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Review Article

GABA RECEPTOR - A WELL ESTABLISHED OLD TARGET

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ABSTRACT

Gamma-Amino butyric acid (GABA) is quantitatively one of the most important neurotransmitters in the central nervous system that targets the ionophoric $GABA_A$ and $GABA_C$ receptors and the metabotropic $GABA_B$ receptors. Of these, it is the $GABA_A$ receptor family which has been the most widely studied since this family is the site of action of a number of clinically important drugs, including benzodiazepines (BZs), barbiturates, and anaesthetics. Since the predominant action of GABA on neurons is inhibitory, activation of GABA receptors, and especially of $GABA_A$ receptors, causes an anticonvulsive effect. $GABA_A$ receptors can be activated either directly by GABA or GABA-agonists, or indirectly by allosteric modulation of these receptors. Since receptor subtypes exhibit a different regional distribution in the central nervous system, the development of subtype-selective $GABA_A$ receptor agonists result in anticonvulsants with fewer side effects. This review describes all types of GABA receptor and its importance in medicinal chemistry.

Keywords: GABA, Agonist, Anticonvulsants

INTRODUCTION

Several amino acids are found in high concentrations in brain, and some have been established as neurotransmitters. *l-Glutamic acid (glutamate)* is the major neurotransmitter for fast excitatory synaptic transmission, where as gama amino butyric acid *(GABA)* is the major neurotransmitter for fast inhibitory synaptic transmission. GABA was shown to fulfill the criteria for establishment as a neurotransmitter. It is synthesized by a specific enzyme, l-glutamic acid decarboxylase (GAD), in one step from l-glutamate. Thus, in addition to its role in protein synthesis, in cofactors such as folic acid and in hormones such as thyrotropin-releasing hormone, and its action as a neurotransmitter itself, glutamate must be available in certain nerve endings for biosynthesis of GABA. Much of the glutamate and GABA used as neurotransmitter is derived from glial storage pools of glutamine.[1] GABA is the principal inhibitory neurotransmitter in the mammalian brain. It mediates fast synaptic inhibition by interaction with the $GABA_A$ receptor. $GABA_A$ is most studied amongst all types of GABA receptor $GABA_A$ receptors are ligand gated ion channels that are modulated by a large number of clinically relevant drugs such as benzodiazepines (BZs), barbiturates, neurosteroids, and anesthetics. They are assembled from individual subunits forming a pentameric structure. Nineteen isoforms of mammalian $GABA_A$ receptor subunits have been cloned α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, p, ρ_{1-3}, and θ. The major receptor subtype of the $GABA_A$ receptor in adults consists of α_1, β_2, and γ_2 subunits, and the most likely stoichiometry is two α subunits, two β subunits, and one γ subunit. The subunit composition of $GABA_A$ receptors influences the effects of modulators. The therapeutically useful properties of benzodiazepines (anxiolytic, anticonvulsant, sedative, and muscle relaxant effects) may result from actions on different $GABA_A$ receptor subtypes. Studies of mice deficient in particular a subunits suggest that the α1-$GABA_A$ subunit is responsible for the sedative properties of benzodiazepines, while the α2-$GABA_A$ subunit is responsible for the anxiolytic properties The δ subunit has been shown to confer significantly increased sensitivity to ethanol at $GABA_A$ receptors.[2]

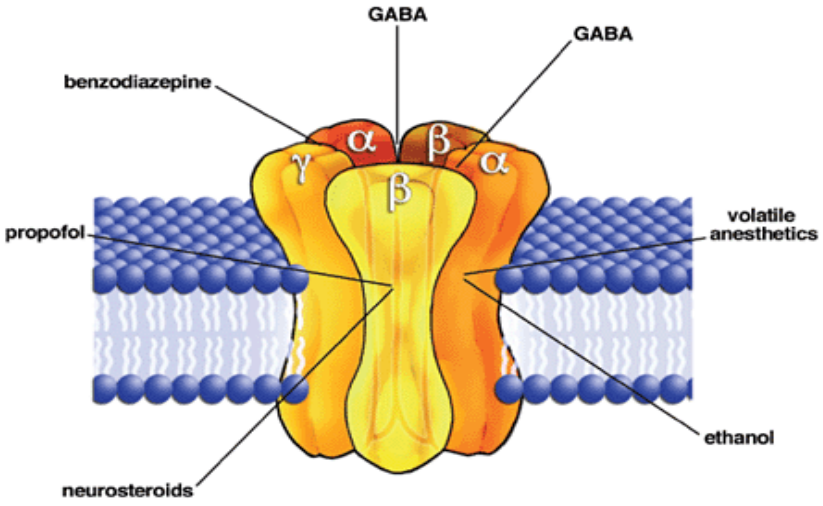

Fig. 1: It shows Main features of the GABA receptor

Chemistry of GABA: It is a small achiral molecule with molecular weight of 103 g/mol and high water solubility. At 25^{0}C one gram of water can dissolve 1.3 grams of GABA. Such a hydrophilic (Log P= -2.13, PSA= 63.3 (A^0) cannot cross blood

brain barrier. It is produced in the brain by decorboxylation of L-glutamic acid by the enzyme glutamic acid decarboxylase (GAD, EC 4.1.1.15). It is a neutral amino acid with pk_1= 4.23 and pK_2= 10.43.[2]

MECHANISM OF ACTION

Prolongation of sodium channel inactivation

Many drugs preferentially block the Na^+ Channels that remain open due to repetitive neuronal firing i.e. they block the use-dependent or voltage dependent Na^+ channels. The higher the frequency of firing the greater is the block. When as neuron fires, the Na^+ channel passes through its active-inactive and resting phases In antiepileptic drugs the duration of inactivated phase and its delay its reversion to the resting phase. This reduces their chances of becoming available for activation again. Example of drug are phenytoin, carbamazepine, Lamotrigine, Lidocain etc.

Inhibition of T-type Calcium current

Ethosuximide is a major drug used for the treatment of absence seizures. It inhibits the low threshold Ca^{+2} currents carried by T-type Ca^{+2} channels. T-type Ca^{+2} current are responsible for generation of the thalamic cortical in petit mal attack inhibition or reduction of the low threshold T-type Ca^{+2} channel therefore, could account for the seizure specific therapeutic action of ethosuximide. Example of other drug is Valproate, Zonisamide etc. [3, 4]

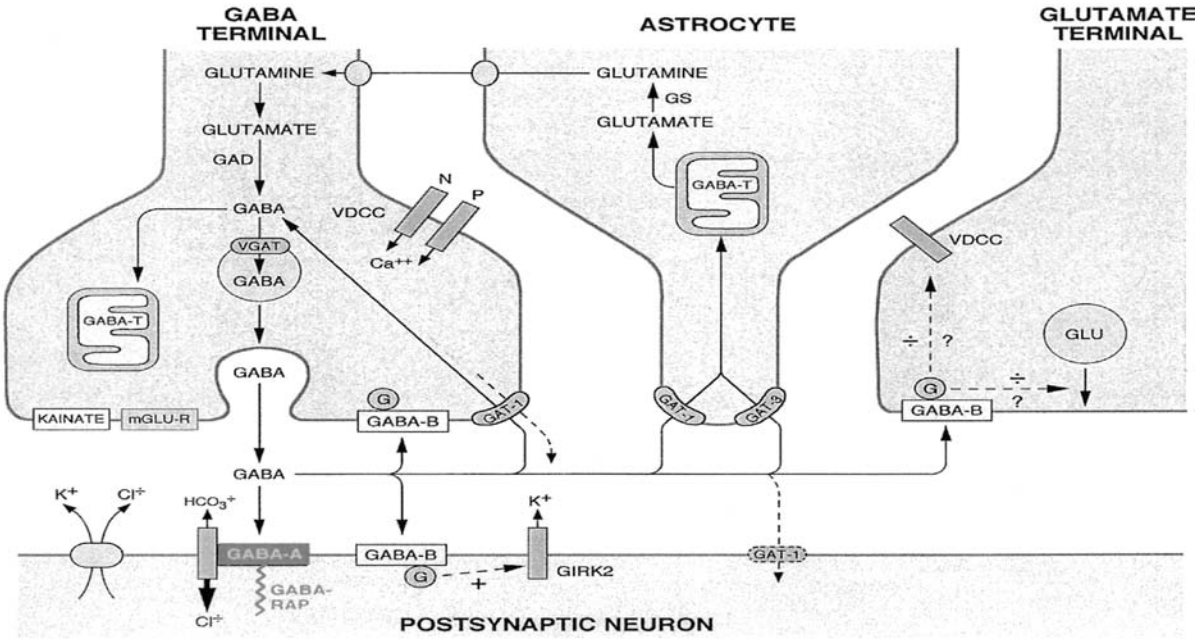

Fig. 2: It shows Schematic GABA synapse. Diagram showing the main features of the GABA synapse. Transporters are indicated by oval symbols, receptors and ion channels by rectangular symbols. A: Transporters: GAT-1, GAT-3, plasma membrane GABA transporters; VGAT, vesicular GABA transporter. B: Receptors: GABA-A, ionotropic GABA receptor; GABA-B, G-protein–coupled GABA receptor; KAINATE, presynaptic kainate receptor; MGLUR, metabotropic glutamate receptor. C: Ion channels: GIRK2, G-D: Enzymes: GABA-T, GABA transaminase; GAD, glutamic acid decarboxylase; GS, glutamate synthetase.

CLASSIFICATION OF GABA-RECEPTOR

The major type of receptor for the inhibitory neuro transmitter gamma amino butyric acid (GABA), called the $GABA_A$ receptor. Molecular cloning of these polypeptide reveals that they show 20-40% identity with each other, and 10-20% identity with polypeptides of nicotinic acetylcholine receptors and strychnine-sensitive glycine receptor. There are two major types of GABA receptors: 1) The ionotropic $GABA_A$ and 2) The metabotropic $GABA_B$ receptors. $GABA_A$ receptor belongs to the ligand gated ion channel super family. It is a heteropentamer, with all of its five subunits contributing to the pore formation. Eight subunit isoforms have been cloned: α, β, γ, δ, ε, π, θ and ρ.1 the native $GABA_A$ receptor, in most cases, consists of 2α, 2β and 1γ subunits [5]

$GABA_A$ Receptor

The $GABA_A$ receptors are widely distributed within the mammalian CNS and exhibit a differential topographical distribution. Systematic modification of the natural agonist demonstrated that $GABA_A$ receptors can be activated by a number of compounds such as muscimol, isoguvacine, 3- aminopropane sulphonic acid, piperidine-4- sulphonic acid and 4,5,6,7-tetrahydro-[5,4-c]- pyridin-3-ol, many of which were subsequently used as radioligands. At equilibrium the binding of $GABA_A$ agonists is heterogeneous with a high affinity component (K values of 10-20 nM) and one or more low-affinity sites with dissociation constants in the range of 100 nM to 1μM. The $GABA_A$ receptor is analogous to the well-characterized nicotinic acetylcholine receptor in that it is a ligand-gated ion channel with a binding site for the natural activator, GABA, and intrinsic to the receptor is the functional response, the chloride ion channel An important advance in the biochemical investigations of the $GABA_A$ receptor was the realization that the anxiolytic benzodiazepine drugs act by a facilitation of GABAergic neurotransmission [6, 7]

$GABA_B$ Receptor

GABA also activates metabotropic GABA receptors, which are widely distributed within the central nervous system and also in peripheral autonomic terminals. Their activation causes an inhibition of both basal and forskolin stimulated adenylate cyclase activity together with a decrease in Ca^{+2} and an increase in K^+ conductance in neuronal membranes. The receptors are activated by baclofen, used in the treatment of spasticity, (+)-baclofen being active isomer. There is evidence that GABA receptor agonists may be useful in the treatment of pain and to reduce the craving for drugs of addiction. There is limited information on the therapeutic potential of GABA receptor antagonists but there is support for the idea that they may

prove valuable in the treatment of absence epilepsy and as cognition enhancers. [6, 7]

GABAc Receptor

In addition to the $GABA_A$ receptors there is a distinct class of ligand gated ion channels that are activated by GABA; referred to as the GABAc receptor. The natural agonist GABA is about an order of magnitude more potent at the $GABA_A$ receptors than at the most common of the GABAc receptors. The GABAc receptors are activated by cis-aminocrotonic acid (CACA), which is not recognized by either the $GABA_A$ or $GABA_B$ receptors, suggesting that they recognize the partially folded conformation of GABA. GABAc receptors are not blocked by bicuculline and do not recognize the benzodiazepines, barbiturates or the neuroactive steroids but, like $GABA_A$ receptors are blocked by picrotoxin, while 1,2,5,6- tetrahydropyridine-4-yl methyl phosphinic acid appears to inhibit GABAc receptors selectively. Pharmacologically they are thus quite distinct. However, molecular cloning studies have revealed that this pharmacological profile is remarkably similar to that exhibited by the subunits when expressed ectopically. Two homologous subunits, 1 and 2, have been identified in human's and these can be expressed as homomers or heteromers, but do not co-assemble with any of the $GABA_A$ receptor subunits.[6, 7]

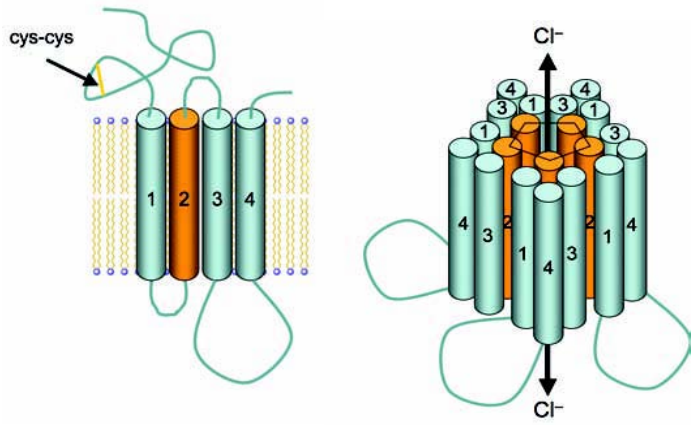

Fig. 3: It shows $GABA_A$ receptor.

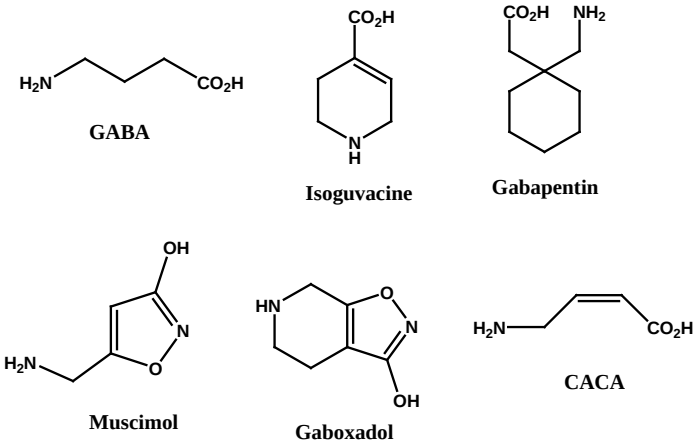

Fig. 4: It shows various $GABA_A$ receptors Agonist

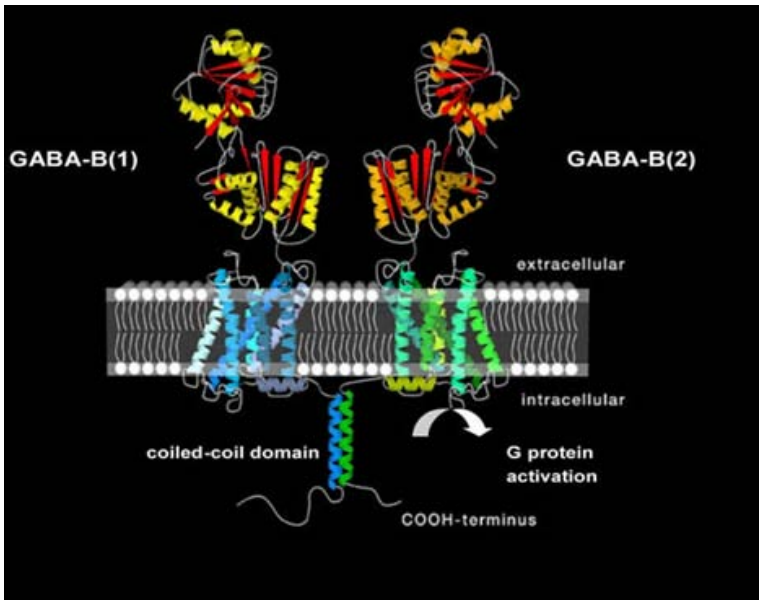

Fig. 5: It shows $GABA_B$ receptor is heterodimer of $GABA_{B1}$ and $GABA_{B2}$ subunits

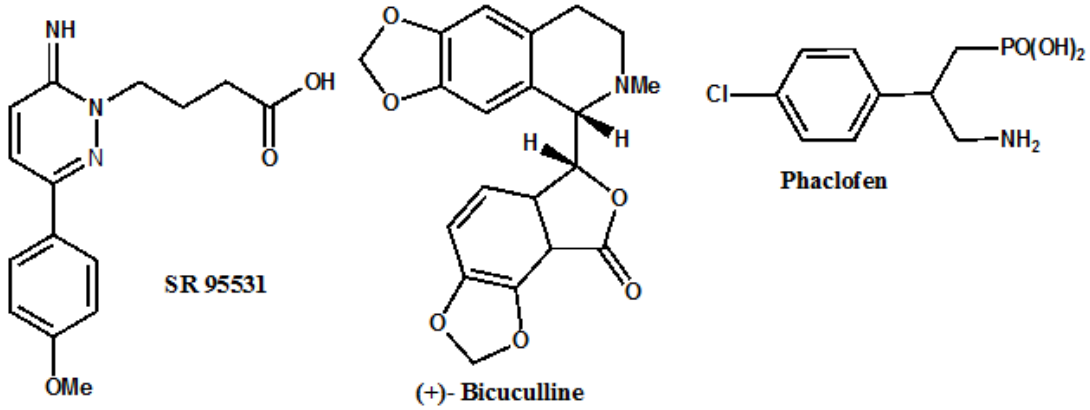

Fig. 6: It shows various $GABA_A$ receptor antagonist

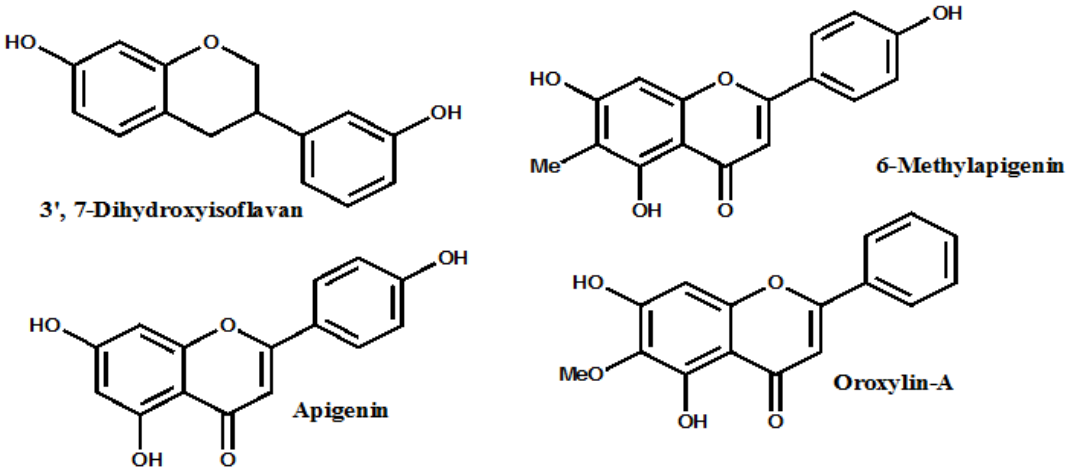

Fig. 7: It shows some representative flavonoids that have shown to influence benzodiazepine binding to brain membranes (3'7-dihyroxyisoflavan, amentoflavone, apigenin, 6-Methylapigenin, and Oroxylin-A), to act at $GABA_A$ receptor as positive modulators (hispidulin) or negative modulators (amentoflavone, apigenin), or at $GABA_C$ receptors as negative modulators (apigenin). In addition, apigenin and (-)-epigallocatechin gallate have been found to have a novel second order modulatory action on the first order modulation of $GABA_A$ receptors by diazepam

Table 1: Table shows Comparative Pharmacology of GABA receptor

Compound	GABAa	GABAb	GABAc
GABA	Agonist	Agonist	Agonist
Muscimol	Agonist	Inactive	Partial agonist
Isoguvacine	Agonist	Inactive	Antagonist
(R)-Baclofen	Inactive	Agonist	Inactive
Bicuculline	Antagonist	Inactive	Inactive
Picrotoxin	Antagonist	Inactive	Antagonist
CACA	Inactive	Inactive	Partial agonist

GABA MODULATORS

Bezodiazepine Site

Benzodiazepines are widely used drugs exerting sedative, anxiolytic, muscle relaxant, and anticonvulsant effects by acting through specific high affinity binding sites on some $GABA_A$ receptors. Benzodiazepines are widely used drugs, which bind to $GABA_A$ receptors with high affinity. These molecules are divided in positive and negative allosteric modulators and antagonists. Mutagenesis studies identified the cleft between α and γ subunits as the binding pocket for benzodiazepines α1H101 was identified as the target of photo affinity labeling by [^{3}H] flunitrazepam and α1Y209 as the target of [^{3}H] Ro15-4513. Pharmacophore modeling attempted to describe the shape of the binding pocket. The benzodiazepine binding site is constituted of six loops from A to F. The important residue a1H101 forming part of loop A has previously been shown to molecularly interact with diazepam and imidazobenzodiazepine derivatives.[8, 9] benzodiazepines enhance the postsynaptic actions of GABA by binding to benzodiazepine receptors which are allosteric modulatory binding sites on GABA (A) receptors. Conversely, there are compounds which bind to the same benzodiazepine receptors, but reduce the postsynaptic actions of GABA. These compounds cause convulsions and are called "inverse agonists" of the benzodiazepine receptors.[10]

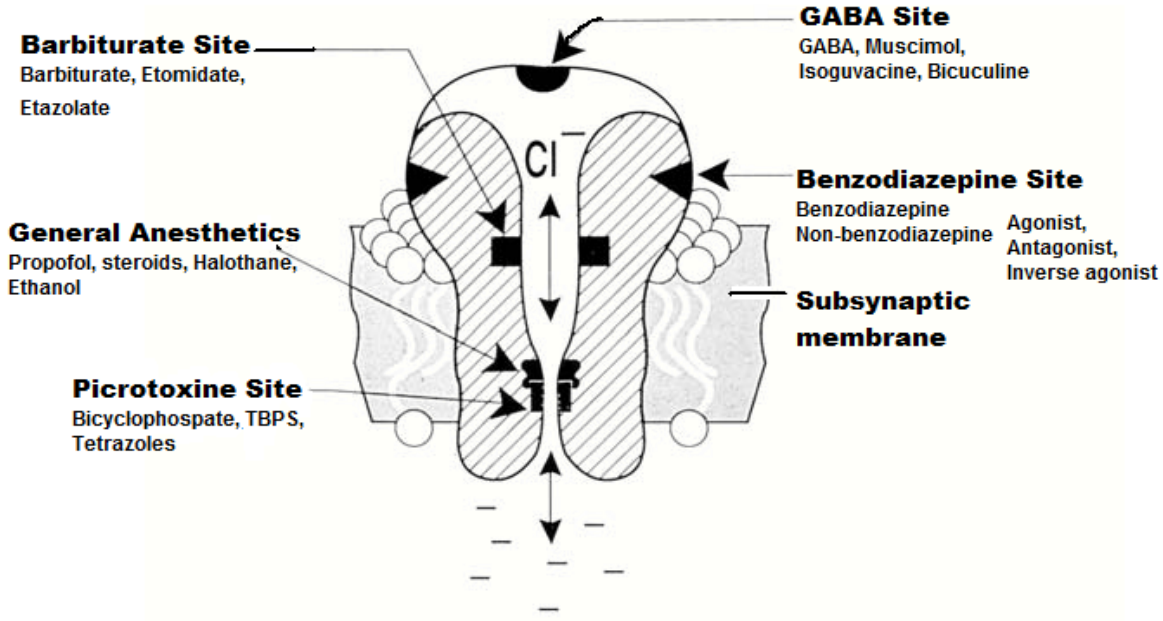

Fig. 8: It shows various sites present at GABA receptor for ligand attachment

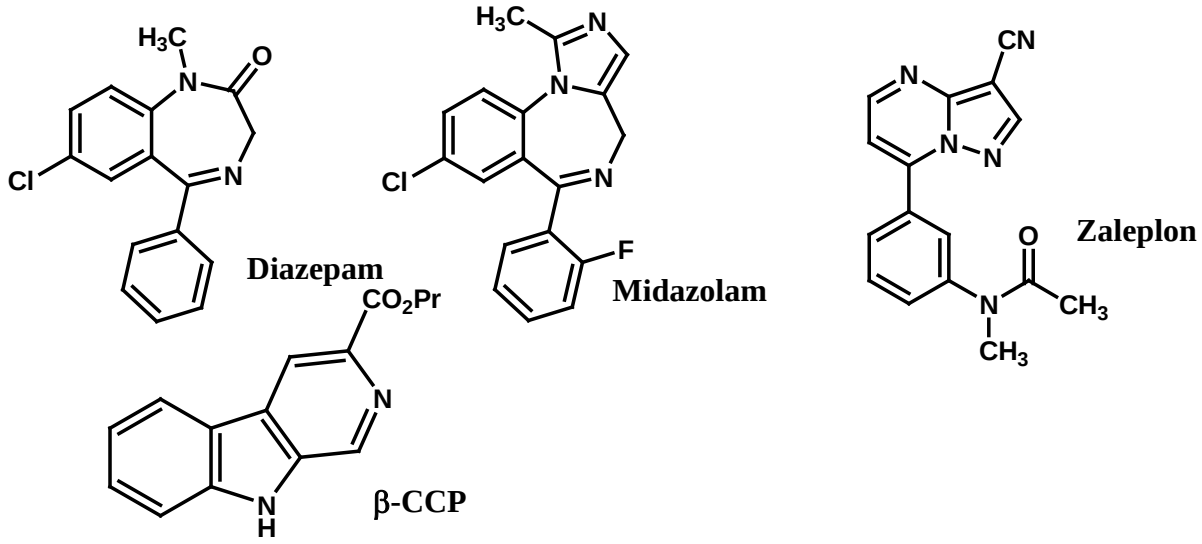

Fig. 9: It shows various benzodiazepine ligands

Other allosteric site

The barbiturates also produce many of their effects by interaction with the GABA receptors of the mammalian CNS. Like the benzodiazepines, they shift the GABA concentration-response curve to the left but unlike the agonist benzodiazepines, the barbiturates also increase the maximum response. They clearly interact with a distinct allosteric site; the barbiturates augment the GABA mediated current by increasing the average channel open time but have little effect on channel opening frequency.

Whereas the benzodiazepines require the presence of a subunit within the GABA receptor oligomer to exert their effects this is not the case for the barbiturates. It is also clear that the barbiturates, at high concentrations, are able to open GABA receptor channels directly, which also distinguishes them from the benzodiazepines. In addition to allosteric sites for the benzodiazepines and barbiturates, the GABA receptors also exhibit high affinity recognition sites for certain steroids. The observation that alphaxalone, the synthetic steroid general anaesthetic, was able to cause stereoselective potentiation of GABA receptor mediated responses in cuneate nucleus slices from rat brain was subsequently confirmed in voltage clamp studies conducted in both neuronal and adrenomedullary chromaffin cells. Although the majority of studies have focused on the GABA receptor it is clear that certain anaesthetics, such as ketamine, nitrous oxide and xenon do not produce their effects through this receptor but probably by inhibition of the N- methyl-D -aspartate receptor. It is also clear that many of the anaesthetics interact with other ligand gated ion channels, in addition to the NMDA receptor, with pronounced effects being seen on the neuronal nicotinic acetylcholine receptors, particularly those containing the α 4 subunit, and the 5-HT receptor.

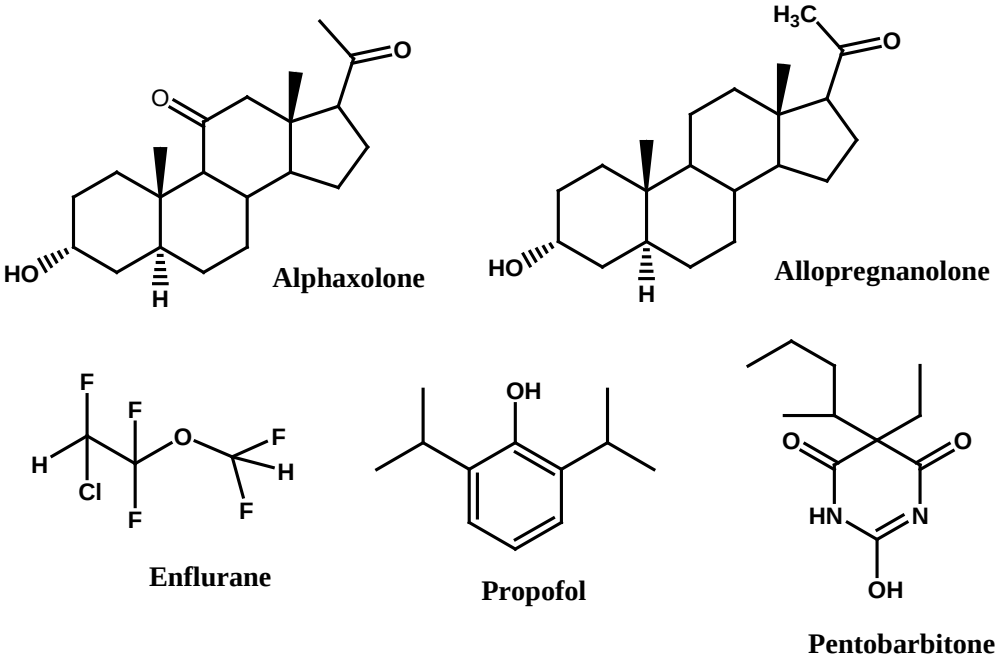

Fig. 10: It shows selected steroids, anesthetics and barbiturate ligands

CONCLUSION

The various agonist and antagonist that were use in both neuroimaging and molecular biology gave us fresh insights into the role of the $GABA_A$ receptor in disease. The latest data confirm the importance of the GABAergic system in the pathogenesis of disease states and help to explain the important role of drugs that bind to $GABA_A$ receptor. A clear understanding of the mechanism underlying dependence will also enable us to develop treatment regimes for using current drugs which will optimize benefits and minimizes any unwanted effects. Thus GABA receptor is a well established old target.

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