Brief Communications

# Postsynaptic $GABA_B$ Receptors Enhance Extrasynaptic $GABA_A$ Receptor Function in Dentate Gyrus Granule Cells

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**Ambient GABA in the brain tonically activates extrasynaptic $GABA_A$ receptors, and activity-dependent changes in ambient GABA concentration can also activate $GABA_B$ receptors. To investigate an interaction between postsynaptic $GABA_B$ and $GABA_A$ receptors, we recorded $GABA_A$ currents elicited by exogenous GABA (10 $\mu$M) from dentate gyrus granule cells (DGGCs) in adult rat hippocampal slices. The $GABA_B$ receptor agonist baclofen (20 $\mu$M) enhanced $GABA_A$ currents. This enhancement was blocked by the $GABA_B$ receptor antagonist CGP 55845 and intracellular solutions containing the GTP analog GDP-$\beta$-s, indicating that baclofen was acting on postsynaptic $GABA_B$ receptors. Modulation of $GABA_A$ currents by postsynaptic $GABA_B$ receptors was not observed in CA1 pyramidal cells or layer 2/3 cortical pyramidal neurons. Baclofen reduced the frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) but did not alter sIPSC amplitude or kinetics. Thus, $GABA_A$ receptors activated at synapses were not modulated by postsynaptic $GABA_B$ receptors. In contrast, tonic GABA currents and currents activated by the $GABA_A$ receptor $\delta$ subunit-selective agonist THIP (10 $\mu$M) were potentiated by baclofen. Our data indicate that postsynaptic $GABA_B$ receptors enhance the function of extrasynaptic $GABA_A$ receptors, including $\delta$ subunit-containing receptors that mediate tonic inhibition in DGGCs. The modulation of $GABA_A$ receptor function by postsynaptic $GABA_B$ receptors is a newly identified mechanism that will influence the inhibitory tone of DGGCs when $GABA_B$ and $GABA_A$ receptors are both activated.**

## Introduction

The inhibitory neurotransmitter $\gamma$-aminobutyric acid (GABA) activates both ionotropic $GABA_A$ receptors and metabotropic $GABA_B$ receptors. $GABA_A$ receptors are $Cl^-$ ion channels that produce electrical signals when activated. $GABA_A$ receptors respond transiently to GABA released from synaptic vesicles and, in many areas of the brain including the hippocampus, high-affinity $GABA_A$ receptors at extrasynaptic sites are activated tonically by ambient GABA (Farrant and Nusser, 2005; Glykys and Mody, 2007). Activation of presynaptic and postsynaptic $GABA_B$ receptors stimulates intracellular G-protein signaling cascades that activate $K^+$ channels, inhibit voltage-gated $Ca^{2+}$ channels, and regulate cyclic AMP (cAMP) and protein kinase A (PKA) (Padgett and Slesinger, 2010). Because postsynaptic $GABA_B$ receptors are located at extrasynaptic sites away from GABA release sites, their activation is limited by GABA uptake and requires patterns of presynaptic activity that lead to GABA spillover and elevations of ambient GABA (Scanziani, 2000; Kulik et al., 2003). Under conditions of increased ambient GABA, such as occur with ischemia, epileptic seizures, or drugs that increase GABA concentration, coactivation of $GABA_A$ receptors and postsynaptic $GABA_B$ receptors will occur (Scanziani et al., 1991; During and Spencer, 1993; Wu et al., 2003; Allen et al., 2004).

In dentate gyrus granule cells (DGGCs), electron microscopy with immunogold labeling has identified $GABA_B$ receptors at perisynaptic sites on dendritic and somatic membranes (Kulik et al., 2003), a distribution pattern that has remarkable overlap with the distribution of extrasynaptic $GABA_A$ receptor subunits that mediate tonic inhibition in DGGCs (i.e., $\delta$ subunits) (Wei et al., 2003). The proximity of postsynaptic $GABA_B$ receptors to extrasynaptic $GABA_A$ receptors on DGGCs suggests that $GABA_A$ receptors will be exposed to intracellular signaling pathways activated by $GABA_B$ receptors. This potential interaction has likely been overlooked, because studies of $GABA_A$ receptors are routinely done in the presence of $GABA_B$ receptor antagonists.

We investigated the interaction between $GABA_B$ receptors and $GABA_A$ receptors in DGGCs. Our data show that activation of postsynaptic $GABA_B$ receptors enhances $GABA_A$ currents caused by exogenous GABA. This newly identified interaction was not present in CA1 pyramidal neurons or layer 2/3 cortical pyramidal neurons. In DGGCs, tonic GABA currents and currents mediated by $\delta$ subunit-containing receptors were also modulated by $GABA_B$ receptor activation. Our results indicate that extrasynaptic $GABA_A$ receptor function will be enhanced when postsynaptic $GABA_B$ receptors are activated, increasing the inhibitory tone of DGGCs.

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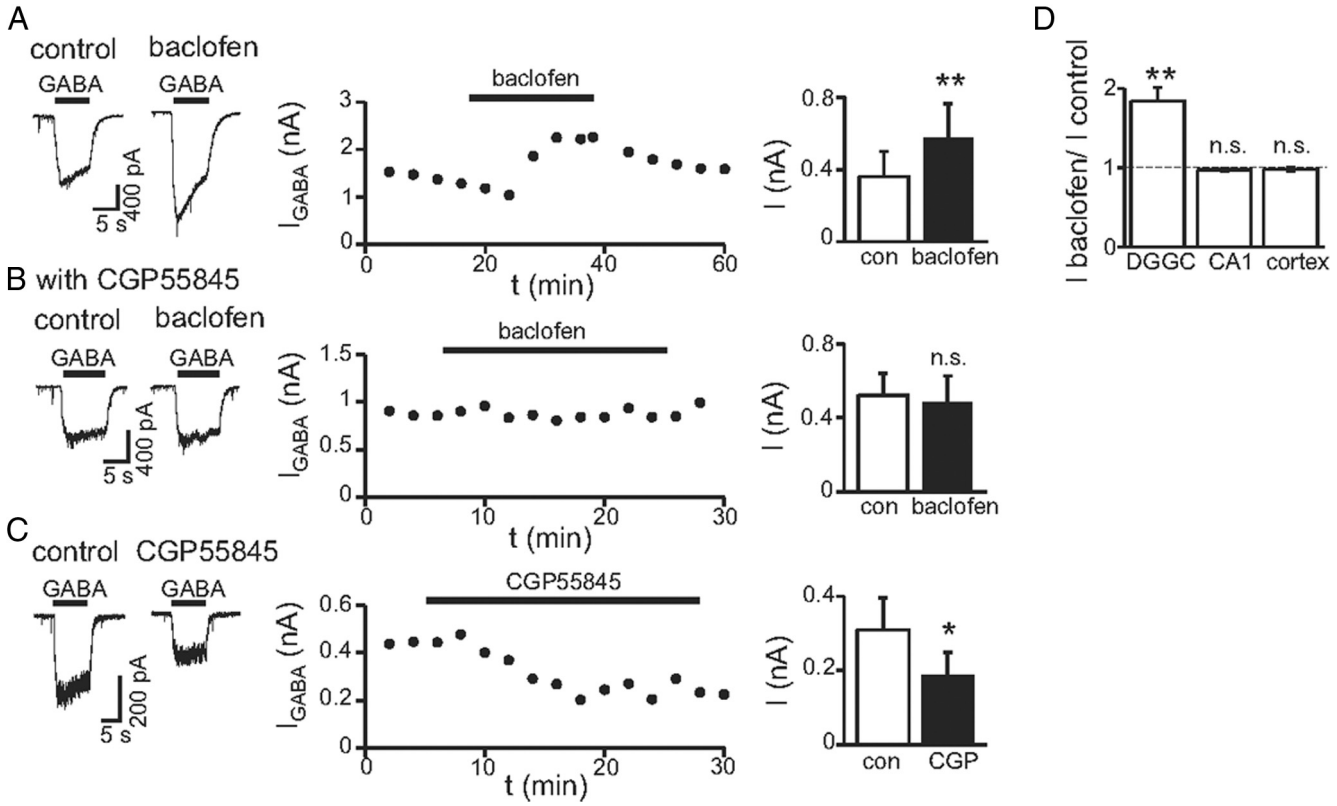


**Figure 1.** $GABA_B$ receptor activation enhanced $GABA_A$ currents in DGGCs, but not CA1 pyramidal neurons or cortical layer 2/3 pyramidal neurons. ***A***, $GABA_A$ currents evoked by focal application of GABA (10 $\mu$M) before and during bath application of baclofen (20 $\mu$M) (left panel). Middle panel shows time course of current change during baclofen application for this cell. Horizontal bars indicate the period of drug application here and in subsequent figures. Right panel shows mean current amplitudes under control conditions (con) and in the presence of baclofen. ***B***, GABA currents in the presence of the $GABA_B$ antagonist CGP 55845 (10 $\mu$M) before and during baclofen application (left), time course of current change for this cell (middle), and mean current under control conditions (con) and in the presence of baclofen (right panel). CGP prevented baclofen effects on $GABA_A$ currents. ***C***, GABA currents before and after application of CGP alone (left), time course for this cell (middle), and mean current amplitude (right). ***D***, Normalized currents (baclofen/control) for experiments on DGGCs, CA1 pyramidal cells, and layer 2/3 pyramidal cells. Error bars represent SEM; $*p < 0.05$, $**p < 0.01$, n.s., nonsignificant.

## Materials and Methods

*Brain slice preparation*. Brain slices were prepared from 4–6 week old Sprague Dawley rats of both sexes. Rats were anesthetized with 4% isoflurane, decapitated, and the brain dissected free. Transverse hippocampal slices (300 $\mu$m) were prepared. These slices contained portions of temporal cortex that were used for experiments on cortical neurons. Slices were cut and stored in a solution containing (in mM): 125 NaCl, 3 KCl, 26 $NaHCO_3$, 1.2 $NaH_2PO_4$, 0.5 $CaCl_2$, 4 $MgCl_2$, 20 dextrose, and 1 kynurenic acid. Slices were cut in ice-cold solution and stored at room temperature. Solutions were continuously gassed with 95% $O_2$/5% $CO_2$. Slices were allowed to recover for 1 h before recording. All animal use protocols were approved by the local Institutional Animal Care and Use Committee.

*Electrophysiology*. Membrane currents were recorded using whole-cell patch clamp techniques. Neurons were visualized with an Axioskop 2 upright microscope with fixed stage (Carl Zeiss). Recordings were made using an Axopatch 200B amplifier, a Digidata 1200 series A-D converter, and pClamp 9 software (Molecular Devices). Data were acquired at 2 kHz and low-pass filtered at 1 kHz. Series resistance was compensated by 50–70% online. If series resistance exceeded 20 MΩ or changed by >20%, the experiment was discarded. Focal application of GABA or bicuculline was made by pressure ejection (Picospritzer II, General Valve) from a patch pipette containing (in mM): 150 NaCl, 3 KCl, 2 $CaCl_2$, 2 $MgCl_2$, 10 dextrose, and 10 HEPES with pH adjusted to 7.4 with NaOH. The pressure ejection pipette was positioned ~20–30 $\mu$m from the soma. The recording chamber was continuously superfused at ~2–2.5 ml/min with a bath solution containing (in mM): 134 NaCl, 3 KCl, 1.4 $NaH_2PO_4$, 24 $NaHCO_3$, 10 dextrose, 2 $MgCl_2$, 2 $CaCl_2$, and 1 kynurenic acid (pH 7.35–7.4 when bubbled with 95% $O_2$/5% $CO_2$). Osmolarity was adjusted to 300–305 mOsm with $H_2O$. Patch pipettes were pulled from borosilicate glass with filament (Sutter Instrument). Pipettes had resistances of 3–4 MΩ when filled with intracellular solution containing (in mM): 125 CsCl, 10 QX-314 chloride, 10 HEPES, and 1 EGTA (pH corrected to 7.25 with CsOH). Osmolarity was adjusted to 275–285 mOsm with $H_2O$ as needed. Data acquisition was started 4–6 min after establishing a whole-cell recording. Experiments were performed at room temperature (~23°C). All chemicals were purchased from Sigma except SKF 89976a (Tocris-Cookson) and QX-314 (Alomone Labs). Baclofen was used at 20 $\mu$M (Dutar and Nicoll, 1988), and CGP55845 was used at 10 $\mu$M (Chen and Regehr, 2003).

*Analysis*. Data analysis was performed with Clampfit (pClamp 10) and Origin (v6.1, Microcal Software) software. Tonic currents were measured as the change in holding current caused by the $GABA_A$ receptor antagonist bicuculline methiodide (40 $\mu$M), based on Gaussian fits to all-points current amplitude histograms constructed from 2–10 s of data with a bin width of 1 pA. Fits were performed using a Levenberg–Marquardt algorithm in Clampfit, and the holding current was taken as the center of the Gaussian curve. IPSCs were analyzed using template matching event detection. Data are presented as mean ± standard error of the mean (SEM), and all error bars represent SEM. Statistical analyses were performed using Microsoft Excel. A two-tailed, paired or homoscedastic Student's *t* test was used with a *p* value ≤ 0.05 considered as significant.

## Results

### $GABA_B$ receptor activation enhanced $GABA_A$ receptor currents in a cell type-specific manner

To investigate an interaction between metabotropic $GABA_B$ receptors and ionotropic $GABA_A$ receptors, we made focal applica-

tions of GABA (10 $\mu$M) to activate $GABA_A$ currents in DGGCs ($V_m$ = −60 mV). Bath application of the $GABA_B$ receptor agonist baclofen (20 $\mu$M) increased GABA-evoked currents by 83 ± 18% (control, −358 ± 143 pA vs baclofen, −577 ± 184 pA, $n = 5$, $p < 0.01$) (Fig. 1*A*). Currents in the presence of baclofen were inhibited by bicuculline (20 $\mu$M) to a similar extent as under control conditions (control, 91 ± 2% inhibition, baclofen, 95 ± 1% inhibition, $n = 3–4$, $p = 0.26$), indicating that currents enhanced by baclofen were also mediated by $GABA_A$ receptors (data not shown). Modulation of $GABA_A$ currents by baclofen was blocked by the $GABA_B$ receptor antagonist CGP55845 (CGP, 10 $\mu$M). In the presence of CGP, $GABA_A$ currents were −521 ± 120 pA at baseline and −486 ± 138 pA after application of baclofen ($n = 5$, $p = 0.38$) (Fig. 1*B*). These data indicate that activation of $GABA_B$ receptors augments $GABA_A$ receptor function in DGGCs. CGP by itself reduced $GABA_A$ currents, demonstrating baseline activation of $GABA_B$ receptors (and modulation of $GABA_A$ receptors) during application of GABA. On average, CGP alone reduced $GABA_A$ currents from −309 ± 87 pA to −187 ± 62 pA ($n = 5$, $p < 0.05$) (Fig. 1*C*).

We tested the effects of baclofen on GABA-evoked currents in hippocampal CA1 pyramidal cells and cortical layer 2/3 pyramidal cells. In contrast to results from DGGCs, baclofen did not modulate $GABA_A$ currents in these other cell types (CA1: control −669 ± 173 pA vs baclofen −647 ± 163 pA, $n = 4$, $p = 0.19$; Layer 2/3: control −457 ± 103 pA vs baclofen −445 ± 96 pA, $n = 6$, $p = 0.28$) (Fig. 1*D*).

### Modulation of $GABA_A$ current required postsynaptic G-protein activation

Bath-applied baclofen activates both presynaptic and postsynaptic $GABA_B$ receptors, raising the possibility of an indirect action (e.g., via modulation of GABA release). Because $GABA_B$ receptors are G-protein coupled, transduction of receptor activation requires guanine nucleotide exchange. This process involves dissociation of GDP from inactive G proteins and binding of GTP. Thus, postsynaptic $GABA_B$ receptor signaling can be prevented by intracellular GDP-$\beta$-S, a nonhydrolyzable GDP analog (Harayama et al., 1998; Lin and Dun, 1998). We recorded $GABA_A$ currents from DGGCs with intracellular solutions containing GDP-$\beta$-S (0.5 mM) and no GTP (Fig. 2*A*). Intracellular GDP-$\beta$-S prevented baclofen-induced potentiation of $GABA_A$ currents (control, −615 ± 141 pA vs baclofen, −532 ± 118 pA, $n = 5$, $p = 0.12$) (Fig. 2*A*). These results indicate that baclofen modulates $GABA_A$ currents via postsynaptic $GABA_B$ receptors and a G-protein signaling pathway.

### Modulation of $GABA_A$ current was independent of synaptic vesicle release

Although changes in GABA release were not predicted to affect responses to exogenous GABA, we wished to exclude a contribution of vesicular GABA release to the effects of baclofen. To address this issue, we inhibited vesicular release of GABA by pretreating slices with the $H^+$-ATPase inhibitor concanamycin A (ConA, 0.5 $\mu$M, 2 h). ConA treatment reduced the frequency of spontaneous IPSCs (sIPSCs) by 75% ($n = 9$, $p < 0.05$) (data not shown). However, ConA treatment did not affect the baclofen-induced potentiation of $GABA_A$ currents (control, −437 ± 157 pA vs baclofen, −974 ± 167 pA, $n = 5$, $p < 0.01$) (Fig. 2*B*).

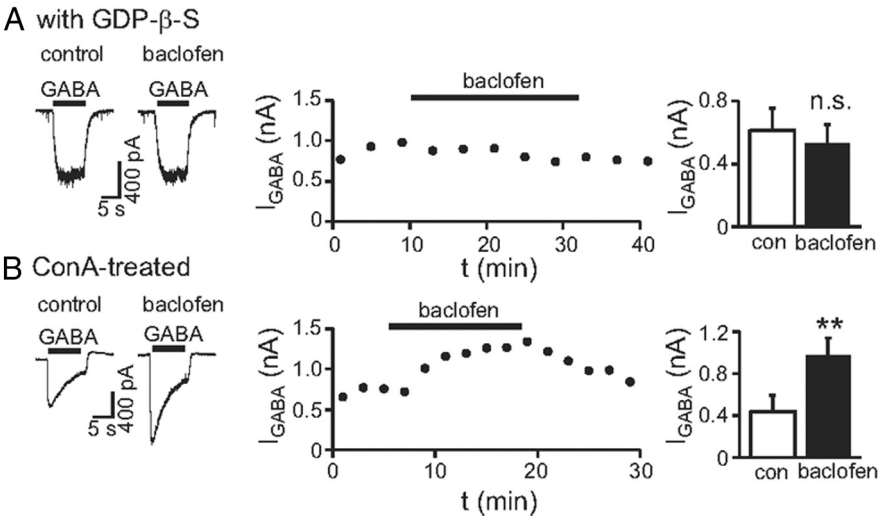


**Figure 2.** Modulation of $GABA_A$ currents by baclofen required postsynaptic G-protein activation and was independent of presynaptic vesicle release. ***A***, $GABA_A$ currents recorded with intracellular GDP-$\beta$-S to inhibit postsynaptic G proteins (left), time course of current change for this cell (middle), and mean current under control conditions (con) and in the presence of baclofen (right panel). Intracellular GDP-$\beta$-S blocked the effect of baclofen. ***B***, Currents recorded from a DGGC pretreated with concanamycin A to inhibit vesicular GABA release (left). Baclofen increased $GABA_A$ currents after ConA treatment (middle, current time course; right, mean current). *$p < 0.05$, **$p < 0.01$.

### Baclofen potentiated tonic $GABA_A$ receptor currents, but not synaptic $GABA_A$ receptor currents

The data presented above show that postsynaptic $GABA_B$ receptors can potentiate $GABA_A$ currents elicited by exogenous GABA. Distinct types of $GABA_A$ receptors with unique subunit compositions are transiently activated at synapses by vesicular GABA release or tonically activated by ambient GABA at extrasynaptic sites (Farrant and Nusser, 2005). To determine whether extrasynaptic $GABA_A$ receptors were subject to modulation by postsynaptic $GABA_B$ receptors, we measured tonic $GABA_A$ current as the change in holding current caused by focal application of bicuculline (40 $\mu$M). Similar to its effect on exogenous GABA currents, baclofen potentiated tonic currents (control, −7.5 ± 1 pA vs baclofen, −15.2 ± 0.1 pA, $n = 5$, $p < 0.01$) (Fig. 3*A*,*B*). Tonic currents were unaffected by baclofen in the presence of CGP (CGP, −5.5 ± 1.2 pA vs baclofen/CGP, −4.8 ± 0.9, $p = 0.44$, $n = 5$) (Fig. 3*C*). In contrast to GABA-evoked currents, CGP alone did not affect tonic currents (control, −13.6 ± 3.0 pA vs CGP, −15.3 ± 3.4, $n = 4$, $p = 0.17$) (Fig. 3*C*). This indicates that $GABA_B$ modulation of tonic currents is not basally active and requires periods of increased ambient GABA (such as periodic application of exogenous GABA, i.e., Fig. 1*C*). Following inhibition of GABA uptake by SKF 89976a (SKF, 30 $\mu$M) to increase ambient GABA and tonic current, blocking $GABA_B$ receptors with CGP significantly reduced tonic current (from −86.8 ± 17.9 pA to −45.9 ± 9.6 pA, $n = 5$, $p < 0.01$) (Fig. 3*D*,*E*). These data indicate that $GABA_B$ receptors modulate $GABA_A$ receptors that mediate tonic currents.

Tonic currents in DGGCs are primarily mediated by δ subunit-containing $GABA_A$ receptors (Glykys et al., 2008). To confirm that baclofen potentiates currents produced by δ

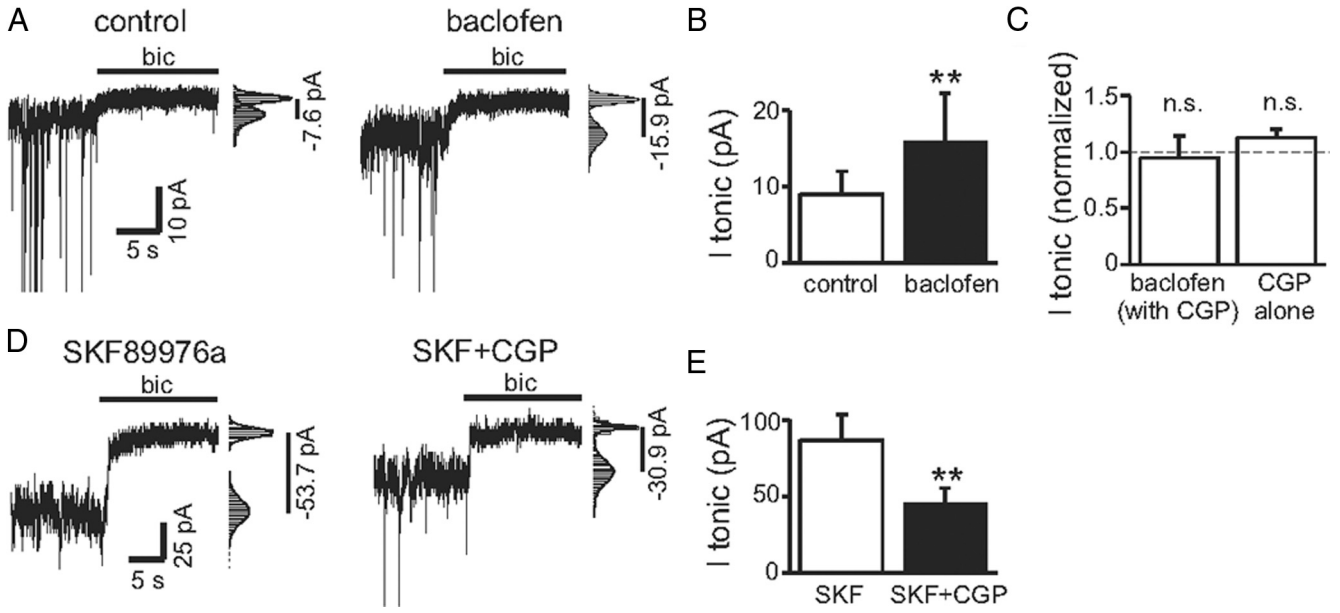


**Figure 3.** Postsynaptic $GABA_B$ receptors increased tonic $GABA_A$ currents. ***A***, Tonic currents under baseline conditions (left) and during baclofen application (right). The histograms and Gaussian fits used to measure holding current before and during focal application of bicuculline (bic, 40 $\mu$M) are shown to the right of each trace, and each tonic current amplitude is indicated. ***B***, Mean tonic current under control conditions and in the presence of baclofen. ***C***, Tonic currents during application of baclofen (with CGP) or CGP alone normalized to control. ***E***, Tonic currents in the presence of the GABA uptake inhibitor SKF 89976a (30 $\mu$M) before and during CGP application. ***D***, Mean tonic currents in the presence of SKF or SKF + CGP. $GABA_B$ antagonism by CGP reduced the large tonic current seen in the presence of SKF; $^{**}p < 0.01$, n.s., nonsignificant.

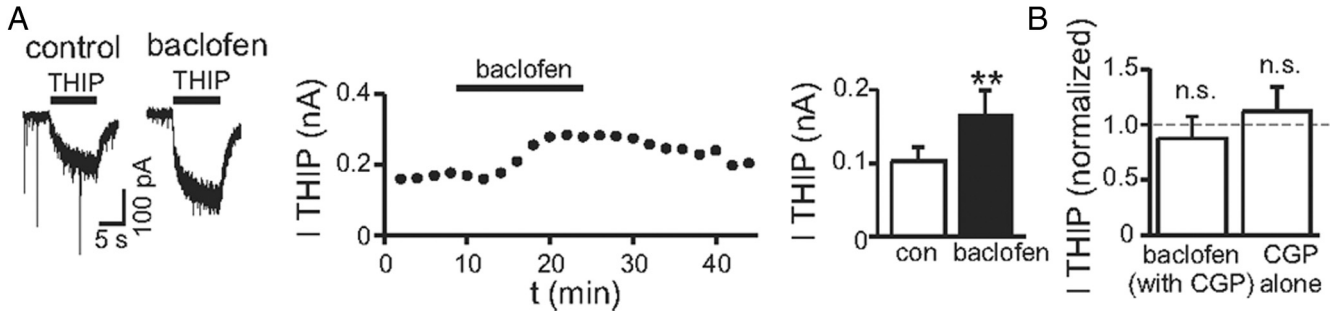


**Figure 4.** $GABA_B$ receptors increased currents evoked by the $GABA_A$ receptor δ subunit-selective agonist THIP. ***A***, Currents evoked by THIP (10 $\mu$M) (left), the time course of current change for this cell (middle), and the mean THIP-induced currents under control conditions (con) and during baclofen application (right). ***B***, THIP currents during application of baclofen (with CGP) or CGP alone normalized to control; $^{**}p < 0.01$, n.s., nonsignificant.

subunit-containing $GABA_A$ receptors, we used the δ subunit-selective agonist THIP (10 $\mu$M). Baclofen increased currents evoked by THIP (control, $-103 \pm 19$ pA vs baclofen, $-167 \pm 32$ pA, $n = 5$, $p < 0.05$) (Fig. 4*A*). In the presence of CGP, baclofen had no effect on THIP-induced currents (CGP, $-48 \pm 13$ pA vs baclofen/CGP, $-46 \pm 14$ pA, $p = 0.56$, $n = 5$) (Fig. 4*B*). Similar to tonic currents, CGP alone did not affect THIP currents (control, $-85.5 \pm 18.9$ pA vs CGP, $-88.0 \pm 19.3$ pA, $n = 4$, $p = 0.50$) (Fig. 4*B*). These results demonstrate that δ subunit-containing $GABA_A$ receptors are a target of postsynaptic $GABA_B$ receptors.

Measurements of sIPSCs showed that baclofen reduced their frequency to $52 \pm 6\%$ of control values ($n = 5$, $p < 0.05$) but did not significantly affect sIPSC amplitude, 10–90% rise times, or decay times ($n = 5$, $p = 0.94$, 0.44, and 0.30, respectively) (data not shown). CGP alone did not affect sIPSC frequency, amplitude, or decay times ($p = 0.53$, 0.52, and 0.33, respectively; $n = 4$). These data indicate that $GABA_B$ receptors reduce presynaptic release of GABA but do not alter the properties of $GABA_A$ receptors activated at synapses (Otis and Mody, 1992).

## Discussion

Our results show for the first time that postsynaptic $GABA_B$ receptors can modulate $GABA_A$ receptor function. Specifically, our data indicate that postsynaptic $GABA_B$ receptors enhance the function of $GABA_A$ receptors that produce tonic currents in DGGCs (including δ subunit-containing receptors). Because postsynaptic $GABA_B$ receptors and the $GABA_A$ receptors they modulate are located extrasynaptically (Kulik et al., 2003; Wei et al., 2003), both types of receptors will experience similar levels of ambient GABA. Coactivation of these receptors during periods of increased ambient GABA associated with intense neural activity may represent a feedback mechanism to increase inhibitory tone of DGGCs (Scanziani et al., 1991; During and Spencer, 1993; Scanziani, 2000).

### Mechanism of $GABA_B$ receptor modulation of $GABA_A$ currents

Several lines of evidence indicate that $GABA_A$ currents were modulated by postsynaptic $GABA_B$ receptors. The use of exogenous

GABA to activate $GABA_A$ currents would minimize effects of altered GABA release due to presynaptic $GABA_B$ activation, and $GABA_B$ effects were seen after inhibition of vesicular GABA release with ConA. Altered GABA uptake caused by presynaptic $GABA_B$ receptor activation could potentially account for our observations. However, this is unlikely because $GABA_B$ effects were seen in the presence of the GAT1 antagonist SKF. Additionally, currents produced by the nontransported $GABA_A$ agonist THIP were potentiated by baclofen, indicating that $GABA_B$ receptors enhance $GABA_A$ currents independently of GABA uptake mechanisms (including GAT3). Finally, selectively inhibiting postsynaptic G proteins by including GDP-$\beta$-S in our pipette solutions blocked the effects of $GABA_B$ receptor activation, confirming a postsynaptic site of action.

Our data show that tonic currents caused by ambient GABA are modulated by postsynaptic $GABA_B$ receptors. Experiments using the $\delta$ subunit-selective agonist THIP (Mortensen et al., 2010; Meera et al., 2011) confirmed that receptors containing $\delta$ subunits were potentiated by $GABA_B$ receptors. $GABA_B$ receptor activation did not change sIPSC amplitude or kinetics but reduced sIPSC frequency, indicating that postsynaptic $GABA_B$ receptors did not modulate $GABA_A$ receptors activated at synapses. Because a large number of "synaptic-type" $GABA_A$ receptors (i.e., $\gamma$ subunit containing) are located away from synapses in extrasynaptic membranes (near postsynaptic $GABA_B$ receptors) (Farrant and Nusser, 2005), our data do not exclude the possibility that $GABA_B$ receptors modulate these types of $GABA_A$ receptors in addition to $\delta$ subunit-containing receptors.

Signals mediated by postsynaptic $GABA_B$ receptors are transduced by the G proteins $G_i/G_o$ and $G_{\beta\gamma}$ (Padgett and Slesinger, 2010). A downstream effect of $G_{\beta\gamma}$ is $K^+$ channel activation; however, this is unlikely to have contributed significantly to our results because control currents and currents in the presence of baclofen were both inhibited >90% by $GABA_A$ antagonists, and intracellular QX314 effectively blocks $GABA_B$-activated $K^+$ channels (Nathan et al., 1990; Andrade, 1991). Activation of $G_i/G_o$ inhibits adenylate cyclase, with subsequent reduction in cAMP levels and reduced activation of PKA. Our data show that inhibition of G-protein signaling prevented $GABA_B$ receptor modulation of $GABA_A$ currents. The final effect on $GABA_A$ receptors is not known, but the possibilities include increased single channel conductance, open probability, or surface expression. Future studies using different experimental methods are required to distinguish between these possibilities.

### Cell type specificity of the postsynaptic $GABA_B$–$GABA_A$ interaction

In DGGCs, activation of $GABA_B$ receptors substantially increased $GABA_A$ currents by 83% on average. This strong modulation was absent in CA1 pyramidal neurons and cortical layer 2/3 pyramidal neurons. One salient difference between DGGCs and CA1 pyramidal cells is that tonic inhibition in CA1 pyramidal cells is mediated by $\alpha$5 subunit-containing $GABA_A$ receptors, whereas $\delta$ subunit-containing receptors are dominant in DGGCs (Caraiscos et al., 2004; Glykys et al., 2008). In layer 2/3 pyramidal neurons there is little, if any, functional expression of $\delta$ subunits (although $\delta$ subunit mRNA is present) (Yamada et al., 2007). Thus, we speculate that signals produced by postsynaptic $GABA_B$ receptors may preferentially affect $\delta$ subunits. Our results showed that baclofen did not affect sIPSC characteristics but potentiated tonic currents and THIP-evoked currents, consistent with a selective modulation of $\delta$ subunit-containing receptors by postsynaptic $GABA_B$ receptors. However, other factors in addition to differences in $GABA_A$ receptor subunit expression may also contribute to the cell type specificity of $GABA_B$ receptor effects.

### Functional implications

Tonic inhibition affects neuronal excitability and network behavior (Chadderton et al., 2004; Glykys and Mody, 2006; Pavlov et al., 2009; Duguid et al., 2012), thereby influencing many physiologic and pathophysiologic processes, including synaptic plasticity and epileptic seizures (Maguire et al., 2005; Martin et al., 2010). The effect of tonic inhibition is generally inhibitory, but in some cell types (i.e., thalamocortical cells) increasing tonic inhibition is maladaptive and contributes to pathologic patterns of neuronal firing (Cope et al., 2009). Our results add to the ways that tonic inhibition can be modulated, including GABA uptake and release by transporters, drugs that increase GABA concentrations, voltage-dependent modulation of extrasynaptic $GABA_A$ receptors, and neurosteroids (Overstreet and Westbrook, 2001; Nusser and Mody, 2002; Stell et al., 2003; Wu et al., 2003; Pavlov et al., 2009; Ransom et al., 2010). The enhancement of tonic inhibition by postsynaptic $GABA_B$ receptors described here is predicted to reduce cellular excitability of DGGCs by shunting excitatory synaptic currents and raising action potential threshold (Stell et al., 2003; Holter et al., 2010; Arima-Yoshida et al., 2011; Gupta et al., 2012).

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