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Review

Altered expression of δGABA$_A$ receptors in health and disease

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ABSTRACT

γ-Aminobutyric acid type A receptors that contain the δ subunit (δGABA$_A$ receptors) are expressed in multiple types of neurons throughout the central nervous system, where they generate a tonic conductance that shapes neuronal excitability and synaptic plasticity. These receptors regulate a variety of important behavioral functions, including memory, nociception and anxiety, and may also modulate neurogenesis. Given their functional significance, δGABA$_A$ receptors are considered to be novel therapeutic targets for the treatment of memory dysfunction, pain, insomnia and mood disorders. These receptors are highly responsive to sedative-hypnotic drugs, general anesthetics and neuroactive steroids. A further remarkable feature of δGABA$_A$ receptors is that their expression levels are highly dynamic and fluctuate substantially during development and in response to physiological changes including stress and the reproductive cycle. Furthermore, the expression of these receptors varies in pathological conditions such as alcoholism, fragile X syndrome, epilepsy, depression, schizophrenia, mood disorders and traumatic brain injury. Such fluctuations in receptor expression have significant consequences for behavior and may alter responsiveness to therapeutic drugs. This review considers the alterations in the expression of δGABA$_A$ receptors associated with various states of health and disease and the implications of these changes.

This article is part of a Special Issue entitled 'GABAergic signaling'.

1. δGABA$_A$ receptors

1.1. Introduction

Inhibitory neurotransmission critically regulates neuronal function and shapes behavior. In the central nervous system (CNS), the majority of inhibitory transmission is mediated by γ-aminobutyric acid type A (GABA$_A$) receptors, which are chloride-permeable ion channels (Farrant and Nusser, 2005). These receptors are constituted from an array of subunits (α1–6, β1–3, γ1–3, δ, π, θ, ε, ρ1-3), which typically combine in a preferred stoichiometry of 2α:2β:γ or 2α:2β:δ (Farrant and Nusser, 2005), although receptors composed of only α and β subunits also exist (Mortensen and Smart, 2006). GABA$_A$ receptors generate two prominent forms of current: phasic and tonic. Phasic current is rapidly desensitizing and is generated primarily by synaptic GABA$_A$ receptors, whereas tonic current is relatively non-desensitizing and is generated by extrasynaptic GABA$_A$ receptors (Fig. 1). The bulk of tonic current is generated by extrasynaptic GABA$_A$ receptors that contain either the δ subunit (δGABA$_A$ receptors) (Brickley et al., 2001; Stell et al., 2003) or the α5 subunit (α5GABA$_A$ receptors) (Caraiscos et al., 2004; Glykys et al., 2008).

δGABA$_A$ receptors have several remarkable properties that distinguish them as an important receptor subtype in the CNS. First, they generate a persistent, "tonic" current that profoundly affects neuronal excitability (Stell et al., 2003; Chadderton et al., 2004; Maguire et al., 2009; Bonin et al., 2011; Sarkar et al., 2011;

Abbreviations: CA1, *Cornu Ammonis* subfield 1 of the hippocampus; CNS, central nervous system; *Fmr1*-KO, transgenic mice lacking the *Fmr1* gene; FMRP, fragile X mental retardation protein; GABA$_A$ receptor, γ-aminobutyric acid type A receptor; PKC, protein kinase C; THDOC, tetrahydroxydeoxycorticosterone; THIP, 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridine-3-ol; THPROG, 3α,5α-tetrahydroprogesterone; α5GABA$_A$ receptor, α5 subunit–containing γ-aminobutyric acid type A receptor; δGABA$_A$ receptor, δ subunit–containing γ-aminobutyric acid type A receptor.

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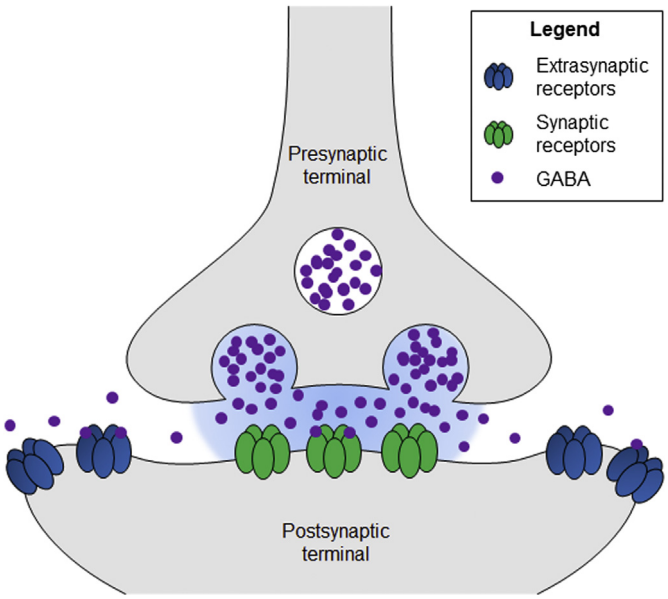

Fig. 1. Schematic of a typical synapse expressing $GABA_A$ receptors. Synaptic $GABA_A$ receptors (*green*) are found in postsynaptic regions in close proximity to the presynaptic terminal. These receptors are exposed to high concentrations of GABA (*purple*), which occur following action potential-dependent vesicular release of transmitter. In contrast, extrasynaptic $GABA_A$ receptors (*blue*) are located outside the postsynaptic region and are exposed to low, ambient concentrations of GABA.

Duguid et al., 2012). Second, they regulate a variety of behaviors, including memory, anxiety and nociception (Wiltgen et al., 2005; Shen et al., 2007, 2010; Bonin et al., 2011; Sarkar et al., 2011; Whissell et al., 2013b; Cushman et al., 2014; Lee et al., 2014; Paydar et al., 2014) and are therefore a therapeutic target in the treatment of neurological and neuropsychiatric disorders (Maguire and Mody, 2008; Olmos-Serrano et al., 2011; Christensen et al., 2012; Maguire et al., 2014). Third, and most importantly, $\delta GABA_A$ receptors exhibit a remarkable capacity for dynamic changes in expression levels under different physiological and pathological conditions. These changes reshape behavior and alter the sensitivity of neuronal networks to therapeutic drugs and other compounds that target $\delta GABA_A$ receptors (Table 1). Whereas previous reviews have addressed the functional and pharmacological properties of extrasynaptic $GABA_A$ receptors (Farrant and Nusser, 2005; Brickley and Mody, 2012; Egawa and Fukuda, 2013), to date no review has specifically addressed alterations in the expression of $\delta GABA_A$ receptors in health and disease. Here, we provide a brief overview of the expression and function of $\delta GABA_A$ receptors in the CNS, and discuss how the properties of these receptors change in the context of various physiological and pathological conditions.

1.2. Expression of $\delta GABA_A$ receptors in the CNS

$\delta GABA_A$ receptors are expressed at high levels in the dentate gyrus subfield of the hippocampus and in the thalamus, cortex and cerebellum (Pirker et al., 2000; Brickley et al., 2001; Stell et al., 2003; Jia et al., 2005; Drasbek and Jensen, 2006). Lower levels are expressed in the amygdala (Herman et al., 2013; Lindemeyer et al., 2014; Marowsky and Vogt, 2014; Martin et al., 2014), hypothalamus (Verkuyl et al., 2004; Sarkar et al., 2011), basal ganglia (Santhakumar et al., 2010; Luo et al., 2013; Maguire et al., 2014), brain stem (Lovick and Devall, 2009; Hengen et al., 2011; Vanini and Baghdoyan, 2013) and spinal cord (Takahashi et al., 2006; Peng et al., 2009; Bonin et al., 2011) (Fig. 2). The δ subunit is encoded by the *GABRD* gene, which is located on chromosome 1 in humans and chromosome 4 in mice (Emberger et al., 2000; Simon et al., 2004). Currently, the factors that regulate the expression of the gene are not well understood. The δ subunit typically partners with the α1, α4, α6, β2 or β3 subunits to form receptors with a 2α:2β:δ configuration. To date, three receptor subtypes have been identified: α1βδ, α4βδ and α6βδ. The α1βδ subtype is expressed in interneurons in several brain regions, including the hippocampus and amygdala (Glykys et al., 2007; Ferando and Mody, 2013; Lee and Maguire, 2013; Milenkovic et al., 2013; Marowsky and Vogt, 2014). In contrast, the α4βδ subtype is expressed primarily in projection neurons of the hippocampus and thalamus, whereas the α6βδ subtype is expressed in granule cells of the cerebellum (Pirker et al., 2000). The existence of multiple $\delta GABA_A$ receptor subtypes in different regions of the CNS (comprehensively summarized by Lee and Maguire (2014)) supports a variety of behavioral functions (Fig. 2).

1.3. Functions of $\delta GABA_A$ receptors

The functional relevance of $\delta GABA_A$ receptors likely stems from their capacity to regulate neuronal excitability through persistent activity. Three properties of $\delta GABA_A$ receptors enable this persistent activity: high sensitivity to GABA, slow kinetics of desensitization (Brown et al., 2002; Wlodarczyk et al., 2013) and a propensity for spontaneous opening in the absence of GABA or other endogenous ligands (Tang et al., 2010; Wlodarczyk et al., 2013). Interestingly, $\delta GABA_A$ receptors regulate neuronal excitability bidirectionally by constraining or enhancing excitability, depending upon the chloride ion (Cl^-) gradient (Ben-Ari et al., 2012). In healthy mature neurons with a low intracellular concentration of Cl^-, $\delta GABA_A$ receptor channel opening decreases excitability by allowing the influx of negatively charged Cl^- ions, which hyperpolarize the cell membrane (Andersen et al., 1980). The capacity of $\delta GABA_A$ receptor activity to decrease excitability also results from a reduction in input resistance. This effect, termed "shunting inhibition," attenuates the depolarization elicited by excitatory events (Andersen et al., 1980; Staley and Mody, 1992; Bonin et al., 2007). Shunting inhibition by $GABA_A$ receptors can be observed in conditions where the reversal potential for Cl^- is slightly hyperpolarized or depolarized relative to the resting membrane potential (Andersen et al., 1980; Staley and Mody, 1992; Bonin et al., 2007). In contrast to their generally inhibitory effect in healthy mature neurons, $\delta GABA_A$ receptors can enhance excitability in damaged mature neurons, immature neurons and other cells with a high intracellular concentration of Cl^-. In these cells, the reversal potential of Cl^- is significantly positive relative to the resting membrane potential. Accordingly, channel opening causes Cl^- efflux and membrane depolarization, which may increase excitability (Ge et al., 2006; Ruiz et al., 2010; Sarkar et al., 2011; Ben-Ari et al., 2012).

$\delta GABA_A$ receptors that are expressed in different brain regions regulate various behaviors. Receptors in the hippocampus may modulate memory processes, as transgenic mice null for the δ subunit gene ($Gabrd^{-/-}$) exhibit altered hippocampus-dependent memory performance (Wiltgen et al., 2005; Shen et al., 2010; Whissell et al., 2013a, 2013b; Cushman et al., 2014). Hippocampal $\delta GABA_A$ receptors likely constrain hippocampus-dependent fear memory (Wiltgen et al., 2005; Shen et al., 2010; Whissell et al., 2013b; Cushman et al., 2014). Interestingly, these receptors may also enhance other memory processes, such as discrimination memory and spatial working memory (Whissell et al., 2013b). Such memory-enhancing functions have been attributed to the promotion of hippocampal neurogenesis (Whissell et al., 2013b). $\delta GABA_A$ receptors in the hippocampus (Shen et al., 2007; Maguire and Mody, 2008) and the amygdala (Lindemeyer et al., 2014; Marowsky and Vogt, 2014) may also regulate anxiety. The increased activity of hippocampal $\delta GABA_A$ receptors reduces

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