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SUPPLEMENT

GABA$_A$ Receptors: Subtypes, Regional Distribution, and Function

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Abstract: Modulatory agents of gamma-aminobutyric acid type A (GABA$_A$) receptors have been widely used for more than 40 years to treat anxiety, epilepsy, and sleep disorders; these drugs are generally safe, well tolerated, and effective. Recently, there has been a substantial growth in understanding of the mechanism of action of these drugs, which act at different sites on GABA$_A$ receptors. A variety of GABA$_A$ receptor subtypes with distinct functional roles have been characterized and an evolving awareness of GABA$_A$ receptor modulation holds promise for the future development of new, more sophisticated drug interventions that can elicit more selective effects by targeting specific subtypes of GABA$_A$ receptors. Advances in genetic engineering have led to the development of transgenic mouse models that have further refined our understanding of the pharmacology and physiology for various GABA$_A$ receptor subunits.

Gamma-aminobutyric acid (GABA) is the most widely distributed inhibitory neurotransmitter in the central nervous system (CNS).[1] As such, GABA limits the excitability of neuronal activity in all areas of the brain.[2] Excessive GABAergic signaling results in sedation, amnesia, and ataxia, whereas the mildest attenuation of GABAergic signaling results in arousal, anxiety, restlessness, insomnia, and exaggerated reactivity.

GABA is synthesized in presynaptic neurons and stored in synaptic vesicles; the rate-limiting step in the process is modulated by the activity of L-glutamic acid decarboxylase, an enzyme that promotes the synthesis of GABA.[3] Upon neuronal activation, GABA is released from vesicles into the synapse, where it can act on postsynaptic receptors, or diffuse into the extracellular space and activate extrasynaptic receptors on postsynaptic neurons. GABA is then removed from the extracellular space by GABA transporters located on presynaptic neurons and glia that take up GABA into cells away from postsynaptic GABA receptors.[4,5] Extracellular levels of GABA are regulated by the balance between GABA release from presynaptic vesicles and GABA uptake by GABA transporters.[5]

There are two main types of GABA receptors: fast-acting ionotropic GABA$_A$ and GABA$_C$ receptors, and slower-acting metabotropic GABA$_B$ receptors.[1] GABA$_A$ receptors are the predominant type of GABA receptor in the brain.[6] It has been estimated that 20% to 50% of all central synapses contain ionotropic GABA$_A$ receptors.[2]

Briefly, GABA$_B$ receptors are metabotropic G-protein-linked receptors, coupled by intracellular signal transduction cascades to calcium and potassium channels. GABA$_B$ receptors are the site of action of the muscle relaxant, baclofen, and are insensitive to drugs that modulate GABA$_A$ receptors.[1] When GABA binds to the GABA$_B$ receptor, there is an increase in potassium conductance and a decrease in voltage-dependent calcium currents, resulting in hyperpolarization of the neuron and inhibition of neurotrans-

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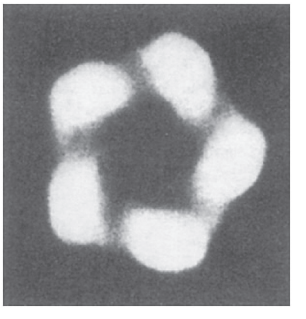

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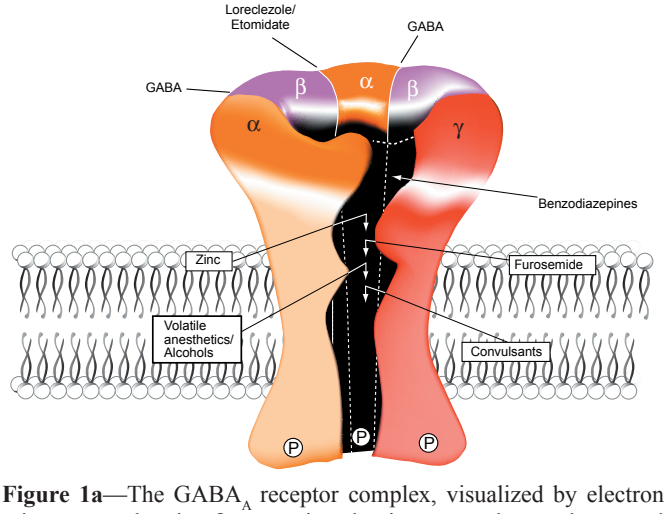
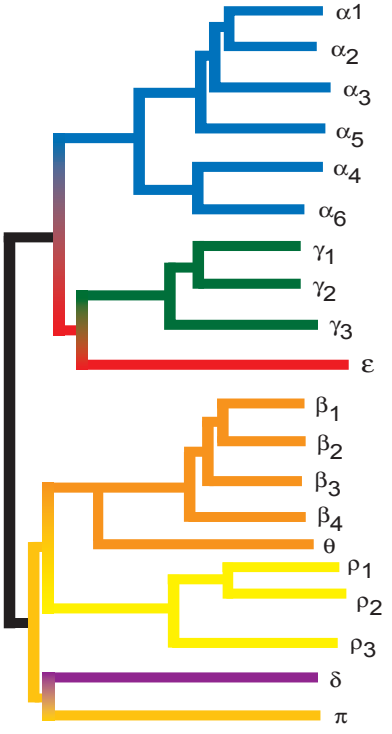


Figure 1a—The GABA$_A$ receptor complex, visualized by electron microscopy, showing five protein subunits arranged around a central pore. Reproduced with permission from Nayeem N et al, J Neurochem. 1994;62:815-8.[8]

Figure 1b—Schematic representation of agonist binding sites and extracellular modulatory domains within the GABA$_A$ receptor. Reproduced with permission from Whiting PJ et al. Ann NY Acad Sci.1999;868:655-53.[9]

2a



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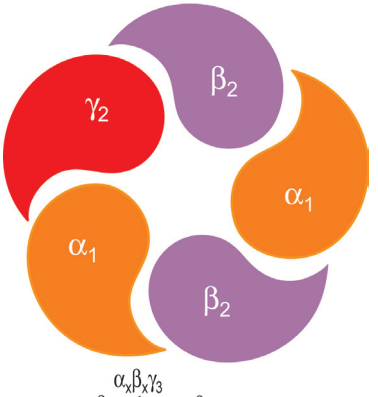

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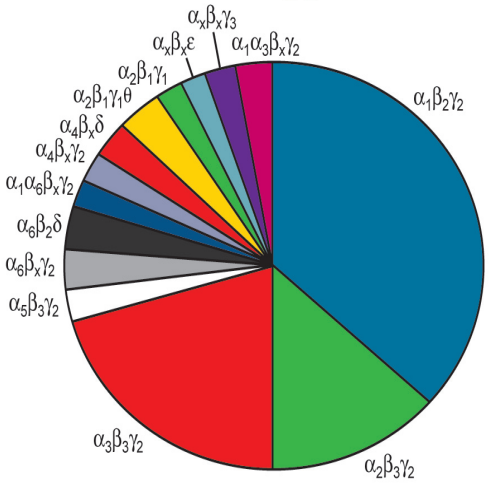

Figure 2a—Dendrogram depicting the known $GABA_A$ receptor subunits and their sequence homologies grouped in clusters.
Figure 2b—The most prevalent $GABA_A$ receptor in the central nervous system is the $\alpha_1\beta_2\gamma_2$ receptor, depicted here with the appropriate stoichiometry of 2:2:1.
Figure 2c—A pie chart representing the approximate abundance of $GABA_A$ receptor subtypes in the rat brain. Subscript x indicates the type of α, β or γ subunit is not known. This is a broad representation, and other receptor subunit combinations probably exist. Reproduced with permission: 2a[4]; 2b[2]; 2c[11].

mission.[7]

$GABA_A$ receptors consist of five protein subunits arranged in a ring around a central pore; upon activation, the receptor allows chloride ions to flow into the cell, (Figure 1a)[2,8] resulting in neuronal hyperpolarization.[2]

Benzodiazepines enhance the effects of GABA by lowering the concentration of GABA required to open the $GABA_A$ channel.[2] Benzodiazepines bind to a modulatory site on the $GABA_A$ receptor that is distinct from the GABA binding site (Figure 1b)[9] and allosterically change the receptor complex to increase the affinity of the receptor to GABA, producing a larger post-synaptic current, prolonging inhibition.[10] Although benzodiazepines do not act directly to open the chloride channel, they modulate the ability of GABA to do so, thus augmenting its inhibitory effects.

In addition to GABA and benzodiazepines, additional psychoactive compounds, such as barbiturates, loreclezole, picrotoxin, and neurosteroids can also bind to the $GABA_A$ receptor and directly open the chloride channel (Figure 1b).[9] Drugs such as barbiturates, chloral hydrate, clomethiazole, and ethanol enhance GABAergic transmission but at high concentrations can directly open the chloride channel. Because of this direct action on the chloride channel, these drugs have a propensity to be fatal in overdose.[2]

Heterogeneity of $GABA_A$ Receptor Subtypes

There is a high level of heterogeneity of functional $GABA_A$ receptors. $GABA_A$ receptors are formed from co-assembly of at least 19 different subunits encoded by different genes (Figure 2a).[4,11] These subunits are grouped into α, β, γ, δ, ε, and σ subunits, according to sequence homology; δ, ε, and σ subunits are less common and their functions have not yet been fully determined. $GABA_A$ receptor subunits assemble into a limited number of pentameric receptors with the general stoichiometry of 2 α, 2 β and 1 γ subunits; δ and ε subunits may substitute for the γ subunit, and the σ subunit may substitute for the β subunit (Figure 2b).[2] The majority of $GABA_A$ receptors expressed in the CNS are $\alpha_1\beta_2\gamma_2$, with $\alpha_3\beta_3\gamma_2$ and $\alpha_2\beta_3\gamma_2$ receptors also highly prevalent (Figure 2c).[11] GABA binds at the junction between subunits α and β, whereas benzodiazepines bind at the interface between subunits α and γ (Figure 1b).[9]

Immunocytochemistry data suggest that there is high expression of $GABA_A$ receptor subunits α_1, β_1, β_2, β_3, and γ_2 throughout the brain, though there are differences in their distribution.[12] The most widely expressed subunits are the α_1 and γ_2 subunits and these subunits are therefore likely constituents of a high proportion of $GABA_A$ receptors. The α_2, α_3, α_4, α_5, α_6 subunits have more confined distributions, which do not often overlap. For example, α_5 subunits are highly localized in the olfactory bulb, hypothalamus, and the hippocampus.[12] The α_4 subunits are concentrated in the thalamus, hippocampus, olfactory tubercle, and basal ganglia. The distribution of the δ subunit parallels that of the α_4 subunits, in the thalamus, striatum, outer layers of the cortex, and the hippocampus.[12] Similar findings in subunit distribution have been demonstrated using in situ hybridization to measure expression levels of mRNA encoding the different $GABA_A$ receptor subunits.[13]

Further specificity of $GABA_A$ receptor expression exists among different neuronal cell types. For example, a neuron-specific pattern of subunit distribution is apparent when the α-subunits are co-visualized in double immunofluorescence staining with mark-

ers for GABAergic, catecholaminergic, or serotoninergic neurons. Neurons within the pallidum express only α_1 subunits, whereas the brainstem reticular formation expresses both α_1 and α_3 subunits. An additional population of α_3-containing, but not α_1-containing, neurons is seen in monoaminergic neurons.[14] Furthermore, most serotonergic neurons in the raphe nuclei express high levels of only the α_3 subunit, but not α_1 subunits; in contrast, GABAergic neurons express both α_1 and α_3 subunits.[15] Thus, great heterogeneity of both subunit type and expression patterns of $GABA_A$ receptors occurs throughout the CNS.

$GABA_A$ receptor subunits are also differentially expressed within specific subcellular regions within individual neurons, and such selective trafficking and localization of $GABA_A$ receptor subunits contributes to the functional properties of $GABA_A$ inhibition.[16,17] For example, within the granule cells of the cerebellum, α_1, α_6, $\beta_{2/3}$, and γ_2 subunits are localized in high concentrations at Golgi cell synapses and in lower concentrations within the extrasynaptic membrane. In contrast, δ subunits are absent from synaptic junctions but are abundant in the extrasynaptic dendritic and somatic membranes. In addition, α_6, γ_2, and $\beta_{2/3}$ subunits, but not the δ subunits, are also concentrated in some glutamatergic mossy fiber synapses.[18] This pattern of subcellular localization has important implications regarding receptor function. The δ-subunit-containing receptors are expressed extrasynaptically, and are thought to play a role in the GABA-mediated overall excitability of postsynaptic neurons through tonic inhibition.[11] Such GABA-mediated tonic inhibition has been observed in granule cells of the cerebellum, dentate gyrus, and in hippocampal interneurons and is thought to occur as a result of extrasynaptic $GABA_A$ receptor activation by spillover of GABA from the synapse.[19,20]

Diverse Functions of $GABA_A$ Receptor Subunits

Although $GABA_A$ receptor subtypes have distinct anatomical and subcellular localizations, it is now known that only a subset of $GABA_A$ receptors mediate the effects of benzodiazepines: $\alpha_1\beta\gamma_2$-, $\alpha_2\beta\gamma_2$-, $\alpha_3\beta\gamma_2$-, and $\alpha_5\beta\gamma_2$-containing receptors bind benzodiazepines with high affinity, but $\alpha_4\beta\gamma_2$-and $\alpha_6\beta\gamma_2$-containing receptors have a lower affinity for benzodiazepines.[11]

The function of specific $GABA_A$ receptor subunits has been unraveled further by pharmacological and behavioral studies of transgenic mice in which different $GABA_A$ receptor subunits are either deleted due to gene ablation (knockout [KO] mice) or mutated in a manner that creates a nonfunctional receptor site (knock-in mice) (Table 1). Several studies have examined the contribution of different $GABA_A$ receptor subunits to the effects of benzodiazepines. Transgenic mouse lines with mutations postulated to alter individual amino acid residues in the benzodiazepine binding site have revealed that a single amino acid is responsible for high-affinity benzodiazepine binding. This is the histidine residue at position 101 of the primary amino acid sequence of the α_1 subunit and at equivalent positions of the sequences of α_2, α_3, and α_5. Low affinity binding is conferred by an arginine in the equivalent position in the protein structure of the α_4 and α_6 subunits. Knock-in mice, containing a mutation to this requisite residue, are insensitive to benzodiazepines but remain responsive to GABA.[21]

Studies of knock-in mice that express a benzodiazepine-insensitive α_1 subunit reveal an important role of α_1 subunits in benzodiazepine-induced sedation. These knock-in mice fail to show the sedative, amnesic effects of diazepam, and the anticonvulsant

Table 1—The Roles of Select $GABA_A$ Receptor Subunits[21]

	α_1	α_2	α_3	α_5	γ_2	β_2	β_3	δ
Effects of benzodiazepines:								
Sedation	+	-	-	-		+		
Anxiolysis	-	+	-/+	-				
Amnesia	+			+				
Myorelaxation	-		+					
Motor impairment	-	-	-					
Anticonvulsant	+	-	-	-				
Ethanol reinforcement	-			+				
Effects of anesthetics	+					+	+	+
Anxiety					+			
Learning/memory				+				+

Adapted from Rudolph U, 1999.[21]

effects of diazepam are partly reduced. These mice do retain other effects of diazepam, including the anxiolytic-like, myorelaxant, motor-impairing, and ethanol-potentiating actions.[21] These results suggest that sedative, amnesic, and anticonvulsant effects of diazepam are mediated in part by wild-type $GABA_A$ receptor subunits, namely the α_2, α_3, and α_5 subunits.[21] The results of this study are supported by other studies that demonstrate that mice with this specific mutation in the α_1 subunit fail to exhibit the sedative effect of benzodiazepines, but exhibit a normal anxiolytic response, equivalent to that of wild-type mice.[22] An earlier study had created mice lacking the α_1 subunit, and these KO mice showed a marked decrease in sleep induced by nonselective benzodiazepine, flurazepam, and the α_1-selective hypnotic drug zolpidem.[23] $GABA_A$ receptor β_2 subunits may also play a role in sleep induced by benzodiazepines as the same paper demonstrates that β_2-subunit KO mice show a marked decrease in sleep induced by the nonselective benzodiazepine, flurazepam, and the α_1-selective drug zolpidem.[23] Together, these results suggest that a drug that acts as an agonist at α_2, α_3, or α_5 subunit-containing $GABA_A$ receptors may provide anxiolysis without inducing sedation.

The anxiolytic effect of benzodiazepines appears to be attributable to the α_2 and/or the α_3 subunit of the $GABA_A$ receptor. Transgenic mice that express a mutated form of the α_2 subunit, in which the histidine at residue 101 is replaced by arginine, fail to exhibit an anxiolytic response to treatment with diazepam.[24] Diazepam has an anxiolytic effect in wild-type and α_3-subunit KO mice, but not in α_2-subunit KO mice, whereas the sedative, motor-impairing, and anticonvulsant actions of diazepam are not impaired in the α_2-or α_3-subunit KO mice.[24]

There is more evidence to support the role for α_2 and α_3 subunits, but not α_1 subunits, in anxiolysis. A novel compound, L838,417, is an antagonist at α_1-containing $GABA_A$ receptors, but has agonist activity at α_2-, α_3-, and α_5-containing receptors, and is a nonsedating anxiolytic. Whether administered to either wild-type mice or α_1-subunit KO mice, L838,417 has an equivalent anxiolytic effect.[22]

Another $GABA_A$ receptor subunit that may play a role in anxiolytic pharmacology is the γ_2 subunit. Transgenic mice that express lower levels of the γ_2 subunit through KO of one of the two alleles display enhanced anxiety-like behavior on the elevated plus maze and forced novel exploratory tests. These mice have unaltered hypnotic response to benzodiazepines.[25]

Other studies in transgenic mouse lines have also elucidated the roles of different $GABA_A$ receptor subunits in anesthesia.

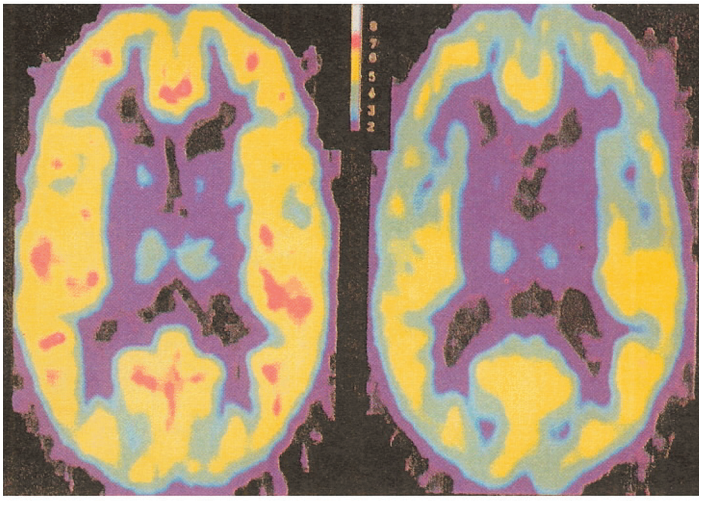

Figure 3—Pseudocolor PET image represents a global decrease in benzodiazepine binding sites in patients with panic disorder (right) versus healthy control patients (left). Reproduced with permission from Tiihonen J.[37]

Male, but not female, α_1-and β_2-subunit KO mice exhibit reduced ethanol-induced sleep, whereas β_2-(but not α_1 -) KO mice of both sexes show diminished sleep in response to the β-selective anesthetic etomidate. These mice showed normal responses to pentobarbital, suggesting that pentobarbital's effects at other ion channels may be crucial to its remaining effects on the CNS.[23]

Another study found that α_1-subunit KO mice exhibit normal ethanol-induced anxiolysis, ataxia, anticonvulsant, and hypnotic effects. The anticonvulsant effects of neurosteroids were also unaltered in these mice. However the α_1-subunit KO mice did exhibit reduced hypnotic response with pentobarbital, etomidate, and midazolam as well as showing an enhanced responses to ketamine.[26] In another study, a mouse line with a mutation of a single residue of the protein sequence of the β_3 subunit of the $GABA_A$ receptor failed to exhibit anesthetic response to treatment with etomidate and propofol, and exhibited slightly decreased responses to the volatile anesthetics enflurane and halothane.[27] In addition, the same strain of mice require higher isoflurane levels for anesthesia.[28] Mutant mice, which do not express α_6 subunits, show normal response to various general anesthetics.[29] However, mice lacking the δ subunit show attenuated sensitivity to this action of neurosteroids, but normal response to etomidate, propofol, and halothane.[30] Thus, whereas anesthetics in general appear to be active at the β_3 subunit, volatile anesthetics may have additional sites of action that have yet to be clearly characterized.

Other interesting findings have been derived from studies of $GABA_A$ receptor subunit KO mouse lines. Mice devoid of the $GABA_A$ receptor β_3 subunit exhibit spontaneous epilepsy and hyperactivity, supporting a link between GABA neurotransmission and epilepsy.[31] Studies of two transgenic mouse lines reveal an important role of α_5 subunits in learning and memory. These include a KO mouse line, which does not express the α_5 subunit,[32] and a mouse line in which the histidine-arginine mutation has been introduced.[33] This point mutation leads to a significant decrease in the expression of the α_5 subunit in the hippocampus, a region of the brain that is known to have an important role in learning and memory.[34] Both lines of these transgenic mice show improved performance in animal models of learning and memory.[32,33] These results suggest that a selective inhibitor of α_5-containing $GABA_A$ receptors could have use as a cognitive enhancer to treat mild cognitive impairment in the elderly or in patients with Alzheimer's disease. Another KO mouse line, devoid of δ subunits of the $GABA_A$ receptor, also demonstrates enhanced performance in a model of learning and memory; compared with controls, female δ-subunit KO mice exhibited enhanced conditional acquisition of tone and context fear.[35]

In Vivo Imaging of Human $GABA_A$ Receptors

A novel technique that offers a promising method for characterizing the roles of $GABA_A$ receptor subtypes in normal physiology and in pathologic disease is the in vivo imaging of $GABA_A$ receptor subunits in the human brain with PET (positron emission tomography) or SPECT (single photon emission computed tomography). PET imaging has been used to measure $GABA_A$ receptor quantity and localization within human subjects using a radiolabeled benzodiazepine-site antagonist, flumazenil. A PET study conducted in patients with panic disorder found a global reduction in $GABA_A$ receptor density throughout the brain when compared with control subjects (Figure 3). The loci with the largest regional decrease in binding, the right orbitofrontal cortex and right insula, are areas thought to be essential in the central mediation of anxiety.[36] Other studies have shown more circumscribed reductions in $GABA_A$ receptor binding in two other anxiety disorders—generalized anxiety disorder (GAD)[37]and post-traumatic stress disorder (PTSD)[38]—suggesting reduced central inhibition may be a common feature of anxiety disorders.

With the development of $GABA_A$ receptor subunit-selective tracers, the roles of the subunits may be examined in vivo in healthy humans and in patients with a variety of disorders. The α_5 subunit-selective agent Ro15-4513 can be used to selectively visualize α_5 subunits in humans by PET, and can lead to further exploration of the functional role of this $GABA_A$ receptor subtype in humans.[39]

CONCLUSIONS

How to Exploit the Heterogeneity of $GABA_A$ Receptors for Drug Development

The emerging understanding of the roles of $GABA_A$ receptors can be utilized in various ways for drug development. Selective drugs can be developed to target specific $GABA_A$ receptor subunits implicated in specific functions. For example, zolpidem is a $GABA_A$ receptor α_1 subunit-selective compound, indicated for the short-term treatment of insomnia. Furthermore, gaboxadol (THIP, 4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol) is an extrasynaptic $GABA_A$-selective agonist that primarily targets benzodiazepine-insensitive $\alpha_4\beta_3\delta$ receptors and is in the late stages of clinical development for the treatment of insomnia.[40] Other potentially useful drugs may be α_2 subunit- or α_3 subunit-selective agonists as nonsedating anxiolytics, and α_5 subunit inverse agonists as memory enhancers.[41,42] Future research will further elucidate the roles of $GABA_A$ receptor subunits and provide applications for this newfound knowledge.

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