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Review

Extrasynaptic $GABA_A$ receptors in the crosshairs of hormones and ethanol

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Abstract

Gamma-aminobutyric acid (GABA) is the main chemical inhibitory neurotransmitter in the brain. In the central nervous system (CNS) it acts on two distinct types of receptor: an ion channel, i.e., an ''ionotropic'' receptor permeable to Cl^- and HCO_3^- ($GABA_A$ receptors) and a G-protein coupled ''metabotropic'' receptor that is linked to various effector mechanisms ($GABA_B$ receptors). This review will summarize novel developments in the physiology and pharmacology of $GABA_A$ receptors ($GABA_A$Rs), specifically those found outside synapses. The focus will be on a particular combination of $GABA_A$R subunits sensitive to ovarian and adrenal cortical steroid hormone metabolites that are synthesized in the brain (neurosteroids) and to sobriety impairing concentrations of ethanol. These receptors may be the final common pathway for interactions between ethanol and ovarian and stress-related neurosteroids.

Keywords: GABA; Inhibition; Ovarian steroids; Stress; Ethanol

1. Introduction

Cell-to-cell chemical communication in the body can take three forms, each having various temporal and spatial limitations: (1) the relatively slow but spatially unrestricted neuroendocrine secretion, (2) the much faster volume transmission that reaches neighboring cells by diffusion of transmitter over hundreds of μm in the extracellular space, and (3) the ultra-fast synaptic transmission that requires specialized structures (synapses) between two communicating cell partners separated roughly by 20 nm. For the brain's principal chemical inhibitory transmitter GABA, fast synaptic transmission has been long thought to be the sole mechanism for communication between cells. More recently, the non-synaptic localization of the metabotropic $GABA_B$ receptors and of a certain type of the ionotropic $GABA_A$Rs has triggered a great interest in the tonic inhibitory transmission, also known as volume or diffusional transmission (Semyanov et al., 2004; Semyanov, 2005; Farrant and Nusser, 2005; Cavelier et al., 2005; Vizi and Mike, 2006). To distinguish between the activation of $GABA_A$Rs at synapses and of those on the outside or on the periphery of synapses one refers to phasic and tonic inhibitions to differentiate between the two types of inhibitory activity. The fast and local and slower but distant modes of GABAergic signaling is one of the principal reasons for the diversity of GABAergic action in the brain (Mody and Pearce, 2004). Many excellent reviews have been written on tonic inhibition and its role in the control of neuronal excitability (Semyanov et al., 2004; Semyanov, 2005; Farrant and Nusser, 2005; Cavelier et al., 2005; Vizi and Mike, 2006), and therefore these topics will not be summarized here. Instead, the present review will focus on the modulation of tonic inhibition by endogenous and exogenous substances highly relevant to our everyday life.

2. The δ subunit containing $GABA_A$ receptors

$GABA_A$ receptors are members of the superfamily of Cys-loop ligand gated ion channels in which five protein subunits (usually different proteins, and thus the name heteropentameric receptors) co-assemble to form a central aqueous pore through the lipid bilayer of the cell membrane (Sine and Engel, 2006). The binding of the ligand produces a conformational change in the receptor, and the central ion pore opens to allow the flow of ions. The channels open and close extremely fast until the

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ligand dissociates from the receptor. In some receptors the binding of the ligand produces a closed conformational state in spite of the continuing presence of the ligand. This state is called ''desensitized'', and is characteristic to many receptors in this family that beside the $GABA_A$Rs also include the nicotinic acetylcholine receptors (nAChR), the glycine receptors, and the ionotropic receptors for serotonin ($5\text{-}HT_3$).

In the case of the $GABA_A$Rs the five co-assembled subunits are different proteins. To date there are 19 different cloned $GABA_A$R subunits, such as α1-6, β1-4, γ1-3, δ, ε, θ, and ρ1-2 (Whiting et al., 1999). Depending on their subunit composition, $GABA_A$Rs have specific anatomical distribution (Pirker et al., 2000) most likely as a result of various cell-specific anchoring and trafficking mechanisms (Moss and Smart, 2001). Moreover, the physiological properties and pharmacology of the receptors are also a function of the subunit composition (Hevers and Luddens, 1998; Mody and Pearce, 2004). Their random assembly five-by-five would result in an enormous number of possible $GABA_A$R combinations. Nature reduced the total number of combinations to no more than a few dozen by limiting the partners that can assemble together, and by imposing strict rules on the number of different subunits of the same class (Whiting et al., 1999). Thus, the most prevalent combination of $GABA_A$Rs in the mammalian brain is the one made of 2α1, 2β2 and 1γ2 subunit arranged around the central pore in a particular order (the α1β2γ 2 subunit combination). The specific $GABA_A$R assemblies made of different combinations have different developmental expression patterns, physiological and pharmacological properties, and are also confined to specific compartments on a given cell (Hevers and Luddens, 1998; Mody and Pearce, 2004). Therefore, these specific $GABA_A$Rs are of great interest for highly specific drug targets for the brain.

The focus of this review is a specific subclass of $GABA_A$Rs that contain the δ subunit. The δ subunit was cloned many years ago, and was promptly shown to have a characteristic expression pattern in the brain and specific pharmacological properties, most importantly lack of benzodiazepine sensitivity, and a mutual exclusion with γ subunits from receptor assemblies (Shivers et al., 1989). The preferred combination partners of δ subunits were the α6 and α4 subunits (from all the α's) and the β2 and β3 subunits (from all the β's). The δ subunits in combination with a6 subunits are mainly found in cerebellar granule cells, which constitute the highest density of δ subunits in the brain (Pirker et al., 2000). Outside of the cerebellum, the preferred partners of δ subunits are the α4 subunits. High densities of α4/δ subunit-containing $GABA_A$Rs are found in the thalamus, striatum, hippocampal dentate gyrus, olfactory bulb, and layers 2–3 of the neocortex. Several studies have confirmed using pharmacological approaches, null mutant mice or both that in the neurons where δ subunits are present, these $GABA_A$Rs are responsible for the mediation of tonic inhibition (Wei et al., 2003, 2004; Stell et al., 2003; Jia et al., 2005; Drasbek and Jensen, 2006; Glykys and Mody, 2006).

The first indication about the peculiar subcellular localization of δ subunit containing $GABA_A$Rs came from studies on cerebellar granule cells. In these neurons, δ subunit containing $GABA_A$Rs are situated far from the synapses, scattered around the cell surface of the neurons (Nusser et al., 1998). In another area of the brain with high levels of δ subunits, in the granule cells of the dentate gyrus, these receptors are localized somewhat closer to the synapses, but still perisynaptically (Wei et al., 2003). This means that these receptors are ideally located to sense GABA overspilled after a synaptic release process from nearby boutons, or to be activated by the ambient levels of GABA present in the extracellular space. However, to function as receptors capable to detect overspilled or ambient GABA, these receptors have to satisfy certain physiological and pharmacological criteria. First, they have to have a high affinity for GABA in order to be activated by the low concentration of transmitter in the extracellular space estimated to be in the range of one to a few μM (Kuntz et al., 2004; Nyitrai et al., 2006). Second, they have to have little desensitization, as receptors in the continuing presence of agonist tend to desensitize and spend their time mainly in the closed configuration. Are these pharmacological properties met for the δ subunit containing $GABA_A$Rs?

Several studies have shown the high affinity for GABA of the receptors containing δ subunits in combination with either α4 or α6 subunits. Their half maximal activation by GABA (EC_{50}) is in the tens of nM range, well within the range of GABA found in the extracellular space (Saxena and Macdonald, 1996; Wallner et al., 2003). The δ subunit containing $GABA_A$Rs also have a low degree of desensitization in the continuous presence of agonist (Wohlfarth et al., 2002; Bianchi and Macdonald, 2003). This property is also important for their role as mediators of a tonic (''always on'') conductance, although a sufficiently large number of desensitizing $GABA_A$Rs may also produce overlapping openings that could sum to generate a tonic current. One of the other interesting pharmacological properties of δ subunit containing $GABA_A$Rs is that GABA is not a very efficacious agonist. This means that the coupling between binding of GABA and the opening of the channel is not the most effective one, in spite of the fact that very low concentrations of GABA can open the channels. Other agonists, such as THIP (gaboxadol) is a more efficacious agonist than GABA itself at these receptors (Brown et al., 2002; Wafford and Ebert, 2006). Thus GABA is a high potency, but low efficacy agonist at the receptors mediating tonic inhibition in many central neurons. This interesting property means that the function of these receptors may be modulated not by further increasing their affinity for GABA, which is already pretty high, but by altering the efficacy of GABA as an agonist. This is precisely what neurosteroids appear to be doing to the δ subunit containing $GABA_A$Rs (Wohlfarth et al., 2002; Bianchi and Macdonald, 2003).

3. Neurosteroid sensitivity

Neurosteroids (also called neuroactive steroids) are metabolites of ovarian steroids such as progesterone and of corticosteroids such as corticosterone (Belelli and Lambert, 2005). Their name indicates that they can be synthesized right in the brain by specific enzymes present in neurons and glial

cells. The most potent positive endogenous modulators of $GABA_A$ receptor function are the 3α-hydroxy ring A-reduced pregnane steroids, that have sedative-hypnotic, anticonvulsant, and anxiolytic effects (Majewska et al., 1986; Belelli and Lambert, 2005). For quite some time there were no specific hypotheses about one or another type of $GABA_AR$ having a higher sensitivity to neurosteroids. The first report on the sensitivity of δ subunit containing $GABA_ARs$ to the neurosteroid THDOC showed a lower sensitivity than that of γ subunit containing $GABA_ARs$ (Zhu et al., 1996). But more recent reports (Brown et al., 2002; Wohlfarth et al., 2002; Bianchi and Macdonald, 2003) have raised the possibility that the steroid sensitivity of δ subunit-containing $GABA_ARs$ may be much higher than previously thought. Indeed, neurosteroids in the nM concentration range, that is in the range assumed to be present in the extracellular space under various physiological and pathological conditions, selectively enhance the magnitude of tonic inhibition in cells in which this inhibition is mediated by δ subunit-containing $GABA_ARs$ (Stell et al., 2003). The effect of neurosteroids on synaptic (phasic) inhibition does not occur until the neurosteroid reaches much higher concentrations than what is supposedly present in the brain (Stell et al., 2003).

It is generally agreed upon, that neurosteroids potentiate the action of GABA at the δ subunit-containing $GABA_ARs$ by increasing the efficacy of the agonist. There is also a change in the desensitization property of the receptors in the presence of the neurosteroid (Wohlfarth et al., 2002; Bianchi and Macdonald, 2003), but not sufficient to prevent the enhancement of the tonic current (Stell et al., 2003). Although various other sites for neurosteroid action have been postulated in the brain, at their physiological concentrations, neurosteroids appear to solely target the tonic inhibition mediated by δ subunit-containing $GABA_ARs$. The net effect is to reduce network excitability (Stell et al., 2003), and thus it is not surprising that acute stress that produces a sudden increase in the levels of the neurosteroid THDOC is known to be anticonvulsant (Reddy, 2003).

4. Ethanol sensitivity

The effects of alcohol on the human body and mind have been known for thousands of years. Late Stone Age beer jugs are proof for the existence of intentionally fermented beverages (around 10,000 B.C.), and it is possible that the consumption of beer may have preceded that of bread. Wine appears in Egyptian pictographs around 4000 B.C. In spite of its long presence in human history, the mechanisms of action of ethanol on the brain are poorly understood. Although drinking and driving laws differ from country to country, here in the U.S. the legal upper limit for blood alcohol level for operating a motor vehicle is 0.08%. This corresponds to approximately 17 mmol/l of ethanol in the blood. Commercial drivers are limited to a maximum of 0.04%, i.e., around 8 mmol/l of ethanol in the blood. Clearly, these ethanol concentrations are in the sobriety impairing range of the drug. Yet, study after study was unable to show effects of ethanol in this low concentration range on specific targets in the brain.

The δ subunit-containing $GABA_ARs$ stand out in this regard. Although their sensitivity to ethanol in various expression systems is still somewhat controversial, some investigators consider them as the ''ethanol receptor'' of the brain (Hanchar et al., 2004; Wallner et al., 2004). The tonic inhibition mediated by these $GABA_ARs$ has an equally a high sensitivity to ethanol (Wei et al., 2004), indicating that the δ subunit-containing $GABA_ARs$ of the brain are a highly likely target for sobriety impairing concentrations of ethanol. Although they may be a preferred target of ethanol in the brain, it is yet unclear how these receptors play a role in alcohol addiction and tolerance.

5. Changes in δ subunit-containing $GABA_ARs$ during changes in steroid hormone levels

We recently demonstrated dynamic, ovarian cycle-linked modifications in specific $GABA_AR$ expression and function (Maguire et al., 2005). During the stage of the estrous cycle in mice when levels of progesterone and of progesterone-derivatives locally synthesized in the brain (neurosteroids) are elevated, there is an increased expression of the $GABA_AR$ δ subunits in the membranes of hippocampal neurons and an increase in $GABA_AR$ δ subunit-mediated tonic inhibition in dentate gyrus granule cells. This increase in $GABA_AR$ δ subunits corresponds to a period of lowered seizure susceptibility and anxiety (Maguire et al., 2005). Other investigators have shown the same receptors to parallel ovarian cycle related changes in the periaqueductal grey matter (Griffiths and Lovick, 2005; Lovick et al., 2005; Lovick, 2006) or to be upregulated in a steroid withdrawal model of pre-menstrual dysphoric disorder (PMDD) (Smith et al., 2006). The changes in the $GABA_AR$ δ subunits during the ovarian cycle and the associated alterations in neuronal excitability and anxiety may be highly relevant to the common psychiatric and neurological disorders such as PMDD, its milder form pre-menstrual syndrome (PMS), and postpartum depression that affect women during fluctuating changes in ovarian steroid levels as during the menstrual cycle and pregnancy.

The mood disorders associated with the menstrual cycle in women share patterns of symptom manifestation worsening during the luteal phase, occurring just prior to or during menses, and/or at the time of ovulation (Smith, 2001; Backstrom et al., 2003; Sundstrom-Poromaa et al., 2003). The prevalence of PMDD is 2–8% of women and a less severe phenotype of PMS is present in 15–25% of women (Wittchen, 2002; Chawla et al., 2002; Backstrom et al., 2003; Halbreich et al., 2003). Despite the high prevalence of PMDD, the World Health Organization (WHO) did not include PMDD or PMS in the comprehensive report regarding the economic burden of mental health disorders. However, studies show an increased number of sick days in women with PMS (Hallman and Georgiev, 1987; Hylan and Sundell, 1999) and a self-reported decrease in productivity (Chawla et al., 2002). During the reproductive age of women (14–51, a conservative estimate), an average of 1400 workdays/person are estimated to be lost due to PMS/PMDD, corresponding to 3.84 years of disability (DALY). In the United States alone this would add up to 14,492,465 DALYs, resulting in a significant

economic burden (Halbreich et al., 2003). In addition to the loss of productivity, health care costs for the treatment of PMDD-associated symptoms such as depression and headaches, also add to the economic impact of the disease (Halbreich et al., 2003). Present treatment of PMDD is mainly limited to SSRI such as Zoloft, in spite of the fact that there seems to be no serotonergic abnormality in affected women (Freeman, 2004). GABAergic mechanisms are much more likely to be involved (Smith, 2001; Backstrom et al., 2003; Sundstrom-Poromaa et al., 2003), but there are few experimental studies on the subject.

Postpartum depressive disorders are also common and symptoms may appear as early as the first 2 weeks after giving birth. The combined period prevalence shows that as many as 19.2% of women have a depressive episode during the first 3 months postpartum, and most of these episodes have onset following delivery (Gavin et al., 2005). A recent study conducted in 1286 women has concluded that PMS/PMDD was a significant risk factor in developing postpartum depression (Bloch et al., 2006). This may indicate that the two mood disorders may share some common mechanisms.

Consistent with the common involvement of the δ subunit-containing $GABA_A$Rs in ovarian-cycle related anxiety and in mediating the effects of ethanol, women with PMS increase their alcohol consumption during the luteal phase (Charette et al., 1990; Mcleod et al., 1994; Tobin et al., 1994), which may be an indication of self-medication since the function of δ subunit-containing $GABA_A$Rs (Sundstrom-Poromaa et al., 2002; Wallner et al., 2003) and the tonic inhibition mediated by them (Wei et al., 2004; Hanchar et al., 2005) are enhanced by sobriety-impairing concentrations of ethanol.

6. Summary

The δ subunit-containing $GABA_A$Rs and the tonic inhibition mediated by them appears to be a common target for stress- and ovarian steroid-derived neurosteroids as well as for sobriety-impairing concentrations of ethanol. This puts them in the crosshairs for finding effective therapies against a large number of psychiatric and neurological disorders related to stress, ovarian cycle, pregnancy and alcoholism.

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