alpha\(_2\) receptors as compared to yohimbine.

With the data available, it is difficult to draw a conclusion regarding the effect of clonidine on reserpinised mice. Adrenoceptors are thought to be essential components in the mechanism of action of GABA agonists (Poncelet et al., 1986) and clonidine is shown to enhance the release of endogenous GABA through alpha\(_2\) and alpha\(_1\) presynaptic adrenoceptors situated on GABAergic nerve endings (Pittaluga and Raiteri 1988). Perhaps an increased release of GABA would have caused the effect. The sedative effect of either reserpine or clonidine can not be considered to be causing this effect as none of them reduced the aggressive score as per se effect. The possible enhanced release of endogenous GABA by clonidine and the depletion of the monoamines by reserpine may have had a synergistic effect in bringing about the anxiolytic effect.

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

Elucidation of the mechanism by which anticonvulsants
exhibit their effects remain unclear. It appears that there are various possibilities, and the mechanisms differ in various animal species. Therefore attempts to unravel the mechanisms, involved in the genesis as well as in the control of seizures need multifactorial approach. A neurotransmitter which apparently show a beneficial effect in the control of seizures may have an unknown mechanism by which it may interact with other neurotransmitters or physiological systems.

When administered in high doses INH induces clonic-tonic convulsions in rats and mice INH being a potent MAO inhibitor, it is reasonable to consider that it will increase the brain monoamine content. Moreover, it is generally known that the classical antidepressants which inhibit the monoamine uptake have proconvulsant activity. Therefore, monoamines may be playing an indirect role in the genesis of convulsions.

In our study, alpha₂ agonists (clonidine and BHT-920) showed anticonvulsant activity against INH-induced seizures. Alpha₂ adrenoceptors located presynaptically on noradrenergic nerve terminals are known to modulate the release of noradrenaline through a negative feedback mechanism (Langer 1977). But NA neurons seem to be located postsynaptically too as destruction of cerebral NA neurons fails to reduce [³H] clonidine or [³H] idazoxan binding in cortical
membranes (P. moule et al., 1983). Post-synaptically located alpha$_2$ adrenoceptors may modulate noradrenaline release either by feedback control or by controlling the release of some other factors capable of regulating noradrenaline efflux (Westfall 1977). As INH is expected to increase the brain monoamine content, it is possible that the anticonvulsant activity of the alpha$_2$ agonists is a modulation of noradrenaline release. But the possibility of alpha$_2$ adrenoceptors influencing the other neurotransmitter systems (GABA, acetylcholine, serotonin) can not be ruled out. Locus ceruleus (LC), the major aggregate of NA neurons in the central nervous system (Amral and Sinnamon 1977) has connections to GABAergic (Redman 1977), cholinergic and serotonergic (Persinger 1987) components. Therefore, the anticonvulsant activity exhibited by clonidine and BHT-920 may be due to an influence of GABAergic transmission.

Isoniazid is demonstrated to lower brain GABA content in rats (Wood and Peesker 1973) and one of the factors responsible for INH-induced seizures is considered to be a decrease of GABA content in some neurons (Loscher and Frey 1977). Drug which facilitate GABAergic transmission are shown to have anticonvulsant activity (Rastogi and Ticku 1985). Further, repeated administration of antidepressants or electroshock is shown to cause an upregulation of GABA$_B$ receptors (Gray and green 1987). Glutamic acid decarboxylase (GAD) the enzyme responsible for the synthesis of GABA requires
pyridoxal phosphate as a coenzyme for its reactions, but INH combines with the latter to form hydrazones and thus inhibit the GAD activity. This activity of INH may be responsible for the induction of seizures as this reaction reduces the GABA content in the brain.

In our study baclofen (GABA_B agonist) exhibited anticonvulsant activity at a lower dose level (5 mg/kg) as compared to GABA and fengabine, the anticonvulsant effect of GABA was not reversed by the GABA_A antagonists, bicuculline and picrotoxin. These results indicate a GABA_B receptor involvement in the convulsant and anticonvulsant activity of drugs. However, the potentiation of the anticonvulsant activity of diazepam was greater when a subeffective dose of diazepam was concomitantly administered with GABA than in the case of baclofen, and there was no death in the case of GABA. The potentiating effect of GABA may be due to a conformational change on the GABA-BZ receptor complex rather than a direct receptor involvement. Thus our results are more in agreement with the report which demonstrate the non-involvement of GABA_A receptors in the anticonvulsant activity of drugs in mice (Ulloque et al., 1986). But the anticonvulsand activity of barbiturates in rats is reported to be mediated through GABA_A receptors (Mehta and Ticku 1986). The reason for these opposing results appears to be more due to the variation in the animal species employed for the study. Rats
and mice may respond differently. But the results of these studies indicate a GABAergic involvement in the convulsant and anticonvulsant activity of drugs. However, more investigations are required to specify the type of the GABA receptor involved and the role of other neurotransmitters in the convulsant and anticonvulsant action of drugs.

STUDIES ON GABA AND NOCICEPTION

Agonists with action at both $\text{GABA}_A$ and $\text{GABA}_B$ receptors have been reported to be implicated in antinociceptive processes in the CNS (Sawynok 1987). Muscimol ($\text{GABA}_A$ agonist) is shown to produce an antinociceptive effect when given ICV in rats. Hammond and Drower (1984) have reported that muscimol produce antinociceptive effect in the tail-flick test, but not in the rat hot plate test. Baclofen ($\text{GABA}_B$ agonist) is shown to elicit antinociceptive effects at spinal and supraspinal sites. Hwang and Wilcox (1986) have reported that neither muscimol nor baclofen has any antinociceptive effect. Thus the evaluation of the antinociceptive effect of GABergic agents present a conflicting picture which may be due to the species difference of the animals.

Results from the present experiments indicate the involvement
of GABAergic agents in the production of analgesia as all the GABAergic agents (except sodium valproate) employed in the study elicited analgesic effect. Furthermore, all the GABAergic employed in this study potentiated the analgesic effect of morphine. Both muscimol and baclofen elicited this effect indicating the involvement of GABA_A and GABA_B receptors in the production of antinociception. However, in our study, the GABA receptor antagonists bicuculline and picrotoxin failed to reverse the antinociceptive effect of either GABA or muscimol, instead these antagonists elicited a paradoxical antinociceptive effect. The absence of a specific GABA_B antagonist makes it difficult to speculate the relative role of GABA_A or GABA_B in eliciting antinociceptive effect.

The effect of GABAergic agents (either alone or in combination with morphine) on tail flick latency was significantly reversed by naloxone, an opioid antagonist, indicating the involvement of opioid receptors in the analgesia elicited by the GABAergic agents. The NRM and NGCPa nuclei which are implicated in the regulation of nociceptive threshold are under a tonic inhibitory noradrenergic (Hammond et al., 1980), serotonergic (Llewelyn et al., 1983) and an excitatory cholinergic (Brodie and Proudfit 1984) inputs. Further, in the production of analgesia, a catecholamine (Kulkarni 1982) and indoleamine (Horak and Masek 1988) mediation is reported to be possible and noradrenergic neurons in the CNS have projections to GABAergic, cholinergic and serotonergic components (Redman 1977).
These reports as well as the results of the present study indicate a possible modulatory interaction between various neurotransmitter systems in the observed action. However, these reports do not explain the paradoxical antinociceptive effect of GABA antagonists.

NEUROPSYCHOPHARMACOLOGICAL PROFILE OF FENGABINE: A GABA AGONIST

The results of the studies with fengabine indicate that it is a potential antidepressant, antiaggressive and anticonvulsant agent. The reversal of the antidepressant and antiaggressive effect of fengabine by bicuculline and picrotoxin suggest a possible GABAergic involvement in its mechanism of action and supports the present developing concept that GABA has a major role to play in many neurological disorders (GABA mimetics are effective in certain behavioural and biochemical animal models of depression (Pilc and Lloyd 1984).

The antidepressant effect of fengabine observed in this study (in forced swimming-induced behavioural model) is contrary to what has already been reported. Zivkovic et al., (1986) found fengabine as an effective antidepressant in other models, whereas in the Porsolt model it was reported to ineffective even up to a 200 mg/kg dose. This variation in results may be due to the dose variation since fengabine at a high dose of 200 mg/kg would enhance the immobility rather than reduce it. Smaller doses are effective
in particular model. Moreover, GABA mimetics in general are found to have a biphasic effect. Furthermore, there are opposing reports that GABAergic agents are cataleptogenic (Pycock and Horton 1976) and anticataleptic (Aley and Kulkarni 1987) which may be due to the biphasic effect of this group of drugs.

Fengabine is reported to be a potent anticonvulsant against chemical (bicuculline, pentyletetrazole and penicillin)-induced seizures, whereas a decrease in GABA transmission is considered (Zivkovic et al., 1986). In the present study fengabine was found to reverse electroshock-induced convulsions. Since anticonvulsant property of a drug is an index of its anti-anxiety effect (Costa et al., 1975), the effect of fengabine on footshock-induced aggression was studied and was found to be effective.

Chronic administration of antidepressants as well as fengabine is demonstrated to cause up-regulation of GABA<sub>B</sub> recognition sites (Pilc and Lloyd 1984). Catecholamines are reported to have a role in the genesis of electroshock-induced seizures (Stull et al., 1977). These reports and the results of the fengabine studies implicate a possible GABAergic and catecholaminergic interaction.

The potentiation of the analgesic effect of morphine by fengabine displays a different mechanism as bicuculline failed to reverse its potentiating effect of morphine analgesia. An interaction
with the opioid receptors may be possible in this action.

The GABA receptor agonist baclofen has been shown to reduce locomotor activity and also have muscle relaxant effects (Bowery 1982). Fengabine reduced locomotor activity at a 10 mg/kg dose, but had no effect on the muscle tone of the animals at 10 and 20 mg/kg doses. Therefore, it is difficult to conclude whether the action of fengabine has any GABA_B receptor involvement or not. However, the antagonism of its effects by bicuculline and picrotoxin is indicative of GABAergic involvement. To specify the type of receptor involved, more detailed study is required. However, the findings from the studies of fengabine are suggestive of its potential as a useful psychopharmacological agents, and development of similar GABA mimetics may be of great value in clinical practice. Moreover, further pursuit along this line may be rewarding as it may lead to better understanding of the pathophysiology of many neurological disorders and an effective approach to their alleviation.

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

To understand the GABAergic mechanism involved in ECS, the effect of acute and chronic ECS and as well that of a few
GABA mimetics on GABA antagonists (bicuculline and picrotoxin)-induced convulsions were studied in mice. It was found that the convulsant effect of bicuculline and picrotoxin are differently affected by ECS. This variation may be considered to be due to the difference in their binding sites as bicuculline and picrotoxin are having separate binding sites on the supramolecular GABA/benzodiazepine receptor complex. The neurochemical changes that occur in the CNS as a result of ECS also may have influenced the results. A potassium evoked release of endogenous NE and 5-HT is demonstrated after a single ECS when the endogenous release of GABA is inhibited (Green et al., 1987). Further, repeated ECS is shown to increase number of postsynaptic 5-HT$_2$ receptors.

On picrotoxin-induced convolution, the effect of baclofen was found to be different from that of progabide and fengabine. This variation may be suggestive of their selectivity of binding sites as baclofen is a GABA$_B$ agonist, fengabine a GABA$_A$ agonist and progabide an agonist at both GABA$_A$ and GABA$_B$ receptor sites (Hill and Bowery 1981; Lloyd et al., 1987; Lloyd et al., 1983). Further, baclofen is demonstrated to have both pre- and postsynaptic involvement (Newberry and Nicoll 1985). However, the neurochemical changes that occur as a result of ECS needs further elucidation. Recent demonstration of GABA$_A$ receptor heterogeneity (Levitan et al., 1988) shows that the intricate nature of GABA/benzodiazepine
receptor complex is far from being understood. The possible development of supersensitivity or impairment to the neuronal system as a result of chronic ECS can not be ruled out.

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

The results of the present study suggest that Ro 15-1788 may be having some intrinsic activity and it does not represent as a neutral antagonist. In the cortical area of the chromically Ro 15-1788 treated animals, the integrated EEG amplitude was found to be reduced (Figure-48) as compared to the control group. In the hippocampal area 48 hours withdrawal also caused reduction in the EEG amplitude as indicated by the lesser number of integrated resets (Figure-56). Moreover, the direction of this intrinsic activity (agonist to inverse agonist) was found to vary according to the nature of the test drug. With chronic administration of Ro 15-1788 (4 mg/kg ip) a dose which is generally devoid of intrinsic activity, about 10% of the animals employed in the present study were found to develop transient convulsions which was precipitated on handling as two animals died on the thirteenth and one animal on the sixth day of chronic treatment. Further, with a low dose (2 mg/kg) of picrotoxin, the chronically Ro 15-1788 treated animals were found to develop severe tonic-clonic convulsions. With pentabarbitone (10 mg/kg), the animals went into a deep stupor stage which lasted
for more than three hours (personal observation). However, the
drugs acting via the benzodiazepine receptors (diazepam, FG7142)
were not found to have any effect, indicating that Ro 15-1788 acts
as a neutral antagonist to drugs which act via the benzodiazepine
receptor.

It has been recently reported that chronic Ro 15-1788
treatment increases the binding of \[^3H\] Ro 15-1788, \[^3H\] flunitrazepam,
\[^{35}S\] TBPS and \[^3H\] Ro 15-4513 in the cerebral cortex of rats.
This increase in receptor density remained upregulated during the
withdrawal period as well (Miller et al., 1987, Kulkarni and
Ticku 1989). The specific binding of \[^3H\] Ro 15-1788 was also
found to be increased in hippocampus (Kulkarni and Ticku 1989).
These findings and the EEG changes observed in the cortex and hippo-
campus tend to suggest that chronic treatment with Ro 15-1788 and
its withdrawal alter the receptor sensitivity of various binding sites
on GABA/benzodiazepine receptor complex. These observations may
have some implications in the development of drug discrimination syndrome
observed in man and animals due to benzodiazepine-like drugs.
Figure-§3. GABA\textsubscript{A} and GABA\textsubscript{B} receptor complexes.
Figure-64. Negative allosteric modulation of ionotropic receptors.