**GABA$_A$ receptors as novel drug targets for treatment of mental disorders**

Abolghasem Esmaeili$^{1,*}$, Kamran Ghaedi$^1$

$^1$Cell, Molecular & Developmental Biology Division, Department of Biology, Faculty of Sciences, University of Isfahan, Isfahan, Iran

*Corresponding Author: email address: aesmaeili@biol.ui.ac.ir (A. Esmaeili)

**ABSTRACT**

A balance between excitatory and inhibitory neurotransmissions in brain is an essential factor for the proper function of the brain. The amino acid gamma-aminobutyric-acid (GABA) is considered as the major inhibitory neurotransmitter in brain. Thus, GABAergic neurons play a key role in regulating behavior. Previous data have revealed the complex subunit structural design for GABA$_A$ receptor channel, in which a pentameric assembly resulting from 5 of at least 21 subunits, grouped in the eight classes alpha ($\alpha_1$-$\alpha_6$), beta ($\beta_1$-$\beta_4$), gamma ($\gamma_1$-$\gamma_4$), delta, pi ($\pi$), epsilon ($\epsilon$), theta ($\theta$) and rho ($\rho_1$-$\rho_3$) permits an immense number of putative receptor isoforms. GABA$_A$Rs are highly diversified in the central nervous system in which this diversity may be related to some mental disorders. Any alteration in expression of the GABA$_A$ receptor genes causes neurophysiological and functional consequences that might be associated with neurological disorders. Some neuropsychiatric disorders, such as anxiety, epilepsy and sleep disorders, are effectively treated with therapeutic agents that act on the GABA$_A$ receptor. In this article, the contribution of GABA$_A$ receptor deficits to central nervous system disorders, in particular anxiety disorders, epilepsy, schizophrenia and insomnia, will be reviewed. The better understanding of GABA and its receptors may help us to find novel therapeutic agents for treatment of mental disorder in future research.

**Keywords:** Epilepsy; Anxiety; Insomnia; Schizophrenia; GABA$_A$ receptor subtypes

**INTRODUCTION**

The amino acid gamma-aminobutyric-acid (GABA) is the major inhibitory neurotransmitter in the CNS [1, 2] that mediates most of its effects through receptors termed GABA$_A$. Previous data have revealed the complex subunits structural design of this receptor channel, in which a pentameric assembly resulting from five of at least 21 subunits, grouped in the eight classes alpha ($\alpha_1$-$\alpha_6$), beta ($\beta_1$-$\beta_4$), gamma ($\gamma_1$-$\gamma_4$), delta, pi ($\pi$), epsilon ($\epsilon$), theta ($\theta$) and rho ($\rho_1$-$\rho_3$) [3-5] permits an immense number of putative receptor isoforms. These varieties are extended the existence of several splicing variant forms, for instance of the $\alpha_6$, $\beta_2$ and $\gamma_2$ subunits [6]. The subunit combination of GABA$_A$ receptor determines the specific effects of allosteric modulators as benzodiazepines (BZs), barbiturates, steroids, and general anaesthetics, some convulsants, polyvalent cations, and ethanol. These agents act through different binding sites some of which are not identified yet [7, 8]. Drugs and endogenous ligands bind either to the extracellular domain or channel domain of the GABA$_A$ receptors and act as positive or negative allosteric modulators [9]. In heterologous expression systems, the presence of alpha, beta subunits are needed for functional channels while, gamma subunits are required to mimic the full repertoire of native receptor for responses to drugs. The knowledge of the complex pharmacology of GABA$_A$ receptors might eventually enable site-directed drug design to elaborate our understanding of GABA-related disorders and of the complex interaction of excitatory and inhibitory mechanisms in neuronal processing. To understand the role of GABA$_A$ receptors in mental disorder many methods including molecular and electrophysiological techniques have been used. In the present study we have shown the role of GABA$_A$Rs in some mental disorders.

**Structure and molecular biology of GABA receptors**

The ligand-gated ion channels (LGICs) super family share a common proposed structure. They have a long extracellular amino terminus (around 200 amino acid), thought to be responsible for ligand channel interactions and forms agonist binding site, and four transmembrane (TM) domains and a large intracellular domain between TM3 and TM4 [2, 10]. The TM3-TM4 loop is an important site for regulation by phosphorylation and for localization at
It is thought that TM2 forms the lining segment of the ion channel. The extracellular amino terminus is believed to incorporate neurotransmitter and some modulator binding sites and it contains a conserved motif, the so-called Cys loop (cysteine loop). The Cys-loop is characterized by two cysteine residues spaced by thirteen otherwise largely divergent amino acid residues (Figure 1). This structure is common within acetylcholine (ACh), glycine and type 3 serotonin (5-HT3) receptor as well.

Channels in GABA_A and glycine receptors are anion-selective, whereas in the ACh and 5-HT3 receptors are cation-selective [12]. There is a significant sequence homology in each receptor gene family. In GABA_A receptor subunits the region between TM3 and TM4 shows a little or no sequence homology, suggesting that this domain can tolerate many changes without affecting any possible functional role [13, 14]. GABA_A receptors are large proteins (450-627 amino acids in length) embedded in the cell membrane of neurons. The channel is formed in the center of receptor that consists of five protein molecules, or subunits [15]. GABA_A receptors are activated directly by GABA. In this phenomenon they mediate fast response to GABA and open channel to allow the inward passage of chloride and bicarbonate ions from outside the cell to inside it.

Chromosomal localization of GABA_A receptor genes

It has been found that each GABA_A receptor subunit is encoded by homologous, distinct genes. Many of the subunit genes are organized in β–α–γ and β–α–γ gene clusters on different chromosomes [16, 17]. In humans, the β1–α4–α2–γ1 subunit genes are localized on chromosome 4p14-q12. The β1 and α4 genes, which are separated by less than 60-kb, are arranged in the head to head orientation [17]. The γ1 transcription unit faces the tail of α2. The α4, β1, and γ1 subunit mRNA are predominately expressed in the undifferentiated neuroepithelium of rat embryo [18]. During postnatal development, down regulation of the α4, β1, and γ1 subunits occurs in some specific region whereas expression levels of most other subunits increase. Highly expression of the α2, α4, and β1 genes in the hippocampal formation of the adult rat [19], shows that cluster organization may be necessary to preserve region-specific gene transcription.

The most abundant GABA_A receptor subunit genes encoding are found in a β2–α6–α1–γ2 cluster on chromosome 5q31.2-q35 [17, 20-24]. The β2 and α6 genes are separated by less than 60-kb, with transcription units facing in opposite directions [17]. The colocalization of the α1, β2, and γ2 subunits may be related to their coordinate gene regulation throughout the nervous system; however, direct observation of coordinate regulation has not been reported. The α6 gene that is head-to-head with β2 is expressed only in cerebellar granule cells [25], suggests that there is also independent regulation of transcription for individual members in this gene cluster.

The β3–α5–γ3 GABA_A receptor subunit genes are localized on chromosome 15q11–q13 [17, 26-31]. Lastly, the putative θ–α3ε gene cluster on chromosome Xq28 is analogous to the cluster on chromosome 15 [16, 17, 32, 33]. The θ-subunit gene is analogous to β, and ε has the same position and transcriptional orientation as the γ-subunit gene in other clusters.

Gene expression can be controlled at multiple levels of transcription, alternative splicing, mRNA stability, translation, post-translational modification, intracellular trafficking, and protein degradation. However, gene regulation is predominantly controlled at the level of transcription initiation [34, 35]. Any abnormal alteration during gene expression could result in changes in function and could lead to mental disorders.

Distribution of GABA_A receptor subunits in the CNS

A variety of studies using in situ hybridization [25, 36] and immunohistochemistry [37-41] have indicated the distribution of GABA_A receptor subunits in the brain. The GABA_A receptor α1, β1, β2, β3,
and γ2 are found throughout the brain with different distribution levels. The α2, α3, α4, α5, α6, γ1, and δ subunits are found in certain regions of the brain (Table 1). Mehta et al (1999) reported the percentage of the binding sites immunoprecipitated by antisera to various subunits of GABA\(_A\) receptors in the adult brain regions. These percentages are as follows: α1 = 70-90%, α2 = 4-28%, α3 = 12-24%, α4 = 0-15%, α5 = 4-14%, α6 = 30-39% (cerebellum), β1 = 2-32%, β2 = 55-96%, β3 = 19-52%, γ1 = 0-19%, γ2 = 50-94%, γ2S = 31-52%, γ2L = 37-65%, γ3 = 0-18%, and δ = 0-23% [43]. These results are in a good agreement with in situ hybridization data which showed in the brain that γ1 and γ3 mRNA are expressed in much smaller amounts relative to γ2 mRNA [25, 36, 44]. Although these data do not show the regional distribution of GABA\(_A\) receptor subunits, they show which subunits are abundant in the brain. Distribution of GABA\(_A\) receptor subunits in the brain are summarised in table 1. Gaba receptor also could be seen in other tissue far from CNS such as sperm [45].

Table 1. Regional distributions of GABAA receptor subunits in the brain (Sieghart, 2002)

<table>
<thead>
<tr>
<th>Region</th>
<th>α1</th>
<th>α2</th>
<th>α3</th>
<th>α4</th>
<th>α5</th>
<th>α6</th>
<th>β1</th>
<th>β2</th>
<th>β3</th>
<th>γ1</th>
<th>γ2</th>
<th>γ3</th>
<th>δ</th>
<th>e</th>
<th>θ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offactory bulb</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>glomerular layer</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>ent. pleniform layer</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>granular layer</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>mamillo cell layer</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Offactory tubercle</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cerebral cortex</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>all layers</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>outer layers</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>inner layers</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>molecular layer</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>hilar neurons</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>str. cornu/parahippocampal</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Septum</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>medial</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>lateral</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Striatum/s. amygdalae</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Sub. f. pallidus</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Thalamus</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>ventral nucleus</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>vent. lat. geniculate</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>dors. lat. geniculate</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>medial and central</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>ventromedial</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>suprachiasmatic</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>paraventricular</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>arcuate</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>med. hypo. area</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Amygdalae</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>lateral</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>basolateral</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>medial and central</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>granule cell layer</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>molecular layer</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Midbrain/Pons</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>ventral tegmental area</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Raphe nuclei</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>inferior colliculus</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Olivary superior</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Medulla</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Tegmental sensory complex</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Dorsal cochlear nucleus</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Solitary tract nucleus</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

+++ = extremely high
++ = high
+ = low

52
Pharmacology of GABA<sub>A</sub> receptors

More than one hundred agents act on GABA<sub>A</sub> receptors. These agents act in different binding sites which some are not known yet [46]. Drugs and endogenous ligands act as positive or negative allosteric modulators on GABA<sub>A</sub> receptors. Compounds bind on either extracellular domain or channel domain of the receptor and act as positive or negative modulators [2]. Benzodiazepines are positive modulators acting on the extracellular domain, whereas β-carbolines act mainly as negative modulators. The presence or absence of the γ<sub>2</sub> subunit in the structure of the GABA<sub>A</sub> receptor can influence the action of positive allosteric modulators [47]. The effect of compounds bind on channel the domain can be positive or negative. Barbiturates and steroid hormones act as positive allosteric modulators, whereas pregnenolone and picrotoxin act as negative modulators. However their effects do not depends on the structure of the receptors [47-49]. Benzodiazepines have been widely prescribed since chlordiazepoxide was first introduced in 1960; and because of their safety and efficacy benzodiazepines became the most prescribed drugs in the 1960s and 1970s. However, because of benzodiazepines side effects and drug abuse the use of benzodiazepines have fallen in recent years, but they are still highly prescribed drugs [50]. Benzodiazepines the one of these agents use to treat anxiety have side effects such as sedation, ataxia, amnesia, tolerance, and physical dependence. Because the physiological and pharmacological role of various native GABA<sub>A</sub> receptor assemblies is not yet known, it is not easy to synthesize compounds selective for particular receptor assembly to get a desired therapeutic effect without any serious side effect. All GABA receptors are sensitive to GABA. The binding of GABA to specific sites on the receptor results in the opening of an intrinsic ion channel and the flux of chloride into the cell, which leads to a hyperpolarization of the cell membrane and an increase in the inhibitory tone. The GABA<sub>A</sub> receptors are targets for many important drugs such as benzodiazepines, general anaesthetics, steroids, convulsants and barbiturates [51]. Benzodiazepines mediate their sedative, amnesic and anxiolytic actions via binding to GABA<sub>A</sub> receptors. The sensitivity of GABA receptors to benzodiazepines depends on the GABA receptor subunits composition and is different from one region of the brain to another [52]. It is suggested that γ subunit has a role as important as subunit in determining benzodiazepines sensitivity [53]. Different variants of the γ subunit can influence both affinity and efficacy of various benzodiazepines site ligands and also the type of α subunit can influence the affinity and efficacy of a number of benzodiazepines such as zolpidem. Receptor combinations which include the α<sub>1</sub> receptor subunits display, benzodiazepines type one pharmacology and bind diazepam, zolpidem and other benzodiazepines with high affinity, while those receptors including the α<sub>2</sub>, α<sub>3</sub>, and α<sub>5</sub> subunits display benzodiazepines type two pharmacology and confer low affinity for this ligand, whereas the α<sub>4</sub> and α<sub>6</sub> subunits confer benzodiazepines insensitivity [54]. The crucial amino acids responsible for potent action of benzodiazepines are located within the N-terminal domains of α and γ, within the putative second and third transmembrane domains [55]. In one study various compounds of benzodiazepines were examined on three different human GABA<sub>A</sub> receptor combinations (α<sub>2</sub>β<sub>1</sub>, α<sub>2</sub>β<sub>1</sub>γ<sub>2</sub>S, α<sub>2</sub>β<sub>1</sub>γ<sub>1</sub>). The data showed significant differences among these GABA<sub>A</sub> combinations. The γ<sub>1</sub> subunit in comparison to γ<sub>2</sub> subunit can confer a different pharmacological profile with regard to benzodiazepine site ligands [53]. The patch-clamp technique will be used to facilitate the further characterisation of these drugs and their GABA<sub>A</sub> receptors. In this thesis the effects of some of the drugs on GABA<sub>A</sub> channels was examined. Understanding the basic mechanism of operation of the GABA<sub>A</sub> receptors may possibly result in more specific drugs and
better treatments of some of the mental disorders. One way make pharmacological screening of GABA subunits easy is using an anion-sensitive yellow fluorescent protein-based assay [56].

The action of nM and µM concentration of diazepam on α1β2γ2 recombinant expressed into Xenopus oocytes is different at low concentration of GABA [55]. At µM concentration diazepam action is independent of the γ2 subunit. Using mutation of rho subunit of corresponding TM2 and TM3 residues and application of diazepam support this results. Together these data suggest that diazepam, at low concentration of GABA creates two distinct components of potentiation. Gamma subunits are relatively insensitive to Zn²⁺ compared to αβ subunit receptors [57].

GABA<sub>A</sub> receptors and mental disorder

Studies on GABA<sub>A</sub> receptors show that these receptors are involved in the pathology of several neurological and psychiatric diseases, such as epilepsy, anxiety, alcoholism [58], Angelman’s syndrome [59], autism [60], depression [61], premenstrual syndrome [62-64], sleep disorders [65], and Alzheimer’s disease [64]. Some psychiatric disease such as, spasticity, and stiff-person syndrome, are related to lack of GABAergic function in the brain.

GABA transmission plays a key role in controlling seizure activity. The exact nature of its effect depends on the particular position in the brain and the pathway involved. Animal studies have helped to describe specific brain regions such as the substantia nigra that are vital in controlling seizure activity. Antiepileptic drugs such as vigabatrin, a drug developed to treat resistant epilepsy, can increase GABA transmission in these regions and may thereby afford seizure protection [66].

The role of gamma-aminobutyric acid (GABA) in depression and anxiety has been described. New data from both animal and human experimentation have helped define the key role for this transmitter in both these mental pathologies [67]. Dysfunction of the gamma-aminobutyric (GABA) in central nervous system has long been associated with anxiety disorders [68-70]. In both human and animal studies, positive modulators of GABA receptors generally possess anxiolytic activity, whereas negative modulators create anxiogenic-like effects [68]. Various GABA analogs and agents affecting transmitter metabolism to enhance GABAergic tone have also been reported to exert anxiolytic effects [71, 72]. Chronic alcoholism leads to localized brain damage, which is eminent in superior frontal cortex but mild in motor cortex. The probability of developing alcohol dependence is associated with genetic markers. GABA<sub>A</sub> receptor expression differs between alcoholics and controls [73, 74].

Many researchers guess that GABAergic dysfunction plays an important role in the mechanism of neural impairment in Angelman syndrome [75, 76].

First round reports have showed altered expression of GABA receptors in the brains of subjects with autism suggesting GABA/glutamate system dysregulation. Significant decreases in GABRA1, GABRA2, GABRA3, and GABRB3 in parietal cortex have been reported. These results reveal that GABA<sub>A</sub> receptors are reduced in the brain regions that have previously been associated in the pathogenesis of autism, suggesting widespread GABAergic dysfunction in the brains of subjects with autism [77, 78].

Adult neurogenesis adjusts plasticity and function in the hippocampus, which is critical for memory and vulnerable to Alzheimer's disease (AD). Promoting neurogenesis may improve hippocampal function in AD brains. However, how amyloid β (Aβ), the key AD pathogen, affects the development and function of adult-born neurons remains unknown. Adult-born granule cells (GCs) in human amyloid precursor protein (hAPP) transgenic mice, an AD model, showed greater dendritic length, spine density, and functional responses than did controls early in development, but were impaired morphologically and functionally during later maturation. Early inhibition of GABA<sub>A</sub> receptors to suppress GABAergic signaling or late inhibition of calcineurin to enhance glutamatergic signaling normalized the development of adult-born GCs in hAPP mice with high Aβ levels. Aβ-induced increases in GABAergic neurotransmission or an imbalance between GABAergic and glutamatergic neurotransmission may contribute to impaired neurogenesis in AD [79].

In comparison to glutamatergic and cholinergic systems, the GABAergic system is relatively spared in AD, but the precise mechanisms underlying differential
vulnerability are not well understood. Using several methods, investigations demonstrate that despite resistance of the GABAergic system to neurodegeneration, particular subunits of the GABA<sub>A</sub> receptor are altered with age and AD, which can induce compensatory increases in GABA<sub>A</sub> receptor subunits within surrounding cells. Although alteration in GABA<sub>A</sub> may be diffident and perhaps low, this may be enough for alteration in the pharmacokinetic and physiological properties of the receptor. Therefore, it is critical to understand the subunit composition of individual GABA<sub>A</sub> receptors in the diseased brain when developing therapeutics that act at these receptors [80].

**GABA<sub>A</sub> receptors alteration in CNS**

Genetics variations in gene expression may be associated with mental disorders. An altered expression of the GABA<sub>A</sub> receptor has neurophysiologic and functional consequences that might relate to the behavioral and epileptic phenotype associated with fragile X syndrome, such as anxiety, depression, epilepsy, insomnia, and learning and memory [81, 82]. Alteration in GABAergic inhibitory action such as alterations in the number of GABA<sub>A</sub> receptors [4], alterations in GABA<sub>A</sub> receptor subunit composition [40, 83, 84], increased sensitivity to Zn2+ inhibition of GABA<sub>A</sub> receptors in the dentate granule cells [84-86], decreases in GABA transporter function [87] disconnection of inhibitory interneurons from excitatory inputs [88] and use-dependent reduction of excitatory drive to inhibitory interneurons [89] is important in the generation of epilepsy. Alterations in GABA<sub>A</sub> receptor subunit gene expression also may be important in mediating Alzheimer’s disease [90, 91], schizophrenia [92-95], and ischemia [96, 97]. In severe cases of Alzheimer’s disease, levels of α1 subunit protein are significantly reduced compared with mild cases within the hippocampal subregions CA1, CA2, and prosubiculum, but not in the dentate gyrus, subiculum, and presubiculum [91]. Furthermore, level of β3, but not β2, mRNA is reduced in the pathologically severe group in all hippocampal subregions except CA4 [90]. GABA<sub>A</sub> receptor subunit mRNA are differentially regulated in the prefrontal cortex of schizophrenics. While modest reductions in α1, α2, α5, β1, β2, and γ2 subunit mRNA have been detected by in situ hybridisation histochemistry [93], reduced levels of γ2S transcripts have been observed using semiquantitive RT-PCR [94]. In human temporal lobe epilepsy (TLE), alterations in GABA receptor binding have been documented [98]. In the CA2 area of TLE patients there is a uniform increase in α1, α2, β2/3, and γ2 subunits in the dentate granule cell layer, while levels of α2 alone increase. Moreover, extensive cell loss in the CA1 and CA3 regions is accompanied by a significant decrease in the α subunit. Mutations in the GABA<sub>A</sub> receptor γ2 subunit [99, 100] and α1 subunit [101, 102] have been described in patients with epilepsy.

Innate genetic errors caused by dysfunction of the GABAergic system have features common in many mental disorders. Patients with 1p36 deletions, missing a series of genes including the delta subunit of the GABA<sub>A</sub> receptor, show neurological and neuropsychiatric anomalies [103]. The genes encoding the alpha 5, beta 3 and gamma 3 subunits of the GABA<sub>A</sub> receptor on chromosome 15 are commonly deleted in patients with Prader-Willi or Angelman syndrome [104] that this altered neurobehavioral function of Prader-Willi patients could arise directly from an altered GABA<sub>A</sub> receptor composition and expression. In addition, beta 3 mutant mice display a phenotype similar to some aspects of Angelman syndrome, including epilepsy, hyperactivity, learning and memory deficits, and poor motor skills [105]. It is suggested that the associated seizures in some experimental mutant mice could be elucidated by an imbalanced neurotransmitter concentration that led to a pathological adjustment of the GABA inhibitory system [106, 107]. Significant decrease in mRNA expression of GAD67, delta alpha 1, alpha 3 and alpha 4, beta 1 and beta 2, and gamma 1 and gamma 2 subunits of the GABA<sub>A</sub> receptor, has been demonstrated in the fragile X mouse [82, 108, 109].

**Agents effect on GABA<sub>A</sub> receptors in mental disorder**

Many drugs that work on the GABA<sub>A</sub> receptor are commercially available. GABA<sub>A</sub> receptors are targets of both various classes of clinically relevant drugs, including benzodiazepines, barbiturates, and general anesthetics, in addition to endogenous components, such as neuroactive steroids, all of which allosterically modulate receptor function [5, 110]. Benzodiazepines are widely used as anxiolytic agents in many countries even though antidepressants are now suggested as the first
choice of treatment for anxiety [111], largely due to their safety profile. Benzodiazepines are very effective in short-term use. A point mutation in the GABAA receptor α2 subunit in transgenic mouse lines selectively disrupted the anxiolytic effects of benzodiazepines, but not other pharmacological effects of benzodiazepines [112]. This demonstrates a key role of the GABA_A receptor α2 subunit in anxiolytic effects of benzodiazepines.

Some neuropsychiatric disorders, such as anxiety, epilepsy, sleep disorders and convulsive disorders, have been effectively treated with therapeutic agents that enhance the action of GABA at the GABA_A receptor in nervous tissue [113].

Expression of specific subtypes of the GABA_A receptor decrease in fragile X syndrome; it is indicate that specific enhancers of this receptor might be suitable drugs to treat the behavioral aspects of the disorder. These compounds with partial agonist properties were already reported to have improved profiles in whole animal behavioral models [114].

The GABA transporter 1 is another novel candidate as a promising target for treatment of anxiety disorders with panic symptoms [115].

CONCLUSION

GABA system as a whole and especially GABA_A receptors have important roles in CNS and have also been strongly linked to several mental disorders such as epilepsy, anxiety, depression and alcoholism with different mechanisms. Previous research found evidences for association of various GABA receptor genes and a range of mental disorder-related phenotypes. Alteration in GABAergic inhibitory action such as alterations in the number of GABA_A receptors, alterations in GABA_A receptor subunit composition and gene expression of the GABA_A receptor has neurophysiologic and functional consequences that might relate to mental disorders. Therefore, the better understanding of relationship of GABA_A receptors and mental disorders potentially could help to find novel drugs to overcome aforementioned disorders and avoid their side effects.

REFERENCES


23. Russek SJ, Farh DH. Mapping of the beta 2 subunit gene (GABRB2) to microdissected human chromosome 5q34-q35 defines a gene cluster for the most abundant GABAA receptor subunit genes. Genomics 1994; 23(3):528-33.


60. Lancel M. Role of GABAA receptors in the regulation of sleep: initial sleep responses to peripherally administered modulators and agonists. Sleep 1999; 22(1):33-42.


