$GABA_A$ receptors as novel drug targets for treatment of mental disorders

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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 (α1-6), beta (β1-4), gamma (γ1-4), delta, pi (π), epsilon (ε), theta (θ) and rho (ρ1-3) permits an immense number of putative receptor isoforms. $GABA_A$Rs are highly diversed 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 (α1-6), beta (β1-4), gamma (γ1-4), delta, pi, epsilon, theta, and rho (ρ1-3) [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 α6, β2 and γ2 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

synapses [11]. 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.

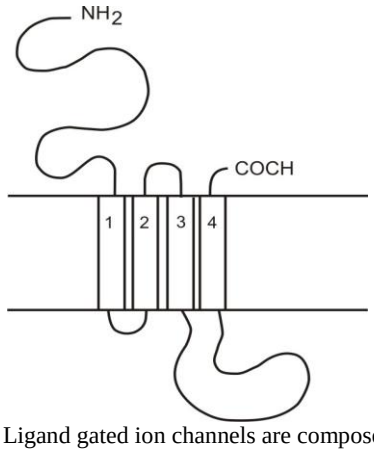

Figure 1. Ligand gated ion channels are composed of five peptide units. Each unit has an N-terminal domain, four transmembrane domains, a large extracellular loop between M3 and M4 and a C-terminus [116].

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 centre 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–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 subutints in the brain (Sieghart, 2002)

Region	α1	α2	α3	α4	α5	α6	β1	β2	β3	γ1	γ2	γ3	δ	ε	θ
Olfactory bulb															
glomerular layer	+++	++	+++	+	++	-	-	+++	+++	-	+++	+	++	-	
ext. plexiform layer	++++	++	+++	+	++	-	+++	++++	++++	-	++++	+	+	-	
granular layer	+++	+++	+	++	+++	-	-	++	+++	-	+++	-	+	-	
mitral cell layer	+++	-	+	-	+++	-	++	+++	-	-	+++	+	++	-	
Olfactory tubrcle	++	++	-	+++	++	-	++	++	+++	-	++	++	++	-	
Cerebral cortex															
all layers	+++	++	++	+++	++	-	+++	+++	+++	-	+++	+	++		
outer layers	+++	++	++	++	++	-	+++	+++	+++	-	+++	+	++	-	
inner layers	+++	++	+++	++	++	-	+++	+++	+++	-	+++	+	++	-	
Hippocampus															
molecular layer	++	+++	-	+++	++	-	+++	++	+++	-	+++	-	++	-	
hilar neurons	+++	-	++	-	-	-	+	+++	-	-	+++	-	++	-	
strat. oriens/radiatum	+++	+++	-	++	+++	-	+++	++	+++	-	+++	+	+	-	
Septum															
medial	+++	++	++	-	+	-	+	+++	++	-	+++	+	-	++	++
lateral	+++	+++	++	++	+	-	+++	++	++	++	+++	+	-		
Basal ganglia															
Striatum/n. acumbens	++	++++	++	+++	+++	-	++	++	++++	++	++	+	++	++	++
Globus paliadus	+++	+	+	++	+	-	+	+++	+	+++	+++	+	+		
Subst. nigra	++	++	++	+	++	-	++	++	-	++	++	++	+	+++	++
Thalamus															
reticular nucleus	++	-	+++	++	++	-	+++	-	+++	-	+++	+	+		
vent. lat. geniculate	++++	++	++	++	+	-	++	+++	++	-	++	+	+	+++	++
dors. lat. geniculate	++++	-	-	++++	+	-	++	++++	++	-	++	++	++++		
medial and central	++	+++	++	+	+	-	+++	+++	+++	+++	++	++	++	+++	+++
Hypothalamus															
ventromedial	++	+++	++	+	+++	-	+++	++	+++	++	+++	++	++	+++	+++
supraopticus	++++	++++	++	++	+	-	++++	+++	++	-	++	++	++		
paraventicular	+++	++++	-	-	++	-	+++	++	+++	-	++	++	++	+++	++
arcuate	++	++	++	++	++	-	++	++	++	-	-	++	++	+++	++
med. preoptic area	+++	+++	++	-	++	-	++	++	++	-	+++	++	++	+++	++
Amygdala															
lateral	+++	+++	+++	++	+	-	+++	+++	+++	-	+++	++	+	++	++
basolateral	+++	+++	+++	++	+	-	+++	+++	+++	-	+++	++	+		
medial and central	++	+++	++	+	+	-	+++	+++	+++	+++	+++	++	++	++	++
Cerebellum															
granule cell layer	++++	++	+	+	++	++++	++	++++	++++	++	+++	-	++++		
molecular layer	+++	+++	-	-	+++	-	++	++	-	-	++	+	-		
Midbrain/Pons															
ventral tegmental area	+++	++	+	-	+	-	+++	++	+++	++	+++	+++	+	-	-
Raphe nuclei	+++	+++	++	-	+	-	+++	+++	++	-	+++	+++	+++	++	+++
Inferior colliculus	+++	-	-	-	+	-	++	+++	+	-	+	+	+		
Olive superioor	+	-	++	-	+	-	+++	-	++	-	++	+	++		
Medulla															
Trigeminal sensory complex	+++	-	+++	+	+	-	++	++	++	++	+++	++	++		
Dorsal cochlear nucleus	+++	++	+++	+	++	+++	+	++	+	+	++	++	+++		
Solitary tract nucleus	+++	+	+++	-	+++	-	++	+	++	-	+++	++	+++		

++++ extremly high

+++ high

++ low

+ very low

Pharmacology of $GABA_A$ receptors

More than one hundred agents act on $GABA_A$ 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 $GABA_A$ 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 γ2 subunit in the structure of the $GABA_A$ 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 $GABA_A$ 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 $GABA_A$ 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 $GABA_A$ 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 α1 receptor subunits display, benzodiazepines type one pharmacology and bind diazepam, zolpidem and other benzodiazepines with high affinity, while those receptors including the α2, α3, and α5 subunits display benzodiazepines type two pharmacology and confer low affinity for this ligand, whereas the α4 and α6 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 $GABA_A$ receptor combinations (α2β1, α2β1γ2S, α2β1γ1). The data showed significant differences among these $GABA_A$ combinations. The γ1 subunit in comparison to γ2 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 $GABA_A$ receptors. In this thesis the effects of some of the drugs on $GABA_A$ channels was examined. Understanding the basic mechanism of operation of the $GABA_A$ 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 Zn^{2+} compared to αβ subunit receptors [57].

$GABA_A$ receptors and mental disorder

Studies on $GABA_A$ 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. $GABA_A$ 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 $GABA_A$ 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 $GABA_A$ 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 $GABA_A$ receptor are altered with age and AD, which can induce compensatory increases in $GABA_A$ receptor subunits within surrounding cells. Although alteration in $GABA_A$ 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 $GABA_A$ receptors in the diseased brain when developing therapeutics that act at these receptors [80].

$GABA_A$ receptors alteration in CNS

Genetics variations in gene expression may be associated with mental disorders. An altered expression of the $GABA_A$ 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 $GABA_A$ receptors [4], alterations in $GABA_A$ receptor subunit composition [40, 83, 84], increased sensitivity to Zn2+ inhibition of $GABA_A$ 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 $GABA_A$ 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 $\alpha 1$ 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 $\beta 3$, but not $\beta 2$, mRNA is reduced in the pathologically severe group in all hippocampal subregions except CA4 [90]. $GABA_A$ receptor subunit mRNA are differentially regulated in the prefrontal cortex of schizophrenics. While modest reductions in $\alpha 1$, $\alpha 2$, $\alpha 5$, $\beta 1$, $\beta 2$, and $\gamma 2$ subunit mRNA have been detected by in situ hybridisation histochemistry [93], reduced levels of $\gamma 2S$ transcripts have been observed using semiquantative 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 $\alpha 1$, $\alpha 2$, $\beta 2/3$, and $\gamma 2$ subunits in the dentate granule cell layer, while levels of $\alpha 2$ 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 $GABA_A$ receptor $\gamma 2$ subunit [99, 100] and $\alpha 1$ 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 $GABA_A$ receptor, show neurological and neuropsychiatric anomalies [103]. The genes encoding the alpha 5, beta 3 and gamma 3 subunits of the $GABA_A$ 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 $GABA_A$ 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 $GABA_A$ receptor, has been demonstrated in the fragile X mouse [82, 108, 109].

Agents effect on $GABA_A$ receptors in mental disorder

Many drugs that work on the $GABA_A$ receptor are commercially available. $GABA_A$ receptors are targets of both various classes of clinically relevant drugs, including benzodiazepines, barbiturates, and general anaesthetics, 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

1. Simeone TA, Donevan SD, Rho JM. Molecular biology and ontogeny of gamma-aminobutyric acid (GABA) receptors in the mammalian central nervous system. J Child Neurol 2003;18(1):39-48.

2. Olsen RW, Tobin AJ. Molecular biology of GABAA receptors. Faseb J 1990; 4(5):1469-80.

3. Darlison MG, Pahal I, Thode C. Consequences of the evolution of the GABA(A) receptor gene family. Cell Mol Neurobiol 2005; 25(3-4):607-24.

4. Whiting PJ. The GABA-A receptor gene family: new targets for therapeutic intervention. Neurochem Int 1999; 34(5):387-90.

5. Barnard EA, Skolnick P, Olsen RW, Mohler H, Sieghart W, Biggio G, et al. International Union of Pharmacology. XV. Subtypes of gamma-aminobutyric acidA receptors: classification on the basis of subunit structure and receptor function. Pharmacol Rev 1998; 50(2):291-313.

6. Korpi ER, Grunder G, Luddens H. Drug interactions at GABA(A) receptors. Prog Neurobiol 2002; 67(2):113-59.

7. Johnston GAR. GABA(C) receptors: Relatively simple transmitter-gated ion channels? Trends in Pharmacological Sciences 1996; 17(9):319-23.

8. Johnston GAR. GABA(A) receptor pharmacology. Pharmacology & Therapeutics 1996; 69(3):173-98.

9. Olsen RW, Tobin AJ. Molecular-Biology of Gaba-a Receptors. Faseb Journal 1990; 4(5):1469-80.

10. Schofield PR, Darlison MG, Fujita N, Burt DR, Stephenson FA, Rodriguez H, et al. Sequence and functional expression of the GABA A receptor shows a ligand-gated receptor super-family. Nature 1987; 328(6127):221-7.

11. Brandon N, Jovanovic J, Moss S. Multiple roles of protein kinases in the modulation of gamma-aminobutyric acid(A) receptor function and cell surface expression. Pharmacol Ther 2002; 94(1-2):113-22.

12. Akabas MH. GABAA receptor structure-function studies: a reexamination in light of new acetylcholine receptor structures. Int Rev Neurobiol 2004; 62:1-43.

13. Whiting PJ, Bonnert TP, McKernan RM, Farrar S, Le Bourdelles B, Heavens RP, et al. Molecular and functional diversity of the expanding GABA-A receptor gene family. Ann N Y Acad Sci 1999; 868:645-53.

14. Moss SJ, Smart TG. Constructing inhibitory synapses. Nat Rev Neurosci 2001; 2(4):240-50.

15. Mihic SJ, Harris RA. GABA and the GABAA receptor. Alcohol Health Res World 1997; 21(2):127-31.
16. Wilke K, Gaul R, Klauck SM, Poustka A. A gene in human chromosome band Xq28 (GABRE) defines a putative new subunit class of the GABAA neurotransmitter receptor. Genomics 1997; 45(1):1-10.
17. Russek SJ. Evolution of GABA(A) receptor diversity in the human genome. Gene 1999; 227(2):213-22.
18. Ma W, Saunders PA, Somogyi R, Poulter MO, Barker JL. Ontogeny of GABAA receptor subunit mRNAs in rat spinal cord and dorsal root ganglia. J Comp Neurol 1993; 338(3):337-59.
19. Wisden W, Seeburg PH. GABAA receptor channels: from subunits to functional entities. Curr Opin Neurobiol 1992; 2(3):263-9.
20. Buckle VJ, Fujita N, Ryder-Cook AS, Derry JM, Barnard PJ, Lebo RV, et al. Chromosomal localization of GABAA receptor subunit genes: relationship to human genetic disease. Neuron 1989; 3(5):647-54.
21. Johnson KJ, Sander T, Hicks AA, van Marle A, Janz D, Mullan MJ, et al. Confirmation of the localization of the human GABAA receptor alpha 1-subunit gene (GABRA1) to distal 5q by linkage analysis. Genomics 1992; 14(3):745-8.
22. Wilcox AS, Warrington JA, Gardiner K, Berger R, Whiting P, Altherr MR, et al. Human chromosomal localization of genes encoding the gamma 1 and gamma 2 subunits of the gamma-aminobutyric acid receptor indicates that members of this gene family are often clustered in the genome. Proc Natl Acad Sci U S A 1992; 89(13):5857-61.
23. Russek SJ, Farb 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 isoform. Genomics 1994; 23(3):528-33.
24. Kostrzewa M, Kohler A, Eppelt K, Hellam L, Fairweather ND, Levy ER, et al. Assignment of genes encoding GABAA receptor subunits alpha 1, alpha 6, beta 2, and gamma 2 to a YAC contig of 5q33. Eur J Hum Genet 1996; 4(4):199-204.
25. Wisden W, Laurie DJ, Monyer H, Seeburg PH. The distribution of 13 GABAA receptor subunit mRNAs in the rat brain. I. Telencephalon, diencephalon, mesencephalon. J Neurosci 1992; 12(3):1040-62.
26. Wagstaff J, Chaillet JR, Lalande M. The GABAA receptor beta 3 subunit gene: characterization of a human cDNA from chromosome 15q11q13 and mapping to a region of conserved synteny on mouse chromosome 7. Genomics 1991; 11(4):1071-8.
27. Wagstaff J, Knoll JH, Fleming J, Kirkness EF, Martin-Gallardo A, Greenberg F, et al. Localization of the gene encoding the GABAA receptor beta 3 subunit to the Angelman/Prader-Willi region of human chromosome 15. Am J Hum Genet 1991; 49(2):330-7.
28. Knoll JH, Wagstaff J, Lalande M. Cytogenetic and molecular studies in the Prader-Willi and Angelman syndromes: an overview. Am J Med Genet 1993; 46(1):2-6.
29. Nakatsu Y, Tyndale RF, DeLorey TM, Durham-Pierre D, Gardner JM, McDanel HJ, et al. A cluster of three GABAA receptor subunit genes is deleted in a neurological mutant of the mouse p locus. Nature 1993; 364(6436):448-50.
30. Sinnett D, Wagstaff J, Glatt K, Woolf E, Kirkness EJ, Lalande M. High-resolution mapping of the gamma-aminobutyric acid receptor subunit beta 3 and alpha 5 gene cluster on chromosome 15q11-q13, and localization of breakpoints in two Angelman syndrome patients. Am J Hum Genet 1993; 52(6):1216-29.
31. Greger V, Knoll JH, Woolf E, Glatt K, Tyndale RF, DeLorey TM, et al. The gamma-aminobutyric acid receptor gamma 3 subunit gene (GABRG3) is tightly linked to the alpha 5 subunit gene (GABRA5) on human chromosome 15q11-q13 and is transcribed in the same orientation. Genomics 1995; 26(2):258-64.
32. Bell MV, Bloomfield J, McKinley M, Patterson MN, Darlison MG, Barnard EA, et al. Physical linkage of a GABAA receptor subunit gene to the DXS374 locus in human Xq28. Am J Hum Genet 1989; 45(6):883-8.
33. Levin ML, Chatterjee A, Pragliola A, Worley KC, Wehnert M, Zhuchenko O, et al. A comparative transcription map of the murine bare patches (Bpa) and striated (Str) critical regions and human Xq28. Genome Res 1996; 6(6):465-77.
34. Latchman DS. How can we use our growing understanding of gene transcription to discover effective new medicines? Curr Opin Biotechnol 1997; 8(6):713-7.
35. Lemon B, Tjian R. Orchestrated response: a symphony of transcription factors for gene control. Genes Dev 2000; 14(20):2551-69.
36. Laurie DJ, Seeburg PH, Wisden W. The distribution of 13 GABAA receptor subunit mRNAs in the rat brain. II. Olfactory bulb and cerebellum. J Neurosci 1992; 12(3):1063-76.

37. Fritschy JM, Mohler H. GABAA-receptor heterogeneity in the adult rat brain: differential regional and cellular distribution of seven major subunits. J Comp Neurol 1995; 359(1):154-94.
38. Gutierrez A, Khan ZU, De Blas AL. Immunocytochemical localization of gamma 2 short and gamma 2 long subunits of the GABAA receptor in the rat brain. J Neurosci 1994; 14(11 Pt 2):7168-79.
39. Pirker S, Schwarzer C, Wieselthaler A, Sieghart W, Sperk G. GABA(A) receptors: immunocytochemical distribution of 13 subunits in the adult rat brain. Neuroscience 2000;101(4):815-50.
40. Sperk G, Schwarzer C, Tsunashima K, Kandlhofer S. Expression of GABA(A) receptor subunits in the hippocampus of the rat after kainic acid-induced seizures. Epilepsy Res 1998; 32(1-2):129-39.
41. Esmaeili A. Distribution and function of GABAA receptor subunits in the amygdala [Research]. Brisbane: Queansland; 2006.
42. Mehta AK, Ticku MK. An update on GABAA receptors. Brain Res Brain Res Rev 1999; 29(2-3):196-217.
43. Johnston GA. GABAA receptor pharmacology. Pharmacol Ther 1996; 69(3):173-98.
44. Pritchett DB, Sontheimer H, Shivers BD, Ymer S, Kettenmann H, Schofield PR, et al. Importance of a novel GABAA receptor subunit for benzodiazepine pharmacology. Nature 1989; 338(6216):582-5.
45. Pritchett DB, Sontheimer H, Gorman CM, Kettenmann H, Seeburg PH, Schofield PR. Transient expression shows ligand gating and allosteric potentiation of GABAA receptor subunits. Science 1988; 242(4883):1306-8.
46. Puia G, Santi MR, Vicini S, Pritchett DB, Purdy RH, Paul SM, et al. Neurosteroids act on recombinant human GABAA receptors. Neuron 1990; 4(5):759-65.
47. Wafford KA. GABAA receptor subtypes: any clues to the mechanism of benzodiazepine dependence? Curr Opin Pharmacol 2005; 5(1):47-52.
48. Semyanov A, Kullmann DM. Relative picrotoxin insensitivity distinguishes ionotropic GABA receptor-mediated IPSCs in hippocampal interneurons. Neuropharmacology 2002; 43(4):726-36.
49. Wafford KA, Bain CJ, Whiting PJ, Kemp JA. Functional comparison of the role of gamma subunits in recombinant human gamma-aminobutyric acidA/benzodiazepine receptors. Mol Pharmacol 1993; 44(2):437-42.
50. Kaufmann WA, Humpel C, Alheid GF, Marksteiner J. Compartmentation of alpha 1 and alpha 2 GABA(A) receptor subunits within rat extended amygdala: implications for benzodiazepine action. Brain Res 2003; 964(1):91-9.
51. Walters RJ, Hadley SH, Morris KD, Amin J. Benzodiazepines act on GABAA receptors via two distinct and separable mechanisms. Nat Neurosci 2000; 3(12):1274-81.
52. Krishek BJ, Moss SJ, Smart TG. Interaction of H+ and Zn2+ on recombinant and native rat neuronal GABAA receptors. J Physiol 1998; 507 (Pt 3):639-52.
53. Davies DL, Alkana RL. Benzodiazepine agonist and inverse agonist coupling in GABAA receptors antagonized by increased atmospheric pressure. Eur J Pharmacol 2003; 469(1-3):37-45.
54. DeLorey TM, Olsen RW. GABA and epileptogenesis: comparing gabrb3 gene-deficient mice with Angelman syndrome in man. Epilepsy Res 1999; 36(2-3):123-32.
55. Buxbaum JD, Silverman JM, Smith CJ, Greenberg DA, Kilifarski M, Reichert J, et al. Association between a GABRB3 polymorphism and autism. Mol Psychiatry 2002; 7(3):311-6.
56. Brambilla P, Perez J, Barale F, Schettini G, Soares JC. GABAergic dysfunction in mood disorders. Mol Psychiatry 2003; 8(8):721-37, 15.
57. Smith SS, Gong QH, Hsu FC, Markowitz RS, ffrench-Mullen JM, Li X. GABA(A) receptor alpha4 subunit suppression prevents withdrawal properties of an endogenous steroid. Nature 1998; 392(6679):926-30.
58. Benes FM. Evidence for altered trisynaptic circuitry in schizophrenic hippocampus. Biol Psychiatry 1999; 46(5):589-99.
59. Steiger JL, Russek SJ. GABAA receptors: building the bridge between subunit mRNAs, their promoters, and cognate transcription factors. Pharmacol The 2004; 101(3):259-81.
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.
61. Gale K. GABA and epilepsy: basic concepts from preclinical research. Epilepsia 1992; 33 Suppl 5:S3-12.
62. Kalueff AV, Nutt DJ. Role of GABA in anxiety and depression. Depress Anxiety 2007; 24(7):495-517.
63. Nutt DJ, Malizia AL. New insights into the role of the GABA(A)-benzodiazepine receptor in psychiatric disorder. Br J Psychiatry 2001; 179:390-6.

64. Lydiard RB. The role of GABA in anxiety disorders. J Clin Psychiatry 2003; 64 Suppl 3:21-7.
65. Nemeroff CB. The role of GABA in the pathophysiology and treatment of anxiety disorders. Psychopharmacol Bull 2003; 37(4):133-46.
66. Ma J, Ye N, Lange N, Cohen BM. Dynorphinergic GABA neurons are a target of both typical and atypical antipsychotic drugs in the nucleus accumbens shell, central amygdaloid nucleus and thalamic central medial nucleus. Neuroscience 2003; 121(4):991-8.
67. Stahl SM. Anticonvulsants as anxiolytics, part 1: tiagabine and other anticonvulsants with actions on GABA. J Clin Psychiatry 2004; 65(3):291-2.
68. Buckley ST, Foley PF, Innes DJ, Loh el W, Shen Y, Williams SM, et al. GABA(A) receptor beta isoform protein expression in human alcoholic brain: interaction with genotype. Neurochem Int 2006; 49(6):557-67.
69. Dodd PR, Buckley ST, Eckert AL, Foley PF, Innes DJ. Genes and gene expression in the brains of human alcoholics. Ann N Y Acad Sci 2006; 1074:104-15.
70. Dan B, Boyd SG. Angelman syndrome reviewed from a neurophysiological perspective. The UBE3A-GABRB3 hypothesis. Neuropediatrics 2003; 34(4):169-76.
71. Egawa K, Asahina N, Shiraishi H, Kamada K, Takeuchi F, Nakane S, et al. Aberrant somatosensory-evoked responses imply GABAergic dysfunction in Angelman syndrome. Neuroimage 2008; 39(2):593-9.
72. Fatemi SH, Reutiman TJ, Folsom TD, Thuras PD. GABA(A) receptor downregulation in brains of subjects with autism. J Autism Dev Disord 2009; 39(2):223-30.
73. Fatemi SH, Folsom TD, Reutiman TJ, Thuras PD. Expression of GABA(B) receptors is altered in brains of subjects with autism. Cerebellum 2009; 8(1):64-9.
74. Sun B, Halabisky B, Zhou Y, Palop JJ, Yu G, Mucke L, et al. Imbalance between GABAergic and Glutamatergic Transmission Impairs Adult Neurogenesis in an Animal Model of Alzheimer's Disease. Cell Stem Cell2009; 5(6):624-33.
75. Rissman RA, De Blas AL, Armstrong DM. GABA(A) receptors in aging and Alzheimer's disease. J Neurochem 2007; 103(4):1285-92.
76. D'Hulst C, Heulens I, Brouwer JR, Willemsen R, De Geest N, Reeve SP, et al. Expression of the GABAergic system in animal models for fragile X syndrome and fragile X associated tremor/ataxia syndrome (FXTAS). Brain Res 2009; 1253:176-83.
77. D'Hulst C, De Geest N, Reeve SP, Van Dam D, De Deyn PP, Hassan BA, et al. Decreased expression of the GABAA receptor in fragile X syndrome. Brain Res 2006; 1121(1):238-45.
78. Rice A, Rafiq A, Shapiro SM, Jakoi ER, Coulter DA, DeLorenzo RJ. Long-lasting reduction of inhibitory function and gamma-aminobutyric acid type A receptor subunit mRNA expression in a model of temporal lobe epilepsy. Proc Natl Acad Sci U S A 1996; 93(18):9665-9.
79. Brooks-Kayal AR, Shumate MD, Jin H, Rikhter TY, Coulter DA. Selective changes in single cell GABA(A) receptor subunit expression and function in temporal lobe epilepsy. Nat Med 1998; 4(10):1166-72.
80. Buhl EH, Otis TS, Mody I. Zinc-induced collapse of augmented inhibition by GABA in a temporal lobe epilepsy model. Science 1996; 271(5247):369-73.
81. Gibbs JW, 3rd, Shumate MD, Coulter DA. Differential epilepsy-associated alterations in postsynaptic GABA(A) receptor function in dentate granule and CA1 neurons. J Neurophysiol 1997; 77(4):1924-38.
82. Williamson S, Faulkner-Jones BE, Cram DS, Furness JB, Harrison LC. Transcription and translation of two glutamate decarboxylase genes in the ileum of rat, mouse and guinea pig. J Auton Nerv Syst 1995; 55(1-2):18-28.
83. Sloviter RS. Decreased hippocampal inhibition and a selective loss of interneurons in experimental epilepsy. Science 1987; 235(4784):73-6.
84. Doherty J, Dingledine R. Reduced excitatory drive onto interneurons in the dentate gyrus after status epilepticus. J Neurosci 2001; 21(6):2048-57.
85. Mizukami K, Ikonomovic MD, Grayson DR, Rubin RT, Warde D, Sheffield R, et al. Immunohistochemical study of GABA(A) receptor beta2/3 subunits in the hippocampal formation of aged brains with Alzheimer-related neuropathologic changes. Exp Neurol 1997; 147(2):333-45.
86. Mizukami K, Ikonomovic MD, Grayson DR, Sheffield R, Armstrong DM. Immunohistochemical study of GABAA receptor alpha1 subunit in the hippocampal formation of aged brains with Alzheimer-related neuropathologic changes. Brain Res 1998; 799(1):148-55.

87. Squires RF, Saederup E. Mono N-aryl ethylenediamine and piperazine derivatives are GABAA receptor blockers: implications for psychiatry. Neurochem Res 1993; 18(7):787-93.
88. Akbarian S, Huntsman MM, Kim JJ, Tafazzoli A, Potkin SG, Bunney WE, Jr., et al. GABAA receptor subunit gene expression in human prefrontal cortex: comparison of schizophrenics and controls. Cereb Cortex 1995; 5(6):550-60.
89. Huntsman MM, Tran BV, Potkin SG, Bunney WE, Jr., Jones EG. Altered ratios of alternatively spliced long and short gamma2 subunit mRNAs of the gamma-amino butyrate type A receptor in prefrontal cortex of schizophrenics. Proc Natl Acad Sci U S A 1998; 95(25):15066-71.
90. Ohnuma T, Augood SJ, Arai H, McKenna PJ, Emson PC. Measurement of GABAergic parameters in the prefrontal cortex in schizophrenia: focus on GABA content, GABA(A) receptor alpha-1 subunit messenger RNA and human GABA transporter-1 (HGAT-1) messenger RNA expression. Neuroscience 1999; 93(2):441-8.
91. Li H, Siegel RE, Schwartz RD. Rapid decline of GABAA receptor subunit mRNA expression in hippocampus following transient cerebral ischemia in the gerbil. Hippocampus 1993; 3(4):527-37.
92. Neumann-Haefelin T, Bosse F, Redecker C, Muller HW, Witte OW. Upregulation of GABAA-receptor alpha1- and alpha2-subunit mRNAs following ischemic cortical lesions in rats. Brain Res 1999; 816(1):234-7.
93. Lloyd KG, Bossi L, Morselli PL, Munari C, Rougier M, Loiseau H. Alterations of GABA-mediated synaptic transmission in human epilepsy. Adv Neurol 1986; 44:1033-44.
94.Baulac S, Huberfeld G, Gourfinkel-An I, Mitropoulou G, Beranger A, Prud'homme JF, et al. First genetic evidence of GABA(A) receptor dysfunction in epilepsy: a mutation in the gamma2-subunit gene. Nat Genet 2001; 28(1):46-8.
95. Wallace RH, Marini C, Petrou S, Harkin LA, Bowser DN, Panchal RG, et al. Mutant GABA(A) receptor gamma2-subunit in childhood absence epilepsy and febrile seizures. Nat Genet 2001; 28(1):49-52.
96. Cossette P, Liu L, Brisebois K, Dong H, Lortie A, Vanasse M, et al. Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy. Nat Genet 2002; 31(2):184-9.
97. Fisher JL. The alpha 1 and alpha 6 subunit subtypes of the mammalian GABA(A) receptor confer distinct channel gating kinetics. J Physiol 2004; 561(Pt 2):433-48.
98. Windpassinger C, Kroisel PM, Wagner K, Petek E. The human gamma-aminobutyric acid A receptor delta (GABRD) gene: molecular characterisation and tissue-specific expression. Gene 2002; 292(1-2):25-31.
99. Lucignani G, Panzacchi A, Bosio L, Moresco RM, Ravasi L, Coppa I, et al. GABA A receptor abnormalities in Prader-Willi syndrome assessed with positron emission tomography and [11C]flumazenil. Neuroimage 2004; 22(1):22-8.
100. DeLorey TM, Handforth A, Anagnostaras SG, Homanics GE, Minassian BA, Asatourian A, et al. Mice lacking the beta3 subunit of the GABAA receptor have the epilepsy phenotype and many of the behavioral characteristics of Angelman syndrome. J Neurosci 1998; 18(20):8505-14.
101. Buzzi A, Wu Y, Frantseva MV, Perez Velazquez JL, Cortez MA, Liu CC, et al. Succinic semialdehyde dehydrogenase deficiency: GABAB receptor-mediated function. Brain Res 2006; 1090(1):15-22.
102. Wu Y, Buzzi A, Frantseva M, Velazquez JP, Cortez M, Liu C, et al. Status epilepticus in mice deficient for succinate semialdehyde dehydrogenase: GABAA receptor-mediated mechanisms. Ann Neurol 2006; 59(1):42-52.
103. Gantois I, Vandesompele J, Speleman F, Reyniers E, D'Hooge R, Severijnen LA, et al. Expression profiling suggests underexpression of the GABA(A) receptor subunit delta in the fragile X knockout mouse model. Neurobiol Dis 2006; 21(2):346-57.
104. El Idrissi A, Ding XH, Scalia J, Trenkner E, Brown WT, Dobkin C. Decreased GABA(A) receptor expression in the seizure-prone fragile X mouse. Neurosci Lett 2005; 377(3):141-6.
105.Mohler H, Fritschy JM, Rudolph U. A new benzodiazepine pharmacology. J Pharmacol Exp Ther. 2002 Jan;300(1):2-8.
106. Gorman JM. Treating generalized anxiety disorder. J Clin Psychiatry 2003; 64 Suppl 2:24-9.
107. Low K, Crestani F, Keist R, Benke D, Brunig I, Benson JA, et al. Molecular and neuronal substrate for the selective attenuation of anxiety. Science 2000; 290(5489):131-4.
108. Wang F, Li J, Wu C, Yang J, Xu F, Zhao Q. The GABA(A) receptor mediates the hypnotic activity of melatonin in rats. Pharmacol Biochem Behav 2003; 74(3):573-8.

109. Haefely W. Pharmacology of benzodiazepine antagonists. Pharmacopsychiatry 1985; 18(1):163-6.
110. Thoeringer CK, Ripke S, Unschuld PG, Lucae S, Ising M, Bettecken T, et al. The GABA transporter 1 (SLC6A1): a novel candidate gene for anxiety disorders. J Neural Transm 2009; 116(6):649-57.
111. Chebib M, Johnston GA. The 'ABC' of GABA receptors: a brief review. Clin Exp Pharmacol Physiol 1999; 26(11):937-40.