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DISTINCT ROLES OF GAMMA-AMINOBUTYRIC ACID TYPE A RECEPTOR SUBTYPES: A FOCUS ON PHASIC AND TONIC INHIBITION

GAMA AMİNOBÜTİRİK ASİT TİP A RESEPTÖR ALT TİPLERİNİN FARKLILAŞMIŞ FONKSİYONLARİ: FAZİK VE TONİK INHİBASYON

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Abstract

The gamma-aminobutyric acid type A receptors ($GABA_ARs$), belonging to the superfamily of Cys-loop receptors, responsible for the inhibitory transmission in the vertebrate central nervous system. Assembled from a pool of 19 subunits, the subunit composition of heteropentameric $GABA_ARs$ impacts on receptor's function, physiology, cellular and subcellular localization in the cell membrane, i.e., synaptic or extrasynaptic. γ2 containing $GABA_ARs$ (γ2-$GABA_ARs$) are clustered in the synapses and mediate classical fast synaptic inhibition called phasic inhibition. δ subunit containing $GABA_ARs$ (δ-$GABA_ARs$) are located extrasynaptically and mediate a different form of inhibition called tonic inhibition critical for the threshold of action potential generation and neuronal excitability. Thus, distinct physiological roles of synaptic and extrasynaptic $GABA_AR$ subtypes lead to the question to ask about the possibility of subtype selective drugs. In the light of accumulating data from X-ray crystal structures of vertabrate, invertabrate and prokaryotic Cys-loop receptor family members, new opportunities arise for the development of novel drugs targeting specificaly these subtypes of $GABA_ARs$ for the treatment of various neuropathological conditions.

Keywords: GABAA Receptors, GABA, phasic inhibition, tonic inhibition, gamma2 (γ2) subunit, delta (δ) subunit, Cys-loop receptors, synaptic, extrasynaptic

Özet

Memelilerde beyinde inhibasyonun iletiminden sorumlu birincil reseptör olan gama amino butirik asit tip A reseptörleri ($GABA_ARs$), Cys-loop reseptörleri familyasina baglidir. 19 alt uniteden olusan bir havuzdan belirli kombinasyonlarla pentamer olarak organize olan bu reseptörlerin kompozisyonu, reseptörün fonksiyonu, fizyolojisi, bulundugu hücre tipi ve sinaptik ya da ekstra-sinaptik gibi hücre zarinda belirli bir lokalizasyonda bulunmasına etki eder. γ2 alt ünitesini bulunduran $GABA_AR$ alt tipi (γ2-$GABA_ARs$) sinaptik olarak lokalize olup fazik inhibasyon olarak bilinen tipik hizli inhibasyonun iletiminden sorumludurlar. δ alt ünitesini bulunduran $GABA_ARs$ (δ-$GABA_ARs$) ekstrasinaptik olarak lokalize olup fazik inhibasyondan daha farkli bir inhibasyon türü olan ve aksiyon potansiyelinin olusmasi için gereken eşik değerinde ve hücre uyarılabilirliğinde rol oynayan tonik inhibasyonun iletiminden sorumludurlar. Sinaptik ve ekstrasinaptik $GABA_AR$ tiplerine özgü bu farklılaşmış fizyolojik görevlerin gittikçe daha belirgin hale gelmesi, ilgili reseptör tiplerine yönelik özel ilaçlarin geliştirilebilmesi ile ilgili ihtimalleri de akla getirmektedir. Zira, son yıllarda omurgali, omurgasiz ve prokaryot kaynaklardan elde edilen Cys-loop reseptör ailesine ait reseptörlerin X-isini kristal yapılarina dair yeni verilerin birikmesiyle çesitli nöropatolojilere yönelik olarak sinaptik ve ekstrasinaptik $GABA_AR$ tiplerini seçici olarak hedefleyebilen yeni ilaçlarin geliştirilmesi mümkün olabilecektir.

Anahtar Kelimeler: *GABA (A) reseptörleri, GABA, fazik inhibasyon, tonik inhibition, gama2 (γ2) , delta (δ), Cys-loop reseptörleri, sinaptik, extrasynaptik*

1. Introduction

Neural circuits mediate brain information processing by the integration of excitatory and inhibitory signals generated by neurotranmitters like Glutamate and GABA respectively. The actions of GABA is mediated by different receptors, including gamma-aminobutyric acid type A receptors (GABAARs) which play a significant role by means of its spatiotemporal activity during brain information processing (Koch et al., 1983). Belonging to family of "Cys-loop receptors", GABAARs are heteropentameric chloride channels responsible for the inhibitory transmission in the vertebrate central nervous system (reviewed in Lester et al., 2004; Unwin, 2005; Sine & Engel, 2006). These GABA-gated heteropentameric channels are permeable to HCO3- and Cl- ions (reviewed by Sieghart and Sperk 2002). Depending on the intracellular Cl- concentration, GABAAR activation can lead to Cl- influx or efflux. In adult neurons, upon activation of the receptor by GABA binding, Cl- usually moves into the cell, causing a strong inhibitory hyperpolarization (Kaila et al., 1997; Rivera, et al., 2005).

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1.1. The structure of the GABAARs

Initially, the atomic structure of a GABAAR subunit complex was determined by the studies based on the snail acetylcholine receptor binding protein (AChBP) and muscle nicotinic acetylcholine receptor from the electric organ of the Torpedo ray fish (Brejc et al., 2001; Cromer et al., 2002; Ernst et al., 2003; Unwin, 2003, 2005; Sine and Engel, 2006). Recently, the crystallized structure of homeric β3 subunit containing GABAAR (GABAAR -β3cryst) at 3A° resolution has been reported (Miller and Aricescu, 2014). This study provides a direct overview for the receptor structure for the first time (Figure 1) which confirms the characteristic elements of eukaryotic Cys-loop receptors (reviewed by Lynagh and Pless, 2014). Thus GABAARs are arranged as heteropentameric structures by which five subunits co-assemble around a central pore. Each subunit has a large extra-cellular N- terminus, four transmembrane domains (TM1–TM4), and a small extracellular C-terminal. There is a large intracellular loop between the third and fourth transmembrane domains.

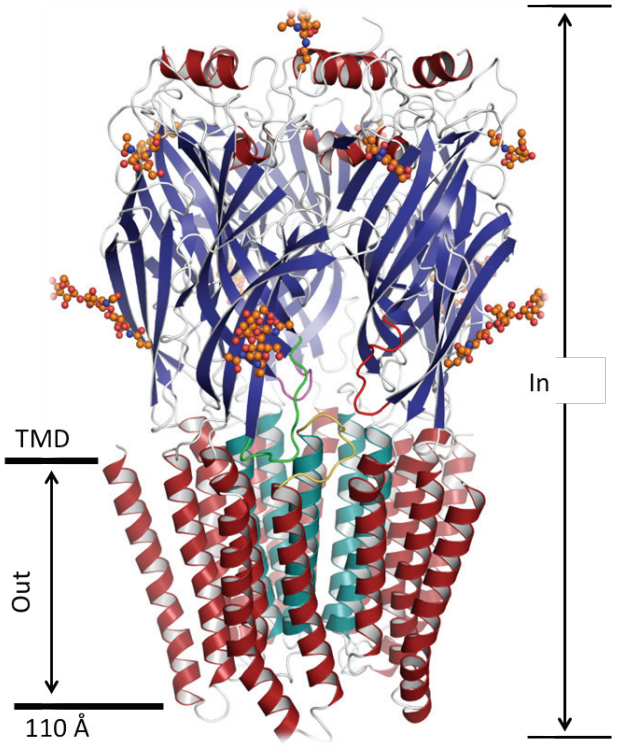

Figure 1: Crystal structure of the human GABA (A) receptor composed of β3 homopentamer (GABA(A)R-β3cryst). α-helices are shown in red, excluding the pore-lining second transmembrane domain, shown in green; β-strands are shown in blue and the loops are shown as grey. Orange ball-and-stick model illustrates the N-linked glycans. (TMD: Transmembrane domain). (Reproduced from Miller & Aricescu, 2014)

1.2. Subunit composition: Tonic and Phasic Inhibition

The GABAARs are assembled from a subunit pool of 19 subunits. These subunits are named as α1–α6, β1–β3, γ1–γ3, δ, ε, θ,π, ρ1–ρ3 (Schofield et al., Korpi et al., 2002a; Rudolph and Mohler, 2006; Whiting, 2006) and expressed in age and anatomy dependent manner (Wisden et al., 1992; Laurie et al., 1992a, b; Fritschy and Mohler, 1995; Schwarzer et al., 2001). Also cell type is a critical factor for the subunit co-assembly. It is known that the δ subunit co-assemble specifically with the α4 and α6 subunits in the forebrain (Cope et al., 2005) and cerebellum respectively (Jones et al., 1997; Peng et al., 2002). The δ represents a rare isoform of GABAAR subunits specifically located at the extrasynaptic sites (Nuser et al., 1998; Wei et al., 2003) in the dentate gyrus granule cells of hippocampus (Sun et al., 2004) and ventrobasal nucleous of the thalamus and neocortex (Chen et al., 2005; Cope et al., 2005; Glykys et al., 2007) besides to cereballar granule cells (Jones et al., 1997; Jehlinger et al., 1998). These δ containing GABAARs receptors (δ-GABAARs) have higher affinity for GABA (Fisher and Macdonald, 1997) and mediate the tonic inhibition (Petrini et al., 2004; Farrant and Nusser, 2005), which is activated by GABA diffusing out of the synaptic cleft (Hamann, et al., 2002). Tonic inhibition is critical for the synaptic integration besides to its role in setting the threshold for the action potential generation and controlling the excitatory synaptic signalling (Hausser and Clark, 1997; Hamann, et al., 2002, Semyanov et al., 2004). It is also important to mention that tonic inhibition is not only mediated by δ-GABAARs, α5 containing GABAARs also mediate the tonic inhibition (Glyks, et al., 2008) which is not the focus of this study. Another GABAARs subtype is the one, that is most abundant in brain: the γ2 containing GABAARs (γ2-GABAARs) are composed of αβγ2 subunits and mediate fast synaptic inhibition (Ernst et al., 2003). They are abundantly clustered in the postsynaptic sites besides to nonsynaptic sites (Somogyi et al., 1996; Nuser et al., 1996, 1998; Fujiyama et al., 2000, 2002, Kullman et al., 2005). Figure 2 shows the phasic and tonic inhibition mediated by synaptic and extrasynaptic GABAARs in the forebrain (Goetz et al., 2007).

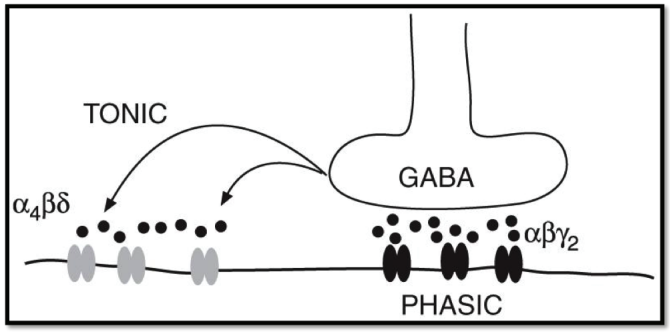

Figure 2: γ2-GABAARs are concentrated at the postsynaptic sites that contain α, β and γ2 subunits (shown as black receptors at the postsynaptic site). They mediate classical fast synaptic inhibition (phasic inhibition) in response to GABA release (black dots in the synptic cleft). δ-GABAARs contain α, β and δ subunits (shown as gray receptors at the extrasynaptic site) and mediate tonic inhibition in response to GABA spillover from the synaptic cleft (arrowed black dots). (Reproduced from Goetz et al., 2007).

1.3. Distinct physiological functions, distinct modulation

As described so far, synaptic and extrasynaptic GABAARs mediate two physiologically distinct forms of GABAergic signalling (Fisher and Macdonald, 1997; Mody and

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Pearce, 2004; Farrant and Nusser, 2005). This is also well reflected in the level of their modulation. For example the γ2-GABAARs are sensitive to Benzodiazepines (BZ) (Prittchett et al., 1989; Wingrove et al., 1997 Sigel and Buhr, 1997). Among the specific combinations of γ2-GABAARs, there are also further differential modulatory effects. Sedative effects of etomidate is mediated by γ2-GABAARs with β2 subunits, and anesthetic effects of etomidate is mediated by γ2-GABAARs with β3 subunit (Reynolds et al., 2003). Etomidate also affects δ-GABAARs similar to allosteric modulatory effect of this anesthetic on γ2-GABAARs (Feng et al., 2014), but by a different kinetic mechanism than that of γ2-GABAARs. The etomidate potentiation of δ-GABAARs occurs by a prolonged deactivation and reduced desensitization of the receptor (Liu et al., 2015) where as the etomidate potentiation of γ2-GABAARs does not involve receptor desensitization (Zhong et al., 2008).

δ-GABAARs are specifically sensitive to physiologically relevant ranges of alcohol a feature that is not found in γ2-GABAARs (Deitrich et al., 1989; Sundstrom-Poromaa et al., 2002; Wallner et al., 2003; 2014; Liang and Olsen 2014). Another difference between the γ2-GABAARs and δ-GABAARs is their modulation by neurosteroids, steroids synthesized in the brain. The most widely explored neurosteroids are allopregnanolone, allotetrahydrodeoxycorticosterone, androstanediol which enhance the activity of both receptor subtypes but this enhancement is stronger for the latter as δ-GABAARs are more senitive to neurosteroids (Wohlfarth et al., 2002; Stell et al., 2003; Carver and Reddy, 2013, Romo-Parra, et al., 2015) As a result, interaction of δ-GABAARs with neurosteroids have a critical status in terms of the potentiation of tonic inhibition and thus impacting on neuronal network excitability, seizure susceptibility, and behavior (Carver and Reddy, 2013). This has already been shown by the studies of δ subunit knock-out mice, which have a reduced inhibition and neurosteroid sensitivity (Spigelman, et al., 2003).

Recent studies in the literature continusously address the differential modulation. An interesting study not only report the differential modulation of γ2-GABAARs and δ-GABAARs but also further dissect δ-GABAARs the in this context (Hoestgaard-Jensen, et al., 2014). The ligand 4,5,6,7-tetrahydroisothiazolo[5,4-c]pyridin-3-ol (Thio-THIP) was found to have a negligible antagonist activity at the α4β2δ subtype unlike its effect on α4β1δ and α4β3δ among δ-GABAARs Moreover, the Thio-THIP displayed weak antagonist activity at α1,2,5β2,3γ2 containing receptors. Some other new studies report the differential modulation in terms of phasic and tonic inhibition. One study reports the potentiation of phasic and tonic currents following the inhibition of nitric oxide synthase (Gasulla and Calvo, 2015), while others suggest phosphorylation related modulation of phasic and tonic currents by CaMKII and PKC, respectively (Joo et al., 2014), or potentiation of tonic inhibition by serotonin (Jang, et al., 2015). However the subunit composition of the receptors that mediate phasic or tonic inhibition in these electrophysiological studies is not known except for the case of Gasulla and Calvo (2015), may be. Since there are many different GABAAR subunits (see the section "Subunit composition: Tonic and Phasic Inhibition"), electrophsiological recordings of phasic and tonic inhibition, without molecular profiling, will only provide a limited understanding of receptor subtype specific modulation. The focus of the present study is only γ2−GABAARs and δ− GABAARs, which mediate phasic and tonic inhibition. On the other hand there is another GABAAR subtype that mediate tonic inhibition for example: the α5 containing extrasynaptic GABAARs (Prenosil et al., 2006; Glyks, et al., 2008). Thus, the studies of electrophsiological recording of phasic and tonic inhibition and their modulation requires further molecular investigation in this context. Nevertheless, accumulating data address the modulation of δ− GABAARs by kinase A and C (phosphorylation) and regulation of tonic inhibition by G-protein coupled receptors (see Conelly et al., 2013 for a detailed review). Modulation of γ2− GABAARs by phosphorylation is already a better explored subject (Kittler and Moss, 2003) and the current emerging data about the modulation of δ− GABAARs by phosphorylation as well as by other ligands described so far will add a new dimension for the distinct modulation of phasic and tonic inhibition mediated by these receptor subtypes for their significance as potential targets of subtype selective drugs.

2. Conclusion

Assembled from a large subunit pool, the rich molecular, cellular and functional diversity of GABAARs is well known (Seeburg et al., 1990; Mody and Pierce, 2004). This diversity manifests itself in the form of distinct physiological functions. Phasic and tonic inhibition mediated by synaptic and extrasynaptic GABAARs is one example of this phenomenon. What is new in the agenda is the emerging data: Studies from X-ray crystal structures of ligand-gated ion channels from prokaryotic and invertebrate organisms (Lynagh and Pless, 2014), together with the crystal structure of human GABAAR (Miller and Aricescu, 2014) and serotonin receptor (Hassaine et al., 2014) accumulate. These accumulating data will trigger the studies of molecular dynamics and homology modeling which will boost the development of new drugs for selective modulation of the GABA receptor subtypes for the treatment of various neuropathological states such as epilepsy (Rogawski et al., 2013), premenstrual dysphoric disorder (Staley and Scharmann, 2005) or alcohol use disorders (Liang and Olsen, 2014).

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