Spatially distinct actions of metabotropic glutamate receptor activation in dorsal lateral geniculate nucleus

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GLUTAMATE ACTIVATES TWO BROAD classes of receptors, ionotropic glutamate receptors and metabotropic glutamate receptors (mGluRs), which can be activated by retinogeniculate and corticothalamic pathways in the dorsal lateral geniculate nucleus (dLGN) (Granseth 2004; Scharfman et al. 1990; Turner and Salt 1998). Multiple mGluR subtypes have been identified, and many of these are differentially localized within the thalamocortical circuit (Conn and Pin 1997). Activation of corticothalamic afferents engages mGluRs producing multiple actions via both pre- and postsynaptic mechanisms (Alexander and Godwin 2005, 2006; Govindaiah and Cox 2006, 2009; McCormick and von Krosigk 1992; Turner and Salt 1999, 2000). Activation of mGluR1 (member of group I mGluRs) either by synaptic activation or selective agonists produces a depolarization of thalamocortical relay neurons (Turner and Salt 2000) and is the likely mechanism that produces a switch in the response mode of thalamocortical relay cells from burst to tonic firing following mGluR1 activation in vivo (Godwin et al. 1996b). In contrast, activation of groups II and III mGluRs attenuates corticothalamic excitation via presynaptic mechanisms (Alexander and Godwin 2005; Turner and Salt 1999).

Local dLGN inhibitory interneurons are unique in that they give rise to two distinct types of output: axonal and dendritic (Famiglietti and Peters 1972; Guillery 1969; Hamos et al. 1985; Montero 1986; Ralston 1971). The conventional axonal output of interneurons forms both axodendritic and axosomatic inhibitory synapses onto thalamocortical neurons and are referred to as F1 terminals. These interneurons also have GABA-containing dendrites that form dendro dendritic synapses onto thalamocortical neurons and are termed F2 terminals. Retinogeniculate axons innervate both F2 terminals and relay neuron dendrite. The F2 terminals in turn synapse nearby onto the same relay neuron dendrite to form a triadic arrangement. Because of the proximity of the F2 terminal to the excitatory retinogeniculate synapse onto the relay neuron, these inhibitory inputs are thought to regulate retinogeniculate transmission focally (Steriade 2004), and these presynaptic dendrites also contain the other member of group I mGluRs, namely mGluR5 (Godwin et al. 1996a). Activation of mGluR5 produces diverse actions on visual responses in dLGN thalamocortical neurons in vivo (de Labra et al. 2005). Furthermore, in vitro studies indicate that mGluR5 activation by agonists or activation of retinogeniculate afferents increases inhibitory activity within thalamocortical neurons via selective activation of F2 terminals (Cox et al. 1998; Cox and Sherman 2000; Govindaiah and Cox 2004, 2006; Lam et al. 2005).

Anatomic studies indicate that retinogeniculate and corticothalamic afferents are differentially distributed on the dendritic arbor of thalamocortical relay neurons and thus may represent distinct functional influences on thalamic gating. Retinogeniculate inputs, and associated triadic arrangements, are preferentially localized on the proximal dendrites (Erisir et al. 1997; Wilson et al. 1984, 1996). In contrast, corticothalamic inputs are preferentially distributed on distal dendrites of thalamocortical neurons (Erisir et al. 1997; Wilson et al. 1984). In addition, group I mGluRs are presumably differentially localized in the dLGN: mGluR1 are localized to dendrites of local interneurons, whereas mGluR3 are localized to thalamocortical neuron dendrites opposite to corticothalamic afferents (Godwin et al. 1996a; Vidnyanszky et al. 1996). Considering the differential localization of mGluRs and their distinct actions in the dLGN, we have investigated the physiological consequences arising from specific mGluR subtypes in dLGN by local activation of these receptors. We found diverse actions of mGluR activation that are heterogeneously distributed along the dendritic axis within thalamocortical neurons. Activation of F2 terminals by mGluR5 activation was primarily restricted to proximal dendrites, whereas the postsynaptic depolarizing actions of mGluR activation via mGluR1 was present at both...
proximal and distal dendritic sites. Depending on how synaptic activation of glutamatergic inputs engage these different receptors, such diverse mGluR-mediated actions could play a critical role in integrating cortical and sensory inputs onto thalamocortical neurons.

**METHODS**

All experimental procedures were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the University of Illinois Animal Care and Use Committee. Care was taken to minimize the number of animals used to complete this series of experiments, and animals were deeply anesthetized to prevent any possible suffering.

**Brain slice preparation.** Thalamic slices were prepared from Sprague-Dawley rats (postnatal age: 14–21 days) as previously described (Govindaiah and Cox 2004, 2006). Briefly, animals were deeply anesthetized with sodium pentobarbital (50 mg/kg ip) and decapitated, and brains were placed into cold (4°C), oxygenated (95% O₂-5% CO₂) slicing solution containing (in mM): 2.5 KCl, 1 MgCl₂, 0.07 CaCl₂, 0.1 EGTA, 10 HEPES, 2 Na-ATP, and 0.4 Na-GTP. Whole cell recordings were obtained from dLGN neurons as described previously (Govindaiah and Cox 2006). Recording pipettes were pulled from borosilicate glass capillaries with tip resistances of 3–5 MΩ. For current-clamp experiments, pipettes were filled with a solution containing (in mM): 117 K-gluconate, 13 CsCl, 1 MgCl₂, 0.07 CaCl₂, 0.1 EGTA, 10 HEPES, 2 Na-ATP, and 0.4 Na-GTP. In some voltage-clamp experiments, electrodes were filled with a cesium-based solution containing (in mM): 117 Cs-gluconate, 13 CsCl, 1 MgCl₂, 0.7 CaCl₂, 0.1 EGTA, 10 HEPES, 1 Na-GTP, 2 MgCl₂, 2 CaCl₂, and 10 glucose at 32°C for ≥60 min before recording. The recording chamber was maintained at 32°C, and slices were continuously superfused with ACSF (3.0 ml/min).

**Recording procedures.** Whole cell recordings were obtained from dLGN neurons as described previously (Govindaiah and Cox 2006). Focal application of the mGluR agonist (RS)-3,5-dihydroxyphenylglycine (DHPG; 50 μM) was accomplished using pressure ejection via a glass pipette (2–3 psi, 10–25 ms). To estimate the spatial spread of pressure ejection, a fluorescent indicator (Alexa Fluor 594; 50 μM) was included in glass pipettes containing DHPG in subsets of neurons as described previously (Crandall et al. 2010). The ejection pressure (2–3 psi) was optimized based on spatial spread of the dye. The radial spread of the dye was estimated <20 μm for a given location.

**Histology.** Immunohistochemistry was performed as described earlier with minor modifications (Venkitaramani et al. 2009). Briefly, rats (postnatal age 17–21 days) were anesthetized with sodium pentobarbital and transcardially perfused with ice-cold 4% paraformaldehyde (PFA) in 0.1 M PBS. The brains were postfixed in 4% PFA overnight and cryoprotected in 10, 20, and 30% sucrose in PBS in succession. The cryopreserved brain tissue was sectioned along the horizontal plane at 40-μm thickness and stored in cryoprotective buffer at −20°C until processed for immunohistochemistry. Tissue sections were washed with PBS, permeabilized in PBS containing 0.2% Triton X-100 (PBS-T), and then blocked with 10% normal donkey serum (NDS) + 3% BSA in PBS-T for 1 h. The sections were incubated overnight at 4°C with primary antibodies [glutamic acid decarboxylases GAD65/67 (Santa Cruz Biotechnology), 1:300; GAD6 (Developmental Studies Hybridoma Bank), 1:400; mGluR5 (Abcam, 1:500)] diluted in 1% NDS + 1% BSA in PBS-T. The sections were washed and incubated with secondary antibodies from Invitrogen (donkey anti-goat Alexa Fluor 647, donkey anti-rabbit Alexa Fluor 555, and donkey anti-mouse Alexa Fluor 488, 1:400) at room temperature for 2 h. The sections were washed extensively with PBS-T and mounted onto precleaned/coated slides. The slides were coverslipped using ProLong Gold antifade, allowed to cure, and sealed with nail polish. Immunofluorescence was visualized on a Leica laser scanning confocal microscope.

**Data analyses.** IPSCs were detected and analyzed using Mini Analysis Program software (Synaptosoft, Leonia, NJ). The threshold for IPSC detection was 10 pA, and automatic detection was verified post hoc by visual analysis (Govindaiah and Cox 2006). Our detection criteria were also tested on recordings in the presence of the GABAA receptor antagonist SR-95531 (10 μM) to verify that false-positive responses were not being detected. For quantification of mIPSCs, mIPSC frequency was binned in 1-s increments. The average mIPSC frequency was calculated from 5-s windows before and following DHPG application. Population data are expressed as means ± SE, and P values <0.05 were considered statistically significant.

**RESULTS**

Bath application of the selective group I mGluR agonist DHPG (25 μM, 15 s) produces a robust, long-lasting increase in mIPSC activity in thalamocortical relay neurons (Fig. 1A). The mIPSCs were completely attenuated by the GABA_A receptor antagonist SR-95531 (10 μM; Fig. 1A). This increased mIPSC activity persisted in the presence of the sodium channel blocker TTX in a subset of neurons (6 of 9). In the remaining 3 neurons, DHPG did not alter mIPSC activity in TTX. These results indicate that the DHPG-mediated effects were similar to that observed in cat dLGN, producing TTX-sensitive increases in spontaneous IPSCs in a subpopulation of thalamic relay neurons (Cox et al. 1998; Cox and Sherman 2000). The TTX-insensitive increase in inhibition is attributable to activation of mGluRs on presynaptic dendrites of interneurons (F2 terminals), whereas the TTX-sensitive increase in inhibition is attributable to activation of axonal output (F1 terminals) via suprathreshold excitation of thalamic reticular nucleus neurons and/or local interneurons (Cox et al. 1998; Cox and Sherman 2000; Govindaiah and Cox 2004, 2006). In this study, we will refer to F2-positive and F2-negative responses, which signify TTX-insensitive and TTX-sensitive responses from our previous work.

Despite anatomic studies indicating that retinogeniculate innervation and accompanying triadic arrangements containing F2 terminals are preferentially located on proximal dendrites of...
Fig. 1. Proximal but not distal (RS)-3,5-dihydroxyphenylglycine (DHPG) application increases miniature inhibitory synaptic current (mIPSC) frequency in dorsal lateral geniculate nucleus (dLGN) thalamocortical neurons. A: current trace showing mIPSCs recorded from a thalamocortical neuron at holding potential of 0 mV in the presence of TTX (1 μM). The group I metabotropic glutamate receptor (mGlur1) agonist DHPG (25 μM) increases the frequency of mIPSCs (“b”) relative to baseline levels (“a”). The spontaneous IPSC activity is completely attenuated by GABAA receptor antagonist SR-95531 (“c,” 10 μM). B: typical thalamocortical neuron loaded with Alexa Fluor 594 (50 μM) to perform focal DHPG application under visual guidance. Whole-cell recordings were obtained from the soma (rec), whereas DHPG was focally applied at different locations surrounding the neuron as indicated by circles. C: representative current traces obtained from a dLGN thalamocortical neuron in the presence of TTX (1 μM) to show the effects of focal DHPG application at different locations. At distal site (100 μM), DHPG produces only an inward current. At more proximal sites, 50 and <10 μM, DHPG application produces a robust increase in the mIPSC frequency (“b”) compared with baseline activity (“a”) in addition to the inward current. Representative current traces before (“a”) and following DHPG application (“b”) are shown in expanded time scale at the bottom. The expanded traces at the bottom correspond to the underlined region in the top traces.

When applied at either proximal or distal locations, but the slow inward current was still present (Fig. 2B). The presence of 2 neuronal populations, F2-positive and F2-negative, is expected considering F2 innervation of thalamocortical neurons occurs in a subpopulation of thalamocortical neurons.

Within F2-positive neurons, the increase in mIPSC frequency produced by DHPG was dependent on the location along the dendritic arbor (Fig. 2Aii). DHPG application at the proximal dendrite (<10 and 25 μm from soma) resulted in robust, significant increase in mIPSC frequency (<10 μm: pre-DHPG: 7.9 ± 0.7 Hz, DHPG: 22.1 ± 1.5 Hz, P < 0.001, n = 10, paired t-test; 25 μm: pre-DHPG: 7.3 ± 1.5 Hz, DHPG: 17.0 ± 2.5 Hz, P < 0.01, n = 6). At intermediate distances (~50 μm), DHPG produced a significant but smaller magnitude increase in mIPSC frequency (pre-DHPG: 6.1 ± 1.2 Hz, DHPG: 8.7 ± 1.9 Hz, n = 7, P = 0.04, paired t-test). DHPG application of DHPG to distal dendrites (~100 μm away from the soma) did not significantly increase mIPSC frequency (pre-DHPG: 6.7 ± 1.1 Hz, DHPG: 9.0 ± 1.9 Hz, n = 7; P > 0.05, paired t-test). In the overall population, the peak effect of DHPG on mIPSC activity reveals a significant difference in the
magnitude of effects comparing proximal dendrite to distal dendrite application \((F = 12.4, P < 0.001, n = 10, 1\text{-way ANOVA}).

In the F2-negative neurons \((n = 6)\), DHPG did not significantly alter mIPSC activity at proximal or distal locations (Fig. 2Bi). DHPG application to proximal dendrite \((<10 \mu m)\) resulted in a small, insignificant increase in mIPSC activity from \(6.3 \pm 1.2 \text{ to } 7.2 \pm 1.3\) Hz \((n = 6; P > 0.05, \text{ paired } t\text{-test})\). Similarly, DHPG application at distal sites \((100 \mu m)\) did not significantly alter mIPSC activity \((control: 7.1 \pm 1.8 \text{ Hz}, DHPG: 7.9 \pm 2.1 \text{ Hz}, n = 6, P > 0.05, \text{ paired } t\text{-test})\).

Considering our previous results indicate that increased inhibition by DHPG is mediated specifically by mGluR5, we tested whether the focal activation by DHPG on IPSCs is significantly altered by the selective mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine hydrochloride (MPEP). In control conditions, DHPG \((50 \mu M)\) application to proximal dendrites significantly increased the mIPSC frequency from \(8.2 \pm 1.2 \text{ to } 23.1 \pm 1.9\) Hz \((Fig. 3; n = 7; P < 0.0001, \text{ paired } t\text{-test})\). In the presence of MPEP \((50–75 \mu M)\), subsequent DHPG application produced a minimal increase in IPSC frequency \((MPEP: 7.9 \pm 1.4 \text{ Hz}, MPEP+DHPG: 9.9 \pm 1.4 \text{ Hz}, \ n = 7)\) confirming the role of mGluR5.

Colocalization of mGluR5 and GAD. Considering previous studies demonstrating the localization of mGluR5 to dendrites of local GABAergic interneurons were carried out in cat dLGN (Godwin et al. 1996a), we determined whether such colocalization occurs within the rat dLGN even though our previous pharmacological data suggest such a distribution (Govindaiah and Cox 2004, 2006). To determine the expression profile of mGluR5 and GABAergic terminals in dLGN, we performed triple labeling with mGluR5, GAD65, and GAD65/67. The GABAergic interneurons in the dLGN were immunostained by both GAD65 (red) and GAD65/67 (blue) antibody (Fig. 4A).

Fig. 4. Expression of mGluR5 and glutamic acid decarboxylase (GAD) in rat dLGN. A and B: colocalization of mGlur5 (green) with GAD65 (red) and GAD65/67 (blue) in cell bodies (white arrowheads) and processes (yellow arrowheads) of GABAergic interneurons. C: higher magnification of region in B illustrating colocalization of mGlur5 in a GAD-containing process. D–F: higher magnification of a representative region showing processes (yellow arrowheads) labeled with GAD67 alone that colocalize with mGlur5 immunoactivity.

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The GABA-containing cell bodies are indicated by white arrowheads (Fig. 4, A and B). The GAD65 immunoreactivity completely colocalized with GAD65/67, as indicated by magenta color (Fig. 4, A–C). However, we observed regions that were only labeled with GAD65/67 antibody but not GAD65 antibody (blue staining), representing GAD67-specific immunoreactivity (Fig. 4, D–F). This is consistent with previously described differences in GAD65 and GAD67 staining (Escalpez et al. 1994). The mGluR₅ (green) immunofluorescence extensively colocalized with both GAD65 and GAD65/67 staining (Fig. 4, A–C). We did not detect mGluR₃ immunolabeling in areas devoid of GAD65/67 staining. Interestingly, we also detected mGluR₃ immunofluorescence in processes (indicated by yellow arrowheads) that were exclusively labeled by GAD67 alone (Fig. 4, D–F). Thus immunohistochemistry supports the electrophysiology data that mGluR₅ is preferentially distributed in presynaptic terminals of GABAergic interneurons.

Postsynaptic actions of mGluR₁ in thalamocortical neurons. Anatomic studies indicate that mGluR₁ are localized to thalamocortical neuron dendrites (Godwin et al. 1996a; Vidnyanszky et al. 1996), and the activation of mGluR₁ has been associated with corticothalamic but not retinogeniculate innervation. Considering corticothalamic innervation may be preferentially distributed to distal dendrites of thalamocortical neurons (Erisir et al. 1997), we tested whether the postsynaptic depolarizing actions of mGluRs may be spatially distributed. Bath application of DHPG (25 μM) in the presence of TTX (1 μM) results in a long-lasting membrane depolarization (Fig. 5A; 11.2 ± 3.4 mV, n = 9), but the source of such actions is unclear. Using focal DHPG application in the presence of TTX, DHPG (50 μM) elicited stable membrane depolarizations when applied at 30-s intervals (Fig. 5B, i and ii). DHPG elicited average membrane depolarizations of 7.6 ± 0.7 mV (n = 14) and 10.1 ± 0.8 mV (n = 14) when focally applied to distal (50–100 μm) and proximal (0–25 μm) dendrites, respectively (Fig. 5Bi). The amplitudes of the depolarizations at these different locations were statistically significant with larger responses evoked by proximal application (P < 0.001, n = 14, paired t-test). As illustrated in Fig. 5C, the selective mGluR₅ antagonist MPEP (50–75 μM) did not significantly alter the membrane depolarizations elicited by DHPG application to proximal dendrites (DHPG: 8.6 ± 0.7 mV, MPEP+DHPG: 7.9 ± 1.0 mV, n = 14; P > 0.9, paired t-test) or to distal dendrites (DHPG: 7.6 ± 0.9 mV, MPEP+DHPG: 6.9 ± 0.8 mV, n = 5; P > 0.8, paired t-test). In contrast, the selective mGluR₁ antagonist LY 367385 (100 μM) strongly attenuated the DHPG-mediated depolarization (Fig. 5C). The depolarization produced by focal DHPG application onto proximal dendrites (DHPG: 8.6 ± 1.4 mV, LY 367385+DHPG: 1.5 ± 0.3 mV, n = 13; P < 0.0001, paired t-test) or distal dendrites (DHPG: 7.3 ± 1.0 mV, LY 367385+DHPG: 1.3 ± 0.4 mV, n = 6; P < 0.0002, paired t-test) were significantly attenuated by LY 367385, indicating the role of mGluR₁ on the postsynaptic depolarization of thalamocortical neurons.

**DISCUSSION**

The present study provides novel physiological evidence that mGluR₅ and mGluR₁ exert distinct effects in a spatially distributed manner. mGluR₅ are localized to dendrites of GABAergic interneurons that synapse onto proximal dendrites of thalamocortical neurons, and activation of these receptors leads to long-lasting inhibition in the thalamocortical neurons. In contrast, mGluR₁ is localized to dendrites of thalamocortical neurons, and the activation of these receptors results in long-lasting membrane depolarization. The differential localization of these mGluR subtypes, association with different neuronal types and distinct actions within the dLGN circuitry, could significantly influence the throughput of retinogeniculate transmission to the primary visual cortex.

**The actions of mGluR₅ and mGluR₁ in dLGN.** Multiple mGluR-dependent actions have been described in dLGN in both in vivo and in vitro preparations, which include both
inhibitory and excitatory actions mediated by presynaptic and/or postsynaptic mechanisms (Alexander and Godwin 2005, 2006; Cox et al. 1998; Cox and Sherman 2000; Godwin et al. 1996b; Govindaiah and Cox 2006; McCormick and von Krosigk 1992; Rivadulla et al. 2002; Turner and Salt 1999, 2000; Zheng et al. 2008). We have previously demonstrated that activation of mGluR2 by agonists or high-frequency synaptic stimulation of retinogeniculate axons leads to long-lasting inhibition in thalamocortical neurons by enhancing GABA release from presynaptic dendrites of interneurons (F2 synapses; Cox et al. 1998; Cox and Sherman 2000; Govindaiah and Cox 2004, 2006). Activation of these F2 terminals occurs independent of action potential discharge in interneurons and is activity-dependent and thought to influence strongly the retinogeniculate synapse, considering the close proximity of F2 terminals to retinogeniculate synapses onto the dendrite of the thalamocortical neuron, which typically forms triadic arrangements. In the present study, we examined the spatial distribution of these F2 synapses along the thalamocortical relay neuron by focal activation of mGluRs. We found that mGluR2-dependent activation of F2 synapses occurs on proximal dendritic sites but not at distal dendritic sites. These findings are consistent with the anatomic localization of retinogeniculate inputs and associated triadic arrangements that are preferentially found on proximal dendrites of dLGN thalamocortical neurons.

Second, we found that focal activation of mGluR1 resulted in slow membrane depolarizations in the dLGN relay neuron. Previously, it has been found that mGluR1 receptors are localized with corticothalamic innervation, which typically is found on distal dendrites of relay neurons (Erisir et al. 1997; Godwin et al. 1996a). One would predict that mGluR activation would thus produce depolarizing actions on distal dendrites, which it did; however, we also found strong depolarizations with DHPG application to proximal dendrites indicating that mGluR1 receptors are also near the soma. It is unknown whether these proximal receptors are innervated by corticothalamic inputs or other excitatory synaptic afferents, although it is unlikely to be retinogeniculate inputs because optic tract stimulation cannot evoke an mGluR2-dependent depolarization in relay neurons (Govindaiah and Cox 2004; McCormick and von Krosigk 1992).

**Physiological significance.** In the visual pathway, dLGN transfers visual information from retina to the primary visual cortex in a dynamic manner (Guillery and Sherman 2002; Sherman 2001, 2005; Sherman and Guillery 2002). At this level, the relay of visual information is regulated by a complex network of synaptic connections, including complex GABAergic innervation from local interneurons (Guillery and Sherman 2002; Sherman 2005; Sherman and Guillery 2002). The GABAergic circuitry within the dLGN has been shown to contribute significantly to the integration of ascending sensory signals, altering the time course of sensory responses and the tuning of sensory-receptive field properties (Sillito and Kemp 1983; Wang et al. 2011; Zhu and Lo 1998). In addition, inhibitory processes also play a crucial role in the regulation of intrathalamic oscillations associated with sleep/wake states (Guido and Weyand 1995; Steriade et al. 1993; von Krosigk et al. 1993). The present study tested the hypothesis that pre- and postsynaptic mGluR subtypes display diverse distribution and may have distinct functional roles in the visual thalamus. We demonstrate that DHPG application to proximal but not distal dendrites produces long-lasting GABA_A receptor-mediated inhibition in thalamocortical neurons. Our physiological evidence is supported by anatomic evidence suggesting the presence of triads formed between retinal axon, interneuron dendrites, and thalamocortical dendrites on proximal dendrites of thalamocortical neurons (Hamos et al. 1985; Wilson 1989). The proximity of the F2 terminals with retinogeniculate afferents position this mGluR2-mediated inhibition in action to regulate/modulate the magnitude of excitations via the retinogeniculate pathway.

In contrast, activation of mGluR1 produces a postsynaptic depolarization along the dendritic axis. Previous studies indicate that activation of corticothalamic, but not retinogeniculate, afferents can produce an mGluR-dependent depolarization in relay neurons. Anatomic evidence suggests that corticothalamic inputs are preferentially distributed on distal dendrites (Erisir et al. 1997; Wilson et al. 1984), which may lead to smaller influences on somatic activity of relay neurons; however, our findings suggest the presence of mGluR1-mediated depolarization of proximal dendrites as well. Although it appears a bit puzzling that mGluR activation would produce apparent opposing actions on proximal dendrites, it will be important for future studies to delineate whether these opposing actions are actually mediated by either different afferent synaptic pathways or perhaps different activation patterns. Previous in vivo studies suggest that the mGluR1-mediated increase in excitation may serve to modulate the firing mode of these thalamic neurons (Godwin et al. 1996b) and thereby alter thalamocortical throughput in a state-dependent manner.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


**REFERENCES**


