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$GABA_B$ receptor modulation of synaptic function

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Abstract

Neuromodulators have complex effects on both the presynaptic release and postsynaptic detection of neurotransmitters. Here we describe recent advances in our understanding of synaptic modulation by metabotropic $GABA_B$ receptors. By inhibiting multivesicular release from the presynaptic terminal, these receptors decrease the synaptic glutamate signal. $GABA_B$ receptors also inhibit the Ca^{2+} permeability of NMDA receptors to decrease Ca^{2+} signals in postsynaptic spines. These new findings highlight the importance of $GABA_B$ receptors in regulating many aspects of synaptic transmission. They also point to novel questions about the spatiotemporal dynamics and sources of synaptic modulation in the brain.

Keywords

$GABA_B$ receptor; NMDA receptor; multivesicular release; calcium signaling; dendrite; spine; two-photon microscopy; two-photon uncaging

Introduction

Neurons throughout the brain communicate via the release and detection of chemical neurotransmitters. Release involves the fusion of vesicles at the presynaptic terminal and detection involves the activation of receptors in the postsynaptic membrane. Both processes are constantly changing, allowing synaptic transmission to be highly plastic over many time scales. These changes can reflect either the intrinsic properties of synapses or the influence of extrinsic chemical neuromodulators. In this review, we describe recent advances in our understanding of the impact of these neuromodulators at the level of individual synapses. We focus on regulation by $GABA_B$ receptors ($GABA_B$–Rs), drawing comparisons when possible to other neuromodulators working via similar mechanisms. Finally, we discuss important questions that remain about synaptic modulation and the technologies that may help provide answers.

Receptor diversity

Gamma aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain and acts via ionotropic and metabotropic receptors to control the electrical and biochemical properties of neurons [1]. $GABA_B$-Rs are metabotropic G-protein coupled receptors found at

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both excitatory and inhibitory synapses in almost all regions of the brain [2]. These receptors are usually thought to release Gβγ subunits that inhibit Ca^{2+} channels [3] and activate K^+ channels [4]. They also release $G\alpha_i/G\alpha_o$ subunits that inhibit adenylyl cyclase (AC) to reduce cAMP levels and decrease protein kinase A (PKA) activity [5]. By interacting with multiple downstream signaling cascades, it is likely that $GABA_B$-Rs have many physiological roles that we have only begun to characterize (Figure 1).

In order to function, $GABA_B$-Rs require two distinct subunits known as $GABA_{B1}$ and $GABA_{B2}$ [6–8]. $GABA_{B1}$ is needed for activation by external agonists and $GABA_{B2}$ is responsible for both signaling and membrane targeting [9,10]. Gene splicing divides $GABA_{B1}$ into two isoforms known as $GABA_{B1a}$ and $GABA_{B1b}$, which differ in their N-terminal regions, where only $GABA_{B1a}$ contains a pair of sushi domains [11]. These domains preferentially target $GABA_{B1a}$ to the presynaptic terminals of excitatory synapses, where it modulates glutamate release [*12]. On the postsynaptic side, both isoforms are found in the dendrites, but only $GABA_{B1b}$ is located in spines [*12]. This isoform seems to provide the majority of coupling to K^+ channels, as knocking out $GABA_{B1b}$ reduces postsynaptic K^+ currents, whereas knocking out $GABA_{B1a}$ has no effect [*12]. $GABA_{B1b}$ is also responsible for inhibition of dendritic Ca^{2+} spikes [13], possibly via a direct effect on voltage-sensitive Ca^{2+} channels (VSCCs) [*14].

Before the advent of gene cloning, pharmacological studies predicted a wide range of $GABA_B$-R isoforms with different functional properties [15,16]. It was thus surprising when only two isoforms were ultimately discovered [17], which have similar agonist binding and signaling properties [2]. This discrepancy was recently resolved by the discovery of auxiliary binding proteins including KCTD (potassium channel tetramerization domain-containing) proteins [18,19], Mupp1 [20], and GISP [21], which together help confer the diversity observed in earlier studies. Understanding the roles of different $GABA_B$-R isoforms and auxiliary binding proteins in synaptic modulation remains an exciting topic for future study.

Presynaptic release

$GABA_B$-Rs are one of many neuromodulatory receptors that can powerfully influence the release of neurotransmitters. Release requires a presynaptic action potential to open VSCCs and allow Ca^{2+} influx to activate the molecular machinery of vesicle fusion. $GABA_B$-Rs inhibit VSCCs to decrease Ca^{2+} influx and reduce release at both excitatory and inhibitory synapses [22,23]. $GABA_B$-Rs can also inhibit release by activating K^+ channels, which shunt the presynaptic action potential and indirectly limit Ca^{2+} influx [24]. Moreover, $GABA_B$-Rs can reduce vesicle priming by decreasing cAMP concentrations in the presynaptic terminal [25]. Results from other neuromodulators suggest that Gβγ subunits can also interact with the fusion machinery to change the mode of release [26]. Thus, GABA and other neuromodulators can act through multiple targets to tightly regulate presynaptic release.

Measuring presynaptic modulation at single synapses is challenging but can be accomplished with a variety of imaging probes. For example, presynaptic Ca^{2+} signals can be imaged with Ca^{2+}-sensitive dyes [22,23], vesicle sorting probed with styryl dyes [27], and $GABA_B$-R subunit interactions studied with FRET measurements [27]. In some cases, modulation of glutamate release can be detected with two-photon optical quantal analysis [28,29]. With this approach, release properties are measured using large NMDA-R Ca^{2+} signals evoked in dendritic spines, where successful events are clearly separated from failures. The influence of different modulators is then assessed by the impact of pharmacological agonists on release probability. This approach has now been used to

demonstrate that $GABA_B$ [**30] muscarinic [*31], and adenosine receptors [32] all inhibit presynaptic release onto postsynaptic spines.

Multivesicular release

Until recently, each presynaptic action potential was usually thought to release only a single vesicle from the presynaptic terminal. However, it is now clear that many different synapses have the ability to release multiple vesicles in response to a single action potential [33]. Multivesicular release (MVR) is pronounced at high release probabilities and is dynamically regulated by activity [32,34]. The ability to release multiple vesicles at individual boutons shifts the synaptic glutamate concentration from a binary to a graded signal. Because postsynaptic glutamate receptors are often not saturated [29,35], this increases the information capacity by extending the dynamic range of synaptic communication.

Recent evidence shows that presynaptic $GABA_B$-Rs suppress MVR to modulate glutamate signals at synapses [**30]. As predicted, $GABA_B$-Rs increase the number of failures detected by optical quantal analysis, suggesting a decrease in release probability. Surprisingly, $GABA_B$-Rs also decrease the amplitude of postsynaptic Ca^{2+} signals evoked by successful release events. Although inhibition of these Ca^{2+} signals could reflect direct modulation of NMDA-Rs, blocking postsynaptic G-protein signaling has no effect on this attenuation. Instead, decreasing the extracellular Ca^{2+} concentration to reduce MVR occludes the $GABA_B$-R-evoked decrease in these Ca^{2+} signals. By inhibiting MVR, $GABA_B$-Rs can decrease the synaptic glutamate concentration and thereby control postsynaptic responses in a graded fashion. Similar results have also been found for muscarinic receptors in the striatum [*31], suggesting that regulation of MVR may be common throughout the brain.

Postsynaptic conductances

The rapid detection of neurotransmitter is accomplished at synapses throughout the brain by ionotropic receptors. At excitatory synapses, these include a variety of both AMPA and NMDA receptors [36]. It is well known that these receptors possess multiple sites for post-translational modifications [37]. Phosphorylation is often considered in terms of receptor trafficking, especially during synaptic plasticity [38]. However, this modification can also change open times, agonist affinity and ion selectivity of channels. For example, the Ca^{2+} permeability of NMDA-Rs is usually under tonic up-regulation by constitutive PKA activity [*39]. By targeting different signaling cascades, $GABA_B$-Rs have the potential to change many properties of postsynaptic transmission.

It has been difficult to detect postsynaptic modulation of ionotropic glutamate receptor function by $GABA_B$-Rs. One complication is the widespread prevalence of presynaptic inhibition, which is difficult to avoid in most experiments. Two-photon glutamate uncaging bypasses the presynaptic terminal and allows direct study of modulation at single spines throughout the dendritic arbor (Figure 2A) [40,41]. Given that $GABA_B$-Rs are located in close proximity to glutamate receptors [42], it was initially predicted that $GABA_B$-Rs would modulate glutamate receptors. Surprisingly, however, $GABA_B$–Rs do not impact either AMPA-R or NMDA-R EPSCs at pyramidal neuron spines in the prefrontal cortex [**30]. This is also true for D2-R modulation at striatal synapses [**43], despite the clear role these and other neuromodulatory receptors play in synaptic plasticity.

Postsynaptic calcium signals

In addition to generating postsynaptic conductances, NMDA-Rs are the predominant source of Ca^{2+} signals in the spines of many neurons throughout the brain [29,44]. These signals

are particularly important for initiating the physiological and morphological changes that occur during synaptic plasticity [38]. $GABA_B$-Rs are usually thought to inhibit these signals by opening a variety of K^+ channels [45] found in both dendrites and spines [42]. The resulting hyperpolarization enhances Mg^{2+} blockade of NMDA-Rs to reduce their overall current and thus Ca^{2+} influx [46,47]. However, the impact of this $GABA_B$-R-evoked hyperpolarization on postsynaptic Ca^{2+} signals remains unexplored at the level of individual spines.

Recent results demonstrate that $GABA_B$-Rs exert direct and powerful inhibition of Ca^{2+} influx through NMDA-Rs (Figure 2B) [**30]. Even though $GABA_B$-Rs do not inhibit NMDA-R EPSCs, they can reduce postsynaptic Ca^{2+} signals by approximately half. This effect is independent of Gβγ subunits, K^+ channel activation, VSCC activation and internal Ca^{2+} stores. Instead, it is mediated by $G\alpha_i/G\alpha_o$ subunits, which inhibit AC to decrease cAMP levels and suppress PKA activity. Because PKA normally enhances Ca^{2+} influx through NMDA-Rs, this enables $GABA_B$-Rs to inhibit Ca^{2+} signals in spines. Similar results have been found for D2-R modulation in the striatum [**43], suggesting this may be a widespread function of neuromodulators that signal via $G\alpha_i/G\alpha_o$ subunits. However, the molecular mechanisms for the selective reduction of NMDA-R Ca^{2+} permeability still need to be resolved. In addition, it will be interesting to determine the roles of auxiliary proteins including AKAPs (A-kinase anchoring proteins) in this new form of synaptic modulation [48].

Future directions

We now know a great deal about how $GABA_B$-Rs and other neuromodulatory receptors regulate synaptic transmission, but there are many important questions remaining. To finish, we briefly explore three future directions in the study of synaptic modulation, addressing new technologies that may help provide answers.

Targets of modulation

Both excitatory post-synaptic potentials (EPSPs) and synaptic Ca^{2+} signals are shaped by interactions between channels and receptors in spines. For example, opening R-type VSCCs generates a Ca^{2+} signal that activates Ca^{2+}-sensitive K^+ Channels and generates a hyperpolarization to block NMDA-Rs [49]. How do $GABA_B$-Rs regulate voltage- and Ca^{2+}-sensitive ion channels to influence these local feedback loops? Recent results indicate that $GABA_B$-Rs can inhibit VSCCs in spines and dendrites throughout the dendritic arbor of cortical pyramidal cells [*14]. It will be interesting to determine if this inhibition leads to any changes in EPSPs and synaptic Ca^{2+} signals, as seen for D2-Rs in the striatum [**43]. $GABA_B$-Rs may also regulate Ca^{2+}-sensitive K^+ channels themselves, as recently discovered for muscarinic receptors in the hippocampus [50], leading to an entirely new kind of synaptic modulation.

Timing of modulation

$GABA_B$-Rs initiate multiple signaling cascades to influence ion channels and glutamate receptors in pre- and postsynaptic structures. What is the temporal profile over which these different cascades regulate the release and detection of glutamate? Answering this question is difficult with classical pharmacology involving the tonic application of specific agonists. Fortunately, a range of caged compounds is now available that are rapidly released with either one- or two-photon excitation. Local uncaging generates a brief pulse of GABA whose effects on EPSCs and Ca signals can be studied over time [*14,51]. FRET probes can also be used to study how this time-locked $GABA_B$-R activation influences protein-protein

interactions in different subcellular compartments [27]. These approaches may help reveal different kinetic profiles for $GABA_B$-R modulation via both Gβγ and $G\alpha_i/G\alpha_o$ subunits [52].

Sources of modulation

Anatomical studies show that a variety of inhibitory interneurons innervate distinct subcellular domains in pyramidal neurons [53]. For example, parvalbumin-positive neurons synapse near the cell body, while somatostatin-expressing neurons target dendrites. Which interneurons are responsible for supplying the GABA that modulates the release and detection of glutamate at excitatory synapses? In some cases, paired recordings can be used to target individual interneurons and assess their modulatory impact. For example, neurogliaform cells release clouds of GABA that can activate $GABA_B$-Rs on dendritic spines [52,54]. Novel optogenetic tools can also be used to target different populations of interneurons and control their firing properties [55,56]. These approaches may ultimately help define the activity patterns needed to activate presynaptic and postsynaptic $GABA_B$-Rs and trigger synaptic modulation [57].

Summary

$GABA_B$-R modulation plays a central role in the ability of neurons to function in circuits. This is highlighted by the consequences of disrupted modulation in the prefrontal cortex in neuropsychiatric diseases [58]. Recent studies have revealed new ways in which $GABA_B$-Rs can control synaptic responses. Thus, $GABA_B$-Rs can suppress MWR to decrease the synaptic glutamate concentration. Unexpectedly, $GABA_B$-Rs can also act via the PKA pathway to decrease postsynaptic NMDA-R Ca^{2+} signals. By also inhibiting VSCCs in spines and dendrites, $GABA_B$-Rs are thus poised to potently regulate Ca^{2+} -mediated plasticity. In addition to $GABA_B$-Rs, these effects are also found with other modulators like acetylcholine and dopamine, suggesting that these processes are occurring at diverse synapses throughout the brain. However, many questions remain about the spatial, temporal and cell-type specific effects of neuromodulators. A variety of new technologies will allow us to better understand the properties of synaptic modulation in normal physiology and disease states.

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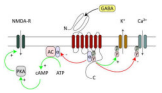

Figure 1. Post-synaptic intracellular $GABA_B$-R signaling

GABA binding to $GABA_B$-R heterodimers releases Gβγ subunits that locally diffuse to open K^+ channels and close Ca^{2+} channels. In addition, released $G\alpha_i/G\alpha_o$ subunits inhibit adenylyl cyclase (AC), which constitutively produces cAMP to activate PKA, with potentially many downstream targets including NMDA-Rs.

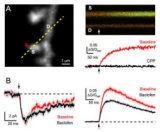

Figure 2. Modulation of postsynaptic NMDA-R Ca signals

A, *Left*, Two-photon image of dendrite and spines, showing uncaging location (*asterisk*) and line-scan position (*dashed yellow line*). *Right*, Line-scans (*top*) show a change in green Ca^{2+} signal after two-photon uncaging, quantified (*bottom*) before (*red*) and after (*black*) wash-in of the NMDA-R antagonist CPP. **B**, Average NMDA-R currents (*left*) and Ca^{2+} signals (*right*) before (*red*) and after wash-in of the $GABA_B$-R agonist baclofen (*black*) (adapted from Chalifoux & Carter, 2010).