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Interneuronal GABA_A receptors inside and outside of synapses

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Abstract

About 20% of the total number of neurons in the brain are interneurons (INs) that utilize GABA as their neurotransmitter. The receptors for GABA have been well studied in principal cells, but INs also express GABA receptors, in particular the GABA_A type (GABA_ARs), which may also be activated in an autocrine manner by the transmitter released by the INs themselves. As more and more neurological and psychiatric disorders are being discovered to be linked to malfunction or deficits of INs, this review will cover how interneurons communicate with each other through the activation of synaptic and extrasynaptic GABA_ARs. The properties of GABA_ARs specific to INs may differ significantly from those found on principal cells to open the prospect of developing IN-specific drugs.

Introduction

In the mammalian brain inhibition and some forms of synchrony are generated by a complex and widely diversified network of interneurons (INs) [1,2] that release their transmitter (GABA) on an equally varied set of GABA receptors. Of these, the GABA_A receptors (GABA_ARs) are a class of heteropentameric ligand-gated ion channels permeable to Cl⁻ and HCO₃⁻ generally composed of three subunits out of an array of 19 (α₁₋₆, β₁₋₃, γ₁₋₃, δ, ε, θ, π, ρ₁₋₃), with the clockwise α₁β₂α₁β₂γ₂ arrangement most commonly found in the brain [3–6]. Different subunits confer unique characteristics to the receptors including agonist affinity and efficacy, desensitization rate, and pharmacology [7,8]. Many widely used anxiolytic, hypnotic and anesthetic drugs act upon GABA_ARs with specific subunits, e.g., different α determine the sedative or anxiolytic effects of benzodiazepines [9,10]. Some receptors are naturally insensitive to benzodiazepines (α₄-, α₆-, or δ-GABA_ARs), while others confer a high degree of sensitivity to various exogenous or endogenous molecules, as is the case of ethanol and neurosteroids on δ-GABA_ARs [11,12]. Lastly, the localization of GABA_ARs (synaptic or extrasynaptic) determines whether they mediate rapid synaptic (phasic) events activated by fast (<1 ms) and large (~ 1 mM) GABA transients in the

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synaptic cleft, or a persistently activated (tonic) conductance by low levels (100–1,000 nM) of GABA present in the extracellular space. Only a few subunit combinations (δ - or $\alpha 5$ -GABA_ARs) have a high affinity for and a marginal desensitization to GABA, or can open with a sufficiently large probability in the absence of agonists to mediate a tonic conductance [12–14].

The composition and assembly of GABA_ARs on principal cells, their subcellular localization, plasticity in health and disease and specific pharmacology is well studied in over three decades of research and clinical applications [10,15]. These include stress, puberty, ovarian cycle, pregnancy, depression, the effects of ethanol, and of various anesthetics related to δ -GABA_ARs [16–21], epilepsies for both δ -GABA_ARs and $\alpha 5$ -GABA_ARs [22,23]), and memory formation and consolidation, LTP induction, anesthesia-induced memory loss, functional plasticity and recovery after stroke, and power of γ oscillations for $\alpha 5$ -GABA_ARs [24–29]. In sharp contrast, research on GABA_ARs of INs has progressed at a much slower pace. This can be ascribed to the inherent complexity of this diverse family of neurons that precludes consensus on a practical categorization of the INs themselves [30]. This review will summarize the physiology of synaptic and extrasynaptic GABA_ARs of INs, their plasticity, and the possibility of a correlation between IN development and their GABA_ARs mediating tonic conductances.

GABA_ARs and tonic/phasic conductances of INs

Compared to principal cells, INs in the forebrain seem to lack some specific GABA_AR subunits. The most striking difference is the absence of $\alpha 4$ - and $\alpha 5$ -GABA_AR, subunits that are involved in mediating tonic inhibition in glutamatergic neurons [12], but some INs in the spinal cord may constitute an exception to this rule [31]. Below, without any presumption of completeness, we will summarize known properties of synaptic and extrasynaptic GABA_ARs in a subset of INs.

Unidentified INs

Reports exist on GABAergic tonic conductances recorded in unidentified or poorly identified INs in many brain areas, particularly in the molecular layer of the dentate gyrus (DGML), virtually all strata of CA1 and CA3 and various layers the neocortex [22,27,32–36]. This conductance is largely mediated by a combination of subunits unique to INs ($\alpha 1/\delta$ -GABA_ARs) and is highly sensitive to modulation by ethanol and neurosteroids [34]. In mice lacking the δ -GABA_ARs (*Gabrd*^{−/−}), CA3 stratum pyramidale (SP)-INs show a complete loss of tonic conductances, whereas in wild type mice the same cells show a THIP-sensitive tonic current, which strongly argues for a δ -GABA_AR mediated tonic inhibition [33]. A recent study showed similar findings in DGML INs and CA1 stratum radiatum (SR) INs of a mouse with δ -GABA_ARs selectively deleted from all GABAergic INs [37]. Although the majority of tonic inhibition in INs seems to be mediated by $\alpha 1/\delta$ -GABA_ARs, other subunits may also be involved, as CA1 SR INs show picrotoxin and zolpidem-sensitive tonic currents (the latter excludes the participation of δ -GABA_ARs) [36], and DGML INs of *Gabrd*^{−/−} mice, in which deletion of δ -GABA_ARs was not restricted to INs, show a compensation in the tonic current, but receptor specificity was not determined [27]. These findings suggest

that some interneurons may entirely or partially rely on δ -GABA_ARs for generating a GABA-dependent tonic conductance.

Unequivocal anatomical and functional evidence from different sources shows heavy δ -GABA_AR presence on at least two kinds of INs of the neocortex and hippocampus [22,37–42]. These are the parvalbumin (PV) expressing INs (PV+INs) and neurogliaform cells (NGFCs).

Parvalbumin expressing INs (PV+INs)

The vast majority of PV+INs in the brain are either basket cells (BCs) or axoaxonic cells (AACs), while a small fraction belong to other IN classes. These two predominant PV+INs target the somata and the axon initial segments of the target cell respectively, and thus are in an ideal position to strongly control neuronal output [1,2,43,44]. Most PV+INs are born in the median ganglionic eminence (MGE), and migrate to populate the hippocampus and the neocortex in late embryonic stages [45–47]. In the hippocampus, they most densely populate the area around the SP, and represent almost the entire population of δ -GABA_AR+ INs in this area [40,41,48]. Deletion of this subunit and the consequent loss of tonic inhibition by these INs has major effects on the frequency of *in vitro* CA3 γ oscillations, a network behavior that is initiated and controlled by PV+BCs [33]. Moreover, selective potentiation of the δ -GABA_AR-mediated tonic conductance with neurosteroids, THIP or ethanol increases the power of γ oscillations (Ferando and Mody, unpublished). The δ -GABA_ARs on PV+INs are modulated during physiological and pathological states, such as pregnancy and epilepsy [22,40,48]. The GABAergic input onto these INs seems to be shunting in nature with kinetics that would help sustain γ oscillations [49], but after periods of intense activation, GABAergic transmission may become excitatory in an activity dependent switch [50]. Several studies have also investigated PV+BC to PV+BC synaptic connections. As expected from an IN type controlling fast network activity, PV+BCs have a high degree of reciprocal connectivity [51–53]. Their synaptic GABA_AR-mediated events have faster kinetics, larger amplitudes and higher frequencies than IPSCs elicited in principal cells or in other INs. The PV+BC IPSCs are mediated by $\alpha 1$ -GABA_ARs, subunits heavily expressed in PV+BCs of the cortex and hippocampus [54–58], as well as in PV+INs of the striatum [59]. The rapid synaptic GABA_AR signaling is responsible for the phase coupling of θ/γ oscillations, as demonstrated in mice where synaptic GABA_ARs ($\gamma 2$ -GABA_ARs) were selectively ablated from PV+INs; but the fundamental properties of γ oscillations were unaltered [60]. This is not necessarily surprising considering that of the large number of synapses (>16,000) received by PV+INs only a small fraction (6.4%) are GABAergic [61]. This may also mean that the high density of $\alpha 1$ -GABA_ARs in PV+INs is not confined to synapses, but can be found, most likely paired with δ -GABA_AR, at extrasynaptic sites.

In contrast to most PV+INs found in the cortex and hippocampus, the PV+INs of the reticular nucleus of the thalamus (nRT) express no tonic GABA_AR-mediated conductance [62] and exhibit slowly decaying predominantly $\alpha 3$ -GABA_AR-mediated synaptic events [63,64]. The PV+INs of the nRT are not generated in the MGE, but from prethalamic Olig2-lineage cells at day E 10.5 [65].

Neurogliaform cells (NGFCs) and Ivy cells (IvyCs)

NGFCs/IvyCs of the hippocampus and the cortex are the IN type probably expressing the highest levels of δ -GABA_ARs located extrasynaptically [39,42]. Ontogenetically, NGFCs/IvyCs originate from two sources: the 5HT_{3A}-R+, reelin+ NGFCs/IvyCs derive from the caudal ganglionic eminence (CGE), whereas nNOS+ NGFCs/IvyCs are born in the MGE [45,66,67]. NGFCs/IvyCs release GABA slowly and diffusely, hence have been implicated in GABAergic volume transmission [42], but may also play a role in the dynamics of the θ rhythm [68–72]. In the hippocampus they are mostly localized in the str. lacunosum moleculare (NGFCs), in the DGML and in the CA1 SR (IvyCs). In the cortex, NGFCs are present in all layers [42], with reelin+ CGE-derived NGFCs mostly inhabiting layer 1 [67]. We previously recorded the characteristics of tonic GABA_AR-mediated conductances from INs of the DGML [27,34] that, considering the abundance of NGFCs in this region [70], must have belonged to this group. It appears that these cells express the highly plastic $\alpha 1/\delta$ -GABA_ARs and a corresponding ethanol-sensitive tonic current [34], and a low frequency of spontaneous GABA_AR-mediated events; but specific pharmacological manipulations have not been done to identify the receptors involved [70]. NGFCs of the neocortex also express high levels of δ -GABA_ARs and clearly show a neurosteroid (THDOC)-sensitive tonic GABA_AR-mediated conductance [42]. Strong δ -GABA_ARs labeling is found in the CA1 SLM where NGFCs from both embryological origin are localized [3,45,66]. It remains to be determined whether NGFCs/IvyCs derived from the CGE and MGE express the same type of GABA_ARs.

Somatostatin expressing INs (SOM+INs)

One of the most typical member of the SOM+IN class is the hippocampal oriens-lacunosum moleculare (OL-M) IN, which has its soma in the str. oriens from where it targets the distal dendrites of principal cells in the LM. As most other SOM+INs, OL-M INs seemingly form a fairly homogenous population derived from the MGE [45]. Surprisingly, they have been recently reported to have dual embryonic origins and distinct roles in network oscillations: the 5HT₃-R negative OL-M INs originate from the MGE, while 5HT₃-R positive OL-M INs are derived from the CGE [73]. This bimodal ontogeny also appears to determine the mature subunit composition of AMPARs and NMDARs of INs [74]. Perhaps analogous to how excitation is shaped by development, the specificity of GABA_AR subunits may also be determined by embryonic origins. Interestingly, the presence of tonic inhibition on SOM+INs is yet to be fully investigated. Only a small fraction of dentate hilar SOM+INs express δ -GABA_ARs [41], but in the rest of the hippocampus they express $\alpha 1$ -GABA_AR, the natural δ -GABA_ARs partner in INs, in a diffuse histological distribution characteristic of extrasynaptic localization [57,58]. Moreover, hilar SOM+INs do not express the MGE-marker Nkx2.1 [75], which argues for their CGE origin. Consistent with the anatomical findings [41], hilar SOM+INs identified in SOM-Cre mice also exhibit very little GABA_AR-mediated tonic conductance [76]. No specific characteristics are known about the synaptic GABA_AR-mediated events in SOM+INs, other than that they innervate other types of INs, but they generally do not inhibit each other [53].

Cholecystokinin basket cells (CCK+BCs) and Schaffer collateral-associated INs (SCA-INs)

These two IN types represent a substantial group in the hippocampal formation with specific control of the pyramidal cells' somatic and dendritic compartments, respectively. Both derive from the CGE [45], and are localized in the hippocampal SP (CCK+BCs) and the SR (SCA-INs). The CCK+BCs complement the PV+BCs in providing perisomatic inhibition to the pyramidal cells, but they express an entirely different set of synaptic inputs, receptors, voltage-gated Ca^{2+} channels, and a myriad of other properties that distinguish these two types of soma-targeting GABAergic neuron [43]. CCK+BCs do not express $\alpha 1$ -GABA_AR [57] and as a consequence they most likely do not express δ -GABA_ARs either [40,41,48], although a complete coexpression study has yet to be performed. Compared to PV+BCs, CCK+BCs receive stronger GABAergic somatic synaptic input (83% of somatic synapses [77]). In spite of such abundant synaptic GABAergic innervation, some cortical regular spiking INs (likely CCK+BCs), lack a tonic GABA_A conductance *in vitro* [78]. The SCA-INs make contacts with the apical dendrites of principal cells, and a fraction of them also expresses calbindin [79], which rarely co-localizes with δ -GABA_ARs [41,42]. The question remains open whether INs of the SR reported to have a zolpidem-sensitive GABAergic tonic conductance [35,36], incompatible with a δ -GABA_ARs contribution, were genuine SCA-INs. The INs in the SR show faster IPSCs, have a more depolarized resting membrane potential compared to principal cells [80], with depolarizing or shunting GABAergic conductances depending on the ambient GABA concentration [35].

Conclusions and Outlook

We have presented a brief overview of the GABA_ARs and the corresponding phasic and tonic conductances present on a small sample of hippocampal and cortical INs. However blurred the picture may be, there are certain emerging trends when various properties of tonic inhibition in particular are put in the perspective of the embryonic origins of the INs. At this time, the GABAergic system of INs cannot be as clearly delineated on the basis of IN ontogeny as their glutamate receptors [74]. Nevertheless, in Fig.1 we depicted a simplified scheme for the division of hippocampal INs, based on their CGE or MGE origins, into those that may possess δ -GABA_AR-mediated tonic conductances (MGE-derived) and those that do not (CGE-derived). A thorough investigation of phasic and tonic inhibition in these various INs in the future may answer significant questions about their function under normal and pathological conditions. Knowing the exact localization of δ -GABA_ARs on different IN subtypes will offer a very powerful tool for differential potentiation or dampening of discrete networks, with interesting functional implications for generations of normal and altered brain rhythms in which INs are adamantly involved [2].

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Highlights

Many interneurons (INs) express different GABA_ARs than principal cells.

Subclasses of INs have specific GABA_ARs mediating tonic and phasic conductances.

In most INs, the tonic conductance is mediated by extrasynaptic $\alpha 1/\delta$ - GABA_ARs.

Based on their ontogeny, we propose a binary view of tonic conductances in INs.

There is hope for developing selective compounds altering GABA_ARs of INs.

Figure 1. Schematic representation of δ -GABA_AR-mediated tonic conductances in major subclasses of hippocampal CA1 INs separated by their developmental profile

Left panel: Of the INs born in the medial ganglionic eminence (MGE) some have established $\alpha 1/\delta$ -GABA_AR-mediated tonic conductances while in others the presence of such a conductance is only hypothetical (marked by “?”). *Right panel:* According to evidence to date, INs born in the caudal ganglionic eminence (CGE) do not express δ -GABA_ARs and maybe even no other GABA_AR would underlie a tonic conductance. For further explanation see text. *Abbreviations:* PyrC = pyramidal cell; OL-M = oriens-lacunosum moleculare IN; PV+AAC = parvalbumin+ axo-axonic cell; PV+BC = parvalbumin+ basket cell; NGFC = neurogliaform cell; IvyC = Ivy cell; CCK+BC = cholecystokinin+ basket cell; SCA-IN = Schaffer collateral associated IN; nNOS = neuronal nitric oxide synthase; 5HT_{3A}R = ionotropic serotonin receptor, type 3A.