The physiological properties and therapeutic potential of α_5-GABA$_A$ receptors

Loren J. Martin*, Robert P. Bonin† and Beverley A. Orser†‡§[1]

*Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada, M5S 1A8, †Department of Physiology, University of Toronto, Toronto, Ontario, Canada, M5S 1A8, ‡Department of Anesthesia, University of Toronto, Toronto, Ontario, Canada, M5S 1A8, and §Department of Anesthesia, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada, M4N 3M5

Abstract

The notion that drug treatments can improve memory performance has moved from the realm of science fiction to that of serious investigation. A popular working hypothesis is that cognition can be improved by altering the balance between excitatory and inhibitory neurotransmission. This review focuses on the unique physiological and pharmacological properties of GABA$_A$Rs [GABA (γ-aminobutyric acid) subtype A receptors] that contain the α_5 subunit (α_5-GABA$_A$R), as these receptors serve as candidate targets for memory-enhancing drugs.

Introduction

The GABA$_A$Rs [GABA (γ-aminobutyric acid) subtype A receptors] belong to the cysteine-loop family of ligand-gated receptors, which also includes the nicotinic acetylcholine receptor, glycine receptor, glutamate-gated ion channel, zinc-gated ion channel and ionotropic serotonin receptor [1]. GABA$_A$Rs are membrane-spanning proteins that surround a central pore to form an ion channel in the membrane. Each GABA$_A$R is assembled as a pentamer from a pool of 19 different subunits (α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, π, θ, ρ_{1-3}) [2]. The combination of subunits is specific, and the majority of native receptors in the mammalian brain contain α_1, β_2 and γ_2 subunits in a 2:2:1 stoichiometry [3]. Distinct isoforms of GABA$_A$Rs have different developmental, physiological and pharmacological properties and are localized to specific brain regions and subcellular compartments [4]. As we discuss below, GABA$_A$Rs that contain the α_5 subunit (α_5-GABA$_A$Rs) generate a tonic form of inhibition, are expressed mainly in extrasynaptic locations and play a role in modifying learning and memory behaviors.

Receptor distribution, function and pharmacology

The distribution of α_5-GABA$_A$Rs is relatively sparse and compartmentalized in the mammalian brain [5]. In total, approx. 5% of GABA$_A$Rs contain the α_5 subunit [6], although in the hippocampus, 20–25% of GABA$_A$Rs contain this subunit [6]. The α_5 subunit is predominantly localized to the stratum radiatum and stratum oriens of the CA1 and CA3 regions [5]. The distribution of the α_5 subunit is also exceptionally high in the olfactory bulb [5], where 35% of neurons in the internal granule cell layer express α_5-GABA$_A$Rs [6]. The function of α_5-GABA$_A$Rs in this region remains unknown. Other regions that express the α_5 subunit include the neocortex [7], subiculum [8] and substantia gelatinosa [9]; this subunit is also found in sympathetic preganglionic neurons [10].

Studies from our laboratory have shown that α_5-GABA$_A$Rs generate tonic inhibitory conductance in CA1 hippocampal pyramidal neurons [11]. This tonic conductance is significantly reduced in null mutant mice that have a genetic deletion of the gene that encodes the α_5 subunit (*Gabra5*$^{-/-}$ mice); however, spontaneous synaptic GABAergic inhibition remains unchanged [11]. The tonic conductance is sensitive to midazolam [12], but not to zolpidem [11], which is consistent with the presence of α_5 and γ subunits [13]. The α_5-GABA$_A$Rs display relatively high sensitivity to GABA, and they display slower desensitization kinetics than conventional synaptic GABA$_A$Rs [11,14]. Accordingly, low ambient concentrations of GABA in the extracellular space are thought to activate a proportion of these receptors and generate tonic inhibitory conductance [15]. α_5-GABA$_A$-R-generated tonic conductance has also been reported in cortical neurons [16], dopaminergic neurons of the striatum [17] and neurons in the intermediolateral cell column in spinal cord slices from rats [10]. Recombinant $\alpha_5\beta_3\gamma_2$ receptors have pharmacological properties similar to those of receptors that generate tonic current in CA1 hippocampal neurons [11,18], suggesting that this is the predominant combination of subunits in the hippocampus. Additionally, mass spectrometry identified that the α_5 subunit associates with multiple α, β and γ subunits, but most frequently the β_3 subunit [19].

Immunocytochemistry and *in situ* hybridization studies have indicated that α_5-GABA$_A$Rs are localized mainly, but not exclusively, to extrasynaptic regions of neurons [20–22]. Immunogold staining of the hippocampus showed that α_5-GABA$_A$Rs were located on the dendrites of pyramidal neurons in the CA1 region of the rat hippocampus and

Key words: benzodiazepine, brain, conductance, γ-aminobutyric acid subtype A receptor (GABA$_A$R), hippocampal pyramidal neuron, long-term potentiation (LTP).

Abbreviations used: GABA, γ-aminobutyric acid; GABA$_A$R, GABA subtype A receptor; LTP, long-term potentiation..

[1]To whom correspondence should be addressed (email beverley.orser@utoronto.ca).

cerebral cortex [23]. The clustering of α_5-$GABA_A$Rs is regulated by the binding of radixin, an actin-binding protein that anchors receptors to the cytoskeleton, to the activated form of the receptor [24].

The results of several electrophysiological studies suggest that α_5-$GABA_A$Rs also generate transient inhibitory synaptic potentials [25–27]. In neocortical pyramidal cells, a proportion of synaptic GABAergic events are reduced by the α_5-$GABA_A$R-selective inverse agonist α_5IA [28]. Inhibitory postsynaptic potentials generated by bistratified interneurons were potentiated by diazepam but not enhanced by zolpidem, which is consistent with an α_5-$GABA_A$R subtype [26]. Additionally, α_5-$GABA_A$Rs may contribute to synaptic GABAergic events with slow kinetics in cortical and hippocampal pyramidal neurons [27]. In hippocampal slices prepared from *Gabra5*$^{-/-}$ mice, the amplitude and decay time course of the evoked inhibitory postsynaptic currents were reduced, which suggests that deletion of α_5-$GABA_A$Rs may reduce synaptic inhibition [29]. In contrast, inhibiting α_5-$GABA_A$Rs with low concentrations of the benzodiazepine inverse agonist L-655,708 did not alter spontaneous IPSCs (inhibitory postsynaptic currents) in the CA1 and CA3 regions of the hippocampus, suggesting that spontaneous synaptic currents are not readily influenced by α_5-$GABA_A$R activity [11,30].

Finally, α_5-$GABA_A$R activity can reduce neuronal excitability by shunting mechanisms and/or changes in membrane potential [31]. In the hippocampus, α_5-$GABA_A$R activity reduces the excitability of individual pyramidal neurons [31] and networks of neurons [32] as well as the power of network oscillations [33]. The regulation of network excitability may contribute to α_5-$GABA_A$R regulation of hippocampus-dependent behavioural processes.

Learning, memory and α_5-$GABA_A$Rs

The concept that a decrease in $GABA_A$R activity modifies learning and memory is not new, because it is well-recognized that bicuculline, a non-selective competitive antagonist of $GABA_A$Rs, enhances memory performance [34]. Similarly, non-selective inverse agonists for the benzodiazepine site have been shown to enhance cognitive performance in animal models [35]. However, these drugs have anxiogenic, convulsant and proconvulsant properties that limit their clinical utility [35]. A key question is whether α_5-$GABA_A$Rs can be targeted by subtype-selective drugs to modulate memory without the adverse consequences of a global decrease in GABAergic inhibition.

Two mouse models, the *Gabra5*$^{-/-}$ mouse [29] and a point mutant (α_5H105R) mouse with reduced expression of α_5-$GABA_A$Rs [22], have been used extensively to study the role of α_5-$GABA_A$Rs in cognition. Both types of mice have normal lifespans, breed normally and exhibit no overt compensatory change in other $GABA_A$R subtypes. Initial studies showed that *Gabra5*$^{-/-}$ mice display enhanced acquisition in the matching-to-place version of the hippocampus-dependent water maze task [29], although this finding has not been replicated [36,37]. Furthermore, *Gabra5*$^{-/-}$ mice and α_5H105R mutant mice show improved performance in the trace fear conditioning paradigm but perform similarly to wild-type mice in the non-hippocampus-dependent cued fear conditioning protocol [22,37].

A number of drugs have been developed that have a greater affinity for, or selective activity at, α_5-$GABA_A$Rs than for other $GABA_A$R subtypes. These drugs include L-655,708, Ro15-4513, RY 080, RY 023 and RY 024 [38,39], which may improve memory with a relatively low occurrence of side effects [40]. Inverse agonists with selective binding or preferred efficacy for α_5-$GABA_A$Rs inhibit receptor activity allosterically via the benzodiazepine-binding site. The α_5-$GABA_A$R-function inverse agonist α_5IA improves water maze learning and synaptic plasticity [41]. *In vivo*, this drug has no apparent convulsant, proconvulsant, or anxiogenic properties [41]. Furthermore, an analogue of α_5IA, α_5IA-II, regulates encoding and recall but not consolidation of spatial information [42]. The administration of α_5IA-II either before training or immediately before memory-testing improved the performance of rats in the water maze, whereas α_5IA-II injected following training had no effect. Administration of L-655,708 reduced the time required to find the platform in the Morris water maze and the amount of time spent in the correct quadrant during the probe trial [43].

Inhibitors of α_5-$GABA_A$Rs may be clinically important for the reversal of memory blockade induced by other drugs. For example, the general anesthetics etomidate [36] and isoflurane [44] robustly increase α_5-$GABA_A$R-mediated tonic conductance. This action probably contributes to the drugs' amnesic properties [36,45]. Notably, *Gabra5*$^{-/-}$ mice are resistant to the amnesic properties of etomidate [36], and L-655,708 prevents memory blockade by etomidate in wild-type mice [37]. In human volunteers, the memory-blocking effects of ethanol on the recall of word lists were reversed by α_5IA-II [46], although the effects of α_5IA-II alone on memory performance were not demonstrated. Furthermore, memory impairment caused by the muscarinic antagonist scopolamine can be reversed with BiRY-080, a novel inverse agonist with 130-fold selectivity for α_5-$GABA_A$Rs [47]. Inverse agonists including L-655,708 and α_5IA are not currently available for clinical use; nevertheless, these drugs can serve as prototypes for drug development.

The molecular substrate for hippocampus-dependent learning and memory is thought to be the strengthening of synaptic connectivity, and brain slices have been used to study plasticity in hippocampal networks. LTP (long-term potentiation) of excitatory synaptic transmission in CA1 pyramidal neurons following stimulation of Schaffer collaterals is increased by non-selective inhibition of $GABA_A$Rs [48]. Interestingly, hippocampal slices obtained from *Gabra5*$^{-/-}$ mice and α_5H105R mice showed no differences in synaptic plasticity after high-frequency stimulation, despite enhanced memory behaviours [22,29]. In contrast, application of L-655,708 and α_5IA to brain slices prepared from rats at a concentration that induces preferential binding

to α_5-GABA$_A$Rs increased the LTP induced by theta burst stimulation [41,43]. These conflicting results suggest that, although α_5-GABA$_A$Rs may play an important role in the pharmacological enhancement of LTP, their role in baseline plasticity LTP may be smaller.

On a final note, although α_5-GABA$_A$Rs appear to play an important physiological role in the learning and memory process, these receptors may also contribute to pathological conditions, including ethanol addiction [49], schizophrenia [50], autism [51] and epilepsy [52]. Although there are major discrepancies that must still be addressed, α_5-GABA$_A$Rs will undoubtedly remain at the forefront of studies aimed at understanding the cellular basis of memory and the development of memory-modifying drugs.

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