

GABAA-ρ Receptors in the Central Nervous System

Subjects: [Neurosciences](#)

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Gamma-aminobutyric acid (GABA) is known as the main inhibitory transmitter in the central nervous system (CNS), where it hyperpolarizes mature neurons through activation of GABA_A receptors, pentameric complexes assembled by combination of subunits (α1–6, β1–3, γ1–3, δ, ε, θ, π and ρ1–3). GABA_A-ρ subunits were originally described in the retina where they generate non-desensitizing Cl⁻ currents that are insensitive to bicuculline and baclofen. The GABA_A-ρ receptors are proposed to be involved in extrasynaptic communication and dysfunction involves reduced expression in Huntington's disease (HD) and autism spectrum disorders (ASD).

astroglia

gamma-aminobutyric acid

GABAAρ receptors

1. Introduction

Gamma-aminobutyric acid (GABA) is a non-protein amino acid present in invertebrates and vertebrates, where is considered the main neural transmitter exerting inhibitory activity on neurons and their intricate networks [\[1\]\[2\]](#). However, this neurotransmitter depolarizes astrocytes and neural precursors through the activation of ionotropic GABA_A receptors, pentameric proteins that are modulated by barbiturates and benzodiazepines [\[3\]\[4\]](#). Interneuron–astrocyte communication regulates excitatory/inhibitory (E/I) balance and gliotransmission is accepted to play an important role. Astroglia setting includes the expression of GABA_A receptors to detect interneuron signaling and calcium transients derived from this communication promote the release of gliotransmitters like GABA, known as an important extrasynaptic source for tonic inhibition. In this scenario, the expression of GABA_A-ρ subunits becomes relevant under physiological and pathological conditions. For example, during earlier postnatal neurodevelopment [\[5\]\[6\]\[7\]\[8\]\[9\]\[10\]](#) and as a potential therapeutic target for post-stroke motor recovery [\[11\]](#).

2. Structural Properties, Characterization, and Functions of GABA_A-ρ Receptors

The GABA_A receptor is an ion channel member of the ligand-gated ion channel (ρLGIC) superfamily that opens transiently, inducing the inhibition of action potentials through an inward membrane chloride conductance [\[4\]\[12\]](#). It was identified through bicuculline sensitivity in autonomic brain terminals and in mammalian brain slices [\[13\]](#). This receptor is widely distributed in the central nervous system (CNS) and combinations of nineteen subunits (α1–6, β1–3, γ1–3, δ, ε, θ, π and ρ1–3) occur to coordinate differential neural inhibitions, such as phasic or tonic receptors, depending on the stoichiometry of each channel [\[8\]\[9\]\[10\]](#). In the adult brain, the most common

arrangement is: $\alpha 1$ (2), $\beta 2/3$ (1), and $\gamma 2$ (2) [14][15][16]. Topologically, each subunit contains an amino-terminal domain, where the neurotransmitter recognition site is located, a short extracellular carboxy-terminal domain, two cytoplasmic loops, and four transmembrane regions (Figure 1).

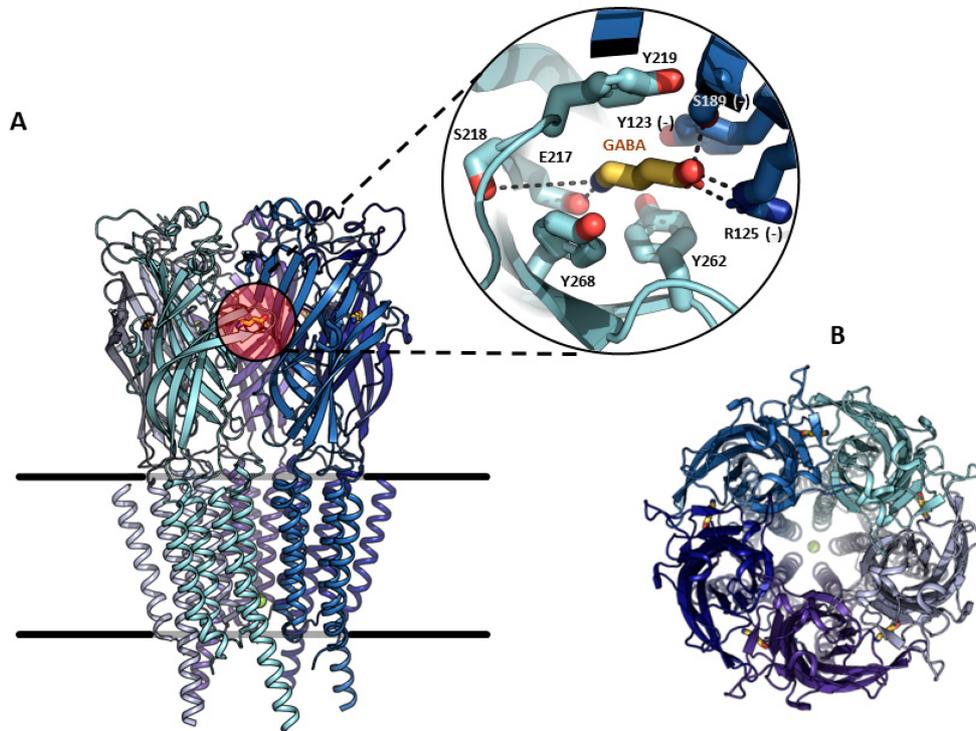


Figure 1. Molecular structure and binding-site of the human GABA_A-p1 receptor. **(A).** View of the pentameric receptor embedded in the plasma membrane, expanding in detail the orthosteric GABA binding site formed by the interface of two subunits in the amino-terminal extracellular domain. Residues interacting with GABA (yellow) from the main subunit (cyan), or complementary (-) subunit (deep blue), are indicated. **(B).** View of the pentamer from the outside of the membrane, showing the central ion-conducting pore. Structure representation was prepared using PyMOL v 2.5.2.

Each subunit is predicted to have a molecular weight between 48 and 64 kDa, based on the amino acid sequence, and form a central pore or ion channel. Pentameric complexes weigh approximately 275 kDa [4]. Classical GABA_A receptors are known to desensitize upon continuous exposure to the ligand; however, GABA_A-p subunits form functional homomeric receptors that do not desensitize [17]. GABA_A-mediated signaling is a key element for the E/I balance of the brain and its dysfunction is linked to motor, cognitive, and psychiatric disorders [16]. GABA_A-p was originally described as a retinal component. There are three genes of GABA_A-p1-3 subunits; the first two were originally cloned from human retinal cDNA libraries [17][18], and the third from a rat retinal cDNA library [19]. The human GABA_A-p1 subunit shows alternative spliced variants and two deletions of 51 and 450 nucleotides, respectively (GABA_A-p1-51 and GABA_A-p1-450), which brought speculations as to the regulation of the expression of full-length GABA_A-p1 subunits, possibly co-assembling with some of the alternative spliced subunits and leading to variants with tissue-specific properties [20]. The first electrophysiological characterization was performed with the archetypical heterologous expression system for the study of ion channels, developed by Ricardo Miledi and

collaborators, by injecting exogenous mRNA in *Xenopus* oocytes and using a two-electrode voltage clamp (TEVC) [21]. This pioneer group injected mRNA preparations from either the brain or retina in *Xenopus* oocytes and found different GABA responses, which were kinetically and pharmacologically different [4]. For example, a slight decay and the magnitude of the current remained almost at maximum as long as the agonist was present in the perfusion bath. On the other hand, GABA responses decayed quickly near the basal level [4]. The sensitivity to the agonist was also very different, as the retinal GABA_A receptor presented an EC₅₀ of 1.48 μM, in contrast to the brain cortex, (EC₅₀ = 84.6 μM). The cloned cDNA coding for the GABA_A-ρ1 subunit expressed in *Xenopus* oocytes displayed a GABA EC₅₀ of 2 μM and was insensitive to bicuculline [4][17]; these results were like those obtained from oocytes injected with retinal mRNA. Several reports have shown heteromerization in different GABA_A-ρ subunits [22][23], as well as in other GABA_A subunits [8][24][25][26], or even in subunits belonging to different members of the pLGIC superfamily [27]. The homomeric GABA_A-ρ1 subunit is insensitive to bicuculline and baclofen, commonly used to discriminate between heteromeric GABA_A channels and metabotropic GABA_B receptors, respectively [28][29][30]. The pharmacological distinctiveness that allowed the discriminating of GABA_A-ρ subunits from different subunits of heteromeric GABA_A receptors was the synthesis of conformationally restricted GABA analogues [31]. The *cis*-isomer, *cis*-4-amino-crotonic acid (CACA) and *trans*-4-amino-crotonic acid (TACA) are GABA_A-ρ1 partial and potent agonists, respectively. Nonetheless, TACA is not selective and is also able to activate typical heteromeric GABA_A receptors; this gives an advantage to using CACA to clearly identify GABA_A-ρ subunits [32][33]. Homomeric GABA_A-ρ1 receptors are insensitive to many of the heteromeric GABA_A allosteric modulators, such as benzodiazepines and barbiturates. However, some drugs have powerful allosteric properties, like the anticonvulsant loreclezole [34] or drugs designed for specific purposes, such as (1,2,5,6-tetrahydropyridine-4-yl) methylphosphinic acid (TPMPA), -*cis*/*trans*-3-aminocyclopentane) butylphosphinic acid ([±]-*cis* and [±]-*trans*-3-ACPBuPA, Piperidin-4-yl) methylphosphinic acid (P4MPA), Piperidin-4-yl seleninic acid (SEPI), and 3-(guanido)-1-oxo-1-hydroxy-phospholane (3-GOHP) [35]; all of them have been used as a source to investigate the involvement of GABA_A-ρ receptors in sleep–waking behavior and antinociception in the peripheral nervous system or in learning, and also to investigate memory enhancers and other cognitive activities [35][36]. The importance of the GABA_A-ρ receptor becomes increasingly clear through its wide expression in the CNS. Additionally, it is highly related to ammonia-induced apoptosis, retinitis pigmentosa, myopia, and may be important for some specific *in vivo* effects of ethanol and Huntington's disease (HD) [16][37]. At the last stage of the preparation of this research the cryogenic electron microscopy structures of GABA_A-ρ1 subunits was reported, in apo state as well as in the presence of TPMPA, picrotoxin (PTX), and GABA, generating different conformations [38]. This milestone is an exciting point in the state-of-the-art of the current research that will help researchers to understand the intricated mechanisms that pharmacologically and functionally define this family of proteins, as a natural step following the pioneering experimental achievements described here.

3. GABA_A-ρ Receptors in Astroglia

Neurons are considered the basic unit for information processing associated with perception and cognition. However, this neurocentric definition has been challenged because they only represent a fraction of the brain cells. Glial cells, on the other hand, are the dominant population and respond to neuronal activity through

neurotransmitter receptor activation [39]. Although the precise decoding of neuron–glia communication in brain function is unknown, glial cells contribute to synapse formation, cell development, myelination, brain microcirculation, neuroprotection, and the modulation of neural activity [40][41]. In this context, the GABA_A receptors mediating synaptic (phasic) or extrasynaptic (tonic) transmission are molecularly and functionally distinct for both neurons and glial cells [42]. Astroglial cells include astrocytes, ependymal cells, radial glia including Bergmann and Müller glia; all of them are identified by the expression of the cytoskeletal glial fibrillary acidic protein (GFAP). Astroglia express functional GABA_A receptors, but their role in the CNS physiology is intriguing, since glial cells do not produce action potentials. Nevertheless, GABA depolarizes astrocytes through GABA_A receptors but has unitary conductances and gating properties similar to those recorded in neurons [43]. Furthermore, specific differences in GABA_A subunit expression were observed between primary cultures of rat cerebellar astrocytes and granular neurons [44]. Initial studies with RT-PCR reported that the total amount of GABA_A receptor subunit mRNA in astrocytes was two orders of magnitude lower than in neuronal cells. Moreover, of all the GABA_A subunits expressed by granular neurons, only $\alpha 6$ and $\gamma 2$ subunits were not expressed by astrocytes. Another difference was that GABA_A- $\alpha 1$, $\alpha 3$, and $\alpha 5$ subunits were abundantly expressed in granular neurons, while GABA_A- $\alpha 1$ and $\alpha 2$ were predominant in cerebellar astrocytes. Likewise, GABA_A- $\beta 1$ and $\beta 3$ were abundantly expressed in both cell types. Finally, GABA_A- $\gamma 2$ and GABA_A- $\gamma 1$ were prevalent in cerebellar granular neurons and astrocytes, respectively [44]. Studies in astrocytes isolated from the thalamus showed that all of them express functional GABA_A receptors that responded to the selective agonist muscimol [45]. The same study showed a GABA_A subunit expression profile through single cell RT-PCR studies. The prevalent subunits were GABA_A- $\alpha 2$, GABA_A- $\alpha 5$, GABA_A- $\beta 1$, and GABA_A- $\gamma 1$ [45]. Overall, these studies reported the heterogeneous expression of GABA_A subunits associated with a brain region. Accordingly, astroglia showed differences in their responses to pharmacological modulators of GABA_A receptors such as benzodiazepines and barbiturates [9][42][46]. For example, DMCM, an inverse benzodiazepine agonist that enhanced GABA_A-mediated currents in astrocytes and inhibited them in neurons, suggests a different subunit composition [42]. Electrophysiological recordings on cerebellar astrocytes in situ showed a heterogeneous array of GABA_A subunits because modulation by benzodiazepines was absent in Bergmann glia [46]. Moreover, modulation by barbiturates, such as pentobarbital, was present in Bergmann glia but absent in ependymal glial cells of the cerebellum [6][46]. These differences are related to a specific GABA_A subunit array that includes GABA_A- Δ or GABA_A- ρ subunits in Bergmann glia and ependymal cells, respectively [6][46]. Additionally, the functional expression of GABA_A receptors was reported in situ via in striatal astrocytes; pentobarbital modulation was absent and GABA_A- ρ subunits were found in more than half of them [9] (**Figure 2**).

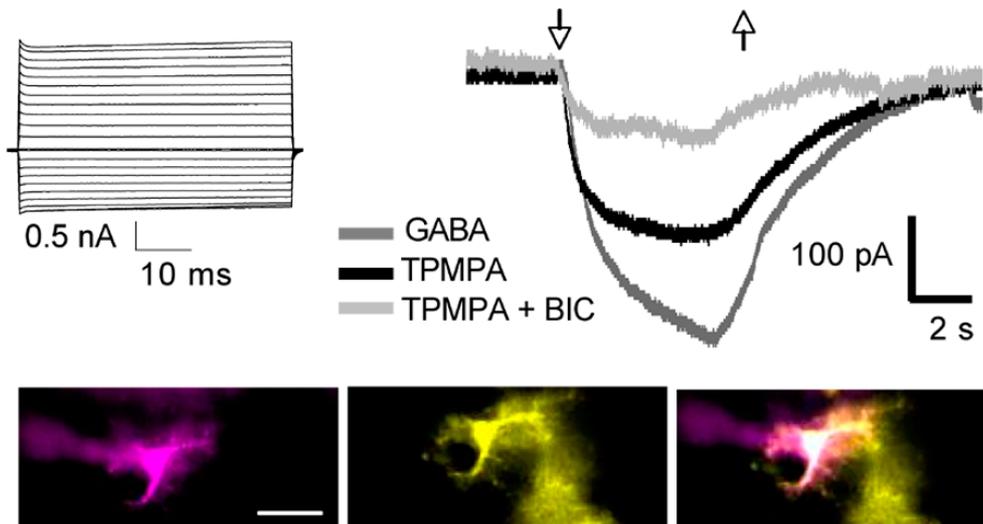


Figure 2. Functional expression of the GABA_A- ρ subunit in astrocytes. Whole-cell patch-clamp recording of an astrocyte in a coronal slice of the dorsal striatum of a GFAP-EGFP mouse. A classic passive current profile obtained from a sulforhodamine B (magenta)-injected cell that was also GFAP-EGFP+ (yellow). The overlay of both signals confirms cell identity. Scale bar represents 20 μ m. Membrane currents were evoked in 50 ms voltage steps ranging from -160 to $+40$ mV, from a holding potential of -70 mV. Astrocytes responded to GABA (10 μ M) and the current was partially reduced by the selective GABA_A- ρ antagonist TPMPA (100 μ M); a further inhibition was observed when the selective GABA-A antagonist bicuculline (BIC, 100 μ M) was added. The arrows indicate the start (up) and end (down) of the agonist/antagonist application.

Although a role for the GABA_A- ρ subunit expressed in glial cells is not yet evident, the three genes have been localized by means of immunogold electron microscopy in astrocytes from the neostriatum and cerebellum [\[51\]](#) (**Figure 3**).

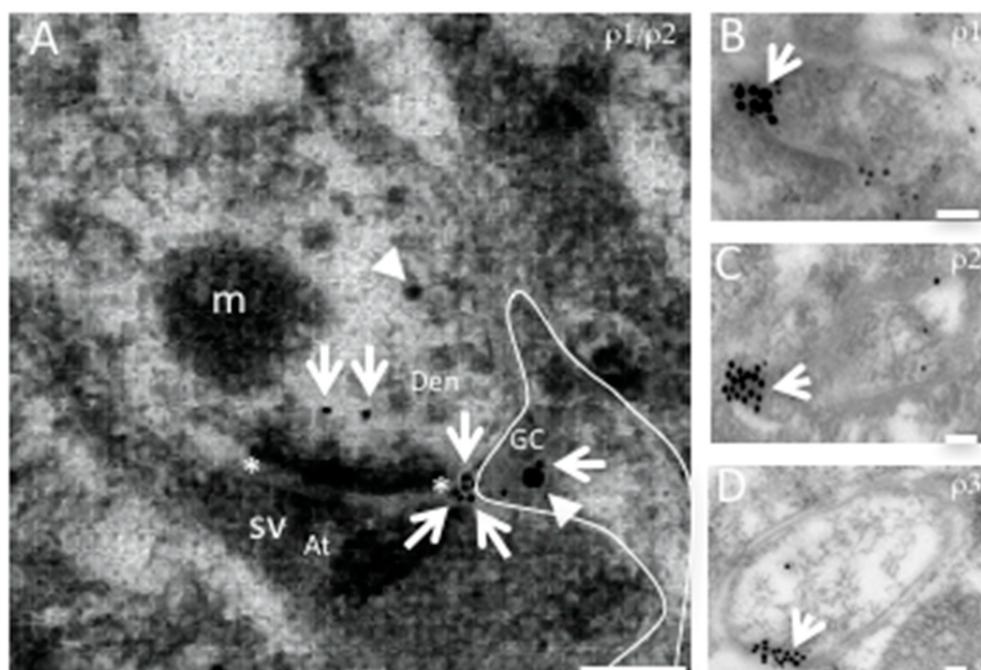


Figure 3. Representative electron micrographs of GABA_A- ρ 1-3 immunogold localization in mouse neostriatum. **(A)**. Axon–dendrite synaptic connection co-expressing GABA_A- ρ 1 (arrow) and - ρ 2, (arrowhead) and a positive glial cell process (GC) for both subunits (outlined). GABA_A- ρ 1 is located at peri- and extrasynaptic spaces. The synaptic active zone is marked with asterisks; presynaptic region is marked with (At: axon terminal), and postsynaptic with (Den: dendrite). GCs with perisynaptic processes showing GABA_A- ρ 1 **(B)**, GABA_A- ρ 2 **(C)** and GABA_A- ρ 3 **(D)** immunogold localization. Scale bar 100 nm. **(B–D)**. Expression of GABA_A- ρ subunits in glial processes. Abbreviations: m: mitochondria, sv: synaptic vesicles. Scale bar 200 nm.

The role of the GABA_A- ρ subunit in cerebellar or neostriatal astroglia during early postnatal development or in the control of precise movements in adults remains unexplored.

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