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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 HCO₃[−] (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_ARs), specifically those found outside synapses. The focus will be on a particular combination of GABA_AR 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

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_ARs 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_ARs at synapses and of those on the outside or on the periphery of synapses one refers to phasic and tonic inhibitions to distinguish 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

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written on tonic inhibition and its role in the control of neuronal excitability (Semyanov *et al.* 2004; Sem'yanov 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.

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 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_ARs also include the nicotinic acetylcholine receptors (nAChR), the glycine receptors, and the ionotropic receptors for serotonin (5-HT₃).

In the case of the GABA_ARs the five co-assembled subunits are different proteins. To date there are 19 different cloned GABA_AR subunits, such as α 1-6, β 1-4, γ 1-3, δ , ϵ , θ , and ρ 1-2 (Whiting *et al.* 1999). Depending on their subunit composition, GABA_ARs 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 combinations five-by-five would result in an enormous number of possible GABA_AR 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_ARs in the mammalian brain is the one made of 2 α 1, 2 β 2 and 1 γ 2 subunit arranged around the central pore in a particular order (the α 1 β 2 γ 2 subunit combination). The specific GABA_AR 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_ARs are of great interest for highly specific drug targets for the brain.

The focus of this review is a specific subclass of GABA_ARs 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 α 6 and α 4 subunits (from all the α 's) and the β 2 and β 3 subunits (from all the β 's). The δ subunits in combination with α 6 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 α 4 subunits. High densities of α 4/ δ subunit-containing GABA_ARs are found in the thalamus, striatum, hippocampal dentate gyrus, olfactory bulb, and layer 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_ARs are responsible for the mediation of tonic inhibition (Wei *et al.* 2003; Stell *et al.* 2003; Wei *et al.* 2004; 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_ARs came from studies on cerebellar granule cells. In these neurons, δ subunit containing GABA_ARs 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 μ M (Kuntz *et al.* 2004; Nyitrai *et al.* 2006). Second, they have to be devoid of 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_ARs?

Several studies have shown the high affinity for GABA of the receptors containing δ subunits in combination with either $\alpha 4$ or $\alpha 6$ 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_ARs 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 essential for their role as mediators of a tonic ("always on") conductance, although a sufficiently large number of desensitizing GABA_ARs may also produce overlapping openings that could sum to generate a tonic current. One of the other interesting pharmacological properties of the δ subunit containing GABA_ARs 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 or gaboxadol are 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_ARs (Wohlfarth *et al.* 2002; Bianchi and Macdonald 2003).

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 it is supposed to reach in the brain (Stell *et al.* 2003).

It is generally agreed upon, that neurosteroids potentiate the efficacy 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 in the brain. 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).

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 4,000 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 California the legal upper limit for blood alcohol level for operating a motor vehicle is 0.08%. This corresponds to approximately 17 mmole/l of ethanol in the blood. Commercial drivers are limited to a maximum of 0.04%, i.e., around 8 mmole/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 (Hancher *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.

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 PMS (pre-menstrual syndrome), and postpartum depression that affect women during fluctuating changes in ovarian steroid levels as take place during the menstrual cycle and pregnancy.

The 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 1,400 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 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 1,286 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_ARs in ovarian-cycle related anxiety and in mediating the effects of ethanol, women with PMS have 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_ARs ((Sundstrom-Poromaa *et al.* 2002;Wallner *et al.* 2003) and the tonic inhibition mediated by them ((Wei *et al.* 2004;Hancher *et al.* 2005) are enhanced by sobriety-impairing concentrations of ethanol.

Summary

The δ subunit-containing GABA_ARs 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.

References

- Backstrom T, Andersson A, Andree L, Birzniece V, Bixo M, Bjorn I, Haage D, Isaksson M, Johansson IM, Lindblad C, Lundgren P, Nyberg S, Odmark IS, Stromberg J, Sundstrom-Poromaa I, Turkmen S,

- Wahlstrom G, Wang MD, Wohlback AC, Zhu D, Zingmark E. Pathogenesis in menstrual cycle-linked CNS disorders. *Steroids and the Nervous System* 2003;1007:42–53.
- Belelli D, Lambert JJ. Neurosteroids: endogenous regulators of the GABA(A) receptor. *Nat Rev Neurosci* 2005;6:565–575. [PubMed: 15959466]
- Bianchi MT, Macdonald RL. Neurosteroids shift partial agonist activation of GABA(A) receptor channels from low- to high-efficacy gating patterns. *J Neurosci* 2003;23:10934–10943. [PubMed: 14645489]
- Bloch M, Rotenberg N, Koren D, Klein E. Risk factors for early postpartum depressive symptoms. *Gen Hosp Psychiatry* 2006;28:3–8. [PubMed: 16377359]
- Brown N, Kerby J, Bonnert TP, Whiting PJ, Wafford KA. Pharmacological characterization of a novel cell line expressing human alpha(4)beta(3)delta GABA(A) receptors. *British Journal of Pharmacology* 2002;136:965–974. [PubMed: 12145096]
- Cavelier P, Hamann M, Rossi D, Mobbs P, Attwell D. Tonic excitation and inhibition of neurons: ambient transmitter sources and computational consequences. *Prog Biophys Mol Biol* 2005;87:3–16. [PubMed: 15471587]
- Charette L, Tate DL, Wilson A. Alcohol-Consumption and Menstrual Distress in Women at Higher and Lower Risk for Alcoholism. *Alcoholism-Clinical and Experimental Research* 1990;14:152–157.
- Chawla A, Swindle R, Long S, Kennedy S, Sternfeld B. Premenstrual dysphoric disorder - Is there an economic burden of illness? *Medical Care* 2002;40:1101–1112. [PubMed: 12409855]
- Drasbek KR, Jensen K. THIP, a hypnotic and antinociceptive drug, enhances an extrasynaptic GABAA receptor-mediated conductance in mouse neocortex. *Cereb Cortex* 2006;16:1134–1141. [PubMed: 16221925]
- Farrant M, Nusser Z. Variations on an inhibitory theme: phasic and tonic activation of GABA(A) receptors. *Nat Rev Neurosci* 2005;6:215–229. [PubMed: 15738957]
- Freeman EW. Luteal phase administration of agents for the treatment of premenstrual dysphoric disorder. *CNS Drugs* 2004;18:453–468. [PubMed: 15139800]
- Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. *Obstet Gynecol* 2005;106:1071–1083. [PubMed: 16260528]
- Glykys J, Mody I. Hippocampal network hyperactivity after selective reduction of tonic inhibition in GABA A receptor alpha5 subunit-deficient mice. *J Neurophysiol* 2006;95:2796–2807. [PubMed: 16452257]
- Griffiths JL, Lovick TA. GABAergic neurones in the rat periaqueductal grey matter express alpha4, beta1 and delta GABAA receptor subunits: plasticity of expression during the estrous cycle. *Neuroscience* 2005;136:457–466. [PubMed: 16226387]
- Halbreich U, Borenstein J, Pearlstein T, Kahn LS. The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder (PMS/PMDD). *Psychoneuroendocrinology* 2003;28:1–23.
- Hallman J, Georgiev N. The Premenstrual-Syndrome and Absence from Work Due to Illness. *Journal of Psychosomatic Obstetrics and Gynecology* 1987;6:111–119.
- Hanchar HJ, Dodson PD, Olsen RW, Otis TS, Wallner M. Alcohol-induced motor impairment caused by increased extrasynaptic GABA(A) receptor activity. *Nature Neuroscience* 2005;8:339–345.
- Hanchar HJ, Wallner M, Olsen RW. Alcohol effects on gamma-aminobutyric acid type A receptors: are extrasynaptic receptors the answer? *Life Sci* 2004;76:1–8. [PubMed: 15501475]
- Hevers W, Luddens H. The diversity of GABA(A) receptors -Pharmacological and electrophysiological properties of GABA(A) channel subtypes. *Molecular Neurobiology* 1998;18:35–86. [PubMed: 9824848]
- Hylan TR, Sundell K. Impact of premenstrual symptoms on functioning and treatment-seeking: Experience from the United States, United Kingdom, and France. *Journal of Womens Health & Gender-Based Medicine* 1999;8:710.
- Jia F, Pignataro L, Schofield CM, Yue M, Harrison NL, Goldstein PA. An extrasynaptic GABAA receptor mediates tonic inhibition in thalamic VB neurons. *J Neurophysiol* 2005;94:4491–4501. [PubMed: 16162835]
- Kuntz A, Clement HW, Lehnert W, van CD, Hennighausen K, Gerlach M, Schulz E. Effects of secretin on extracellular amino acid concentrations in rat hippocampus. *J Neural Transm* 2004;111:931–939. [PubMed: 15206007]

- Lovick TA. Plasticity of GABAA receptor subunit expression during the oestrous cycle of the rat: implications for premenstrual syndrome in women. *Exp Physiol* 2006;91:655–660. [PubMed: 16740643]
- Lovick TA, Griffiths JL, Dunn SM, Martin IL. Changes in GABA(A) receptor subunit expression in the midbrain during the oestrous cycle in Wistar rats. *Neuroscience* 2005;131:397–405. [PubMed: 15708482]
- Maguire JL, Stell BM, Rafizadeh M, Mody I. Ovarian cycle-linked changes in GABA(A) receptors mediating tonic inhibition alter seizure susceptibility and anxiety. *Nat Neurosci*. 2005
- Majewska MD, Harrison NL, Schwartz RD, Barker JL, Paul SM. Steroid-Hormone Metabolites Are Barbiturate-Like Modulators of the Gaba Receptor. *Science* 1986;232:1004–1007. [PubMed: 2422758]
- McLeod DR, Hoehnsaric R, Foster G. Anxiolytic Effects of Alcohol. *Biological Psychiatry* 1994;35:693.
- Mody I, Pearce RA. Diversity of inhibitory neurotransmission through GABAA receptors. *Trends in Neurosciences* 2004;27:569–575. [PubMed: 15331240]
- Moss SJ, Smart TG. Constructing inhibitory synapses. *Nat Rev Neurosci* 2001;2:240–250. [PubMed: 11283747]
- Nusser Z, Sieghart W, Somogyi P. Segregation of different GABA(A) receptors to synaptic and extrasynaptic membranes of cerebellar granule cells. *Journal of Neuroscience* 1998;18:1693–1703. [PubMed: 9464994]
- Nyitrai G, Kekesi KA, Juhasz G. Extracellular level of GABA and Glu: in vivo microdialysis-HPLC measurements. *Curr Top Med Chem* 2006;6:935–940. [PubMed: 16787267]
- Pirker S, Schwarzer C, Wieselthaler A, Sieghart W, Sperk G. GABA(A) receptors: Immunocytochemical distribution of 13 subunits in the adult rat brain. *Neuroscience* 2000;101:815–850. [PubMed: 11113332]
- Reddy DS. Is there a physiological role for the neurosteroid THDOC in stress-sensitive conditions? *Trends in Pharmacological Sciences* 2003;24:103–106. [PubMed: 12628349]
- Saxena NC, Macdonald RL. Properties of putative cerebellar gamma-aminobutyric acid(A) receptor isoforms. *Molecular Pharmacology* 1996;49:567–579. [PubMed: 8643098]
- Semyanov AV. Diffusional extrasynaptic neurotransmission via glutamate and GABA. *Neurosci Behav Physiol* 2005;35:253–266. [PubMed: 15875487]
- Semyanov A, Walker MC, Kullmann DM, Silver RA. Tonically active GABA A receptors: modulating gain and maintaining the tone. *Trends Neurosci* 2004;27:262–269. [PubMed: 15111008]
- Shivers BD, Killisch I, Sprengel R, Sontheimer H, Kohler M, Schofield PR, Seeburg PH. Two novel GABAA receptor subunits exist in distinct neuronal subpopulations. *Neuron* 1989;3:327–337. [PubMed: 2561970]
- Sine SM, Engel AG. Recent advances in Cys-loop receptor structure and function. *Nature* 2006;440:448–455. [PubMed: 16554804]
- Smith SS. Pre-menstrual steroids. *Cell Mol Life Sci* 2001;58:1263–1275. [PubMed: 11577983]
- Smith SS, Ruderman Y, Frye C, Homanics G, Yuan M. Steroid withdrawal in the mouse results in anxiogenic effects of 3alpha,5beta-THP: a possible model of premenstrual dysphoric disorder. *Psychopharmacology (Berl)* 2006;186:323–333. [PubMed: 16193334]
- Stell BM, Brickley SG, Tang CY, Farrant M, Mody I. Neuroactive steroids reduce neuronal excitability by selectively enhancing tonic inhibition mediated by delta subunit-containing GABA(A) receptors. *Proceedings of the National Academy of Sciences of the United States of America* 2003;100:14439–14444. [PubMed: 14623958]
- Sundstrom-Poromaa I, Smith DH, Gong QH, Sabado TN, Li XS, Light A, Wiedmann M, Williams K, Smith SS. Hormonally regulated alpha(4)beta(2)delta GABA(A) receptors are a target for alcohol. *Nature Neuroscience* 2002;5:721–722.
- Sundstrom-Poromaa I, Smith S, Gulinello M. GABA receptors, progesterone and premenstrual dysphoric disorder. *Arch Womens Ment Health* 2003;6:23–41. [PubMed: 12715262]
- Tobin MB, Schmidt PJ, Rubinow DR. Reported Alcohol-Use in Women with Premenstrual-Syndrome. *American Journal of Psychiatry* 1994;151:1503–1504. [PubMed: 8092343]

- Vizi ES, Mike A. Nonsynaptic receptors for GABA and glutamate. *Curr Top Med Chem* 2006;6:941–948. [PubMed: 16787268]
- Wafford KA, Ebert B. Gaboxadol--a new awakening in sleep. *Curr Opin Pharmacol* 2006;6:30–36. [PubMed: 16368265]
- Wallner M, Hanchar HJ, Olsen RW. Ethanol enhances $\alpha(4)\beta(3)\delta$ and $\alpha(6)\beta(3)\delta$ gamma-aminobutyric acid type A receptors at low concentrations known to affect humans. *Proceedings of the National Academy of Sciences of the United States of America* 2003;100:15218–15223. [PubMed: 14625373]
- Wallner M, Hanchar HJ, Otis TS, Olsen RW. Extrasynaptic GABA(A) receptors as mediators of low concentration ethanol effects. *Alcoholism-Clinical and Experimental Research* 2004;28:92A.
- Wei WZ, Faria LC, Mody I. Low ethanol concentrations selectively augment the tonic inhibition mediated by delta subunit-containing GABA(A) receptors in hippocampal neurons. *Journal of Neuroscience* 2004;24:8379–8382. [PubMed: 15385620]
- Wei WZ, Zhang NH, Peng ZC, Houser CR, Mody I. Perisynaptic localization of delta subunit-containing GABA(A) receptors and their activation by GABA spillover in the mouse dentate gyrus. *Journal of Neuroscience* 2003;23:10650–10661. [PubMed: 14627650]
- Whiting PJ, Bonnert TP, McKernan RM, Farrar S, Le Bourdelles B, Heavens RP, Smith DW, Hewson L, Rigby MR, Sirinathsinghji DJS, Thompson SA, Wafford KA. Molecular and functional diversity of the expanding GABA-A receptor gene family. *Molecular and Functional Diversity of Ion Channels and Receptors* 1999;868:645–653.
- Wittchen HU. Prevalence and cost of anxiety disorders in the new century. *European Neuropsychopharmacology* 2002;12:S156–S157.
- Wohlfarth KM, Bianchi MT, Macdonald RL. Enhanced neurosteroid potentiation of ternary GABA(A) receptors containing the delta subunit. *Journal of Neuroscience* 2002;22:1541–1549. [PubMed: 11880484]
- Zhu WJ, Wang JF, Krueger KE, Vicini S. Delta subunit inhibits neurosteroid modulation of GABAA receptors. *J Neurosci* 1996;16:6648–6656. [PubMed: 8824305]