INTRODUCTION
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The inhibitory neurotransmitter gamma aminobutyric acid (GABAergic) synapse is considered to be a site of action for a variety of structurally unrelated drugs with diverse pharmacological effects (Olsen 1981). Several drugs, acting on the central nervous system (CNS) are reported to modulate GABA receptor function. Benzodiazepines and related drugs have been extensively investigated employing behavioural, biochemical and electrophysiological approaches. These studies have shown that at least three different classes of drugs/ligand can modulate GABA/benzodiazepine receptor complex namely GABA, benzodiazepines and barbiturate/picrotoxin sites. The drugs acting at the benzodiazepine site are further classified as agonists, partial agonists, antagonists, partial inverse agonists and inverse agonists. These have similar but distinctly different structural specificities and exhibit stereo-selectivity. In general terms, activation of GABA results in an increased membrane permeability to chloride (Cl\(^-\)) which is associated with hyperpolarising response on presynaptic terminals and nerve fibres. The physiological relevance of the multiple receptors remain unclear. Some of these sites appear to be the pharmacological sites for drugs like sedatives, hypnotics, anxiolytics and anticonvulsants. Allosteric interaction between the different units of the GABA/benzodiazepine receptor complex reflect certain aspects of the physiological receptor
mechanism. Moreover, GABAergic involvement is implicated in several neuropsychiatric disorders (Gold et al., 1980; Grner and Hare 1981).

It is now well accepted that GABA forms part of a heterooligomeric protein structure, a super family of ion channel containing receptors, which include binding sites for different categories of drugs that allosterically modulate the receptor function. Pharmacologically GABA receptors have been classified into GABA_A and GABA_B respectively (Hill and Bowery 1981). More recently, electrophysiological and cloning studies have further illustrated subunits for GABA_A receptor as GABA_Aa and GABA_Ad. The GABA_A has been shown to have still further subunits as GABA_Aal GABA_Aa2 and GABA_Aa3. Another subunit termed Y2 also have been deduced (Levitan et al., 1988; Schofield et al., 1987; Pritchett et al., 1989). Moreover, a cytoplasmic region of the GABA_A receptor has been considered to be a possible phosphorylation site of cyclic AMP (cAMP) dependent protein kinase (Schofield et al., 1987). However, at present, the intracellular factors that influence the sensitivity of the GABA_A receptor remain unclear. GABA_B receptor function is still more obscure. Inspite of the developments in the molecular mechanism of GABA/benzodiazepine receptor supramolecular complex, the exact role of this neurotransmitter systems(S) in the brain has not been fully established. Growing evidences implicate GABA in a variety of neurological and psychiatric disorders, such as epilepsy, mental depression,
Parkinson's disease and pain modulation. The present study makes an attempt to explore the role of GABA and related drugs in some of the animal models of these CNS disorders, to elucidate the regulatory role of this inhibitory neurotransmitter of the mammalian brain.

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. 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 benzodiazepine recognition sites (Barbaccia et al., et al., 1986). A similar increase in GABA_B receptor number is demonstrated in the frontal cortex of mice on chronic treatment with imipramine (Suzdak and Gianutsos 1986). The monoamine hypothesis of depression suggests a functional deficiency of norepinephrine (NE) and 5-hydroxytryptamine (5-HT) and an enhancement of cerebral monoaminergic activity by antidepressants (Post et al., 1973; Garelis et al., 1974; Baldessarini 1980). Baclofen, a GABA_B agonist has been shown to inhibit the release of 5-HT from the preloaded slices of rat cortex (Bowery et al., 1980; Schlicker et al., 1984) and potassium evoked release of endogenous 5-HT from slices of mouse frontal cortex (Gray and Green 1987). While the mechanism responsible for these changes are unknown, it is considered to be possible that the decreased sensitivity of GABA_A receptors could be the result of 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 a common postsynaptic cAMP generating system. GABA agonists appear to potentiate NE induced cAMP accumulation (Hill et al., 1984). Characterisation of the GABA receptor subtypes involved in depression and an understanding of the GABAergic interaction with other neurotransmitter systems (s) may help to add the missing link in the biogenic amine hypothesis of depression.

Neurochemical and pharmacological evidences indicate the involvement of GABAergic mechanism in the control of aggressive behaviour in mice and rats (De Paulis and Vergnes 1983; Hang et al., 1984). Benzodiazepines, the widely prescribed anxiolytics are thought to produce their pharmacological actions via specific high affinity binding sites on the supramolecular receptor complex coupled with Cl$^-$ channel (Costa et al., 1975). In intact animals, activation of GABA$_A$ receptor is shown to be associated with an anti-anxiety action (Williams 1983). Mechanisms involving neurotransmitters other than GABA are also implicated in anxiety. For example, quipazine, a non-specific 5-HT agonist, yohimbine an alpha$_2$ antagonist and FG 7142 (N-methyl-$\beta$-carboline-3-carboxamide), a benzodiazepine inverse agonist are known to induce anxiety (Fellow et al., 1987). These findings indicate that anxiolytics may have multiple sites of action or they may influence neurotransmitter(s) system(s) which
may ultimately result in the modulation of GABAergic function.

A critical role for GABA is demonstrated in the pathophysiology of epilepsy, and agents which facilitate GABAergic transmission are shown to be potent anticonvulsants (Meldrum 1975). Although considerable progress has been made in the development of new anticonvulsants, the definite mechanism of action of most antiepileptic drugs are not totally clear as yet. Most of the observations relate that the anticonvulsant activity of drugs are due to the interaction of these agents with different components of the GABA/benzodiazepine receptor Cl⁻ ionophore complex which results in an enhancement of GABAergic transmission (Rastogi and Ticku 1986). However, the exact role of the two GABA receptors (GABA_A and GABA_B) in the anticonvulsant activity of barbiturates and other anticonvulsant drugs against maximal electroshock-induced seizures is still controversial. There are reports demonstrating the involvement (Mehta and Ticku 1986) as well as non-involvement (Ulloque et al., 1986) of GABA receptors in the anticonvulsant activity of barbiturates against maximal electro shock-induced seizures. Catecholamine involvement has long been suggested in chemo- and electro shock-induced seizures (Oishi et al., 1979; Stull et al., 1977). A reduction in brain monoamine content as in the case of reserpinized animals is reported to increase the susceptibility to seizures (Kulkarni 1981). Clonidine and other related alpha₂ adrenoceptor agonists are shown to have an anticonvul-
sant profile (Kulkarni 1981; Kulkarni and NAGRATH 1983; Kulkarni and Mehta 1983). Further, clonidine is demonstrated to stimulate the release of GABA in rat cerebral cortex synaptosomes (Pittalagua and Raiteri 1988).

Electroconvulsive shock (ECS) is extensively employed as an antidepressant remedy. But the mechanism underlying ECS is not yet clear. Reports on the effects of ECS on biogenic amines are rather contradictory, both after single or multiple shocks. Repeated, but not single ECS to mice is reported to enhance catecholaminergic postsynaptic activity (Modigh 1975) and, catecholamines are shown to have a role in the genesis of electroshock-induced seizures (Stull et al., 1977). A sudden decrease in abnormally elevated GABA levels can also lead to epileptogenic processes (Brailowsky et al., 1988).

Several studies have indicated a role for GABA in analgesia (Buckett 1980; Ho et al., 1976). However, the results available are conflicting. For example, muscimol, and aminoxyacetic acid (AOAA) are reported to enhance the antinociceptive effect of morphine in mice. (Biggio et al., 1977; Yoneda et al., 1979). On the other hand, muscimol is reported to antagonise the antinociception induced by morphine or β-endorphine in rats and the effect of muscimol is shown to be reversed by bicuculline, a GABA\textsubscript{A} receptor antagonist.
(Zonta et al., 1981). Further, in the wire-grid test, muscimol is shown to have no analgesic effect (Christensen et al., 1978) and AOAA antagonises morphine-induced antinociception in mice (Ho et al., 1976).

Benzodiazepines bind to specific receptors with in the CNS and form part of a supramolecular complex which contains binding sites for GABA, picrotoxin, barbiturates (Olsen 1982; Maksay and Ticku 1985; Biggio and Costa 1988). Flumazenil (Ro 15-1788) which antagonises the behavioural and biochemical actions of benzodiazepines (Mohler and Richards 1981) is shown to have antagonistic as well as agonistic activity. In pharmacological doses, it acts as a benzodiazepine antagonist (File and Fellow 1986); while at higher doses, it elicits some intrinsic activity (Mehta and Ticku 1989). Chronic flumazenil treatment is shown to increase the specific binding of $^3$H Ro 15-1788 in cerebral cortex and hippocampus which lasted for seventy two hours (Kulkarni and Ticku 1989). The increase in binding is shown to be due to an upregulation of the binding sites ($B_{\text{max}}$) Kulkarni and Ticku 1989).

Progress in the understanding of the structural requirements of therapeutic agents has led to the development of newer agents. Some of the GABA-mimetics thus developed have been showed further clinical use Fengabine, a GABA A agonist has been investigated for its antidepressant activity (Mush and Garrieau 1986). Because of
the ubiquitous distribution of GABA in CNS it is apt to consider that these agents may have a broad spectrum of therapeutic profile. The speculation that GABA is involved in the pathophysiology of various neurological and psychiatric disorders demand detailed evaluation of these agents in various neurological conditions.

The extensive literature that has appeared in the last one decade has amply demonstrated that many pharmacological and physiological effects can be ascribed to and correlated with changes in the brain levels of GABA and the activity of GABA/benzodiazepine receptor supramolecular complex. The knowledge that GABA functions as an inhibitory transmitter in brain has spurred a prodigious research effort to implicate GABA in the aetiology of a host of neurological and psychiatric disorders. However, evidences are still wanting to authenticate this speculation in certain disease processes and drug action. Recent cloning of GABA receptors and identification of α and β-protein sides would further unravel the mystery of this receptor function in the brain. The better understanding of the molecular nature of the allosteric modulatory centres of GABA receptor family can set drug development in a progressive pathway.