Cell Type–Specific GABA$_A$ Receptor–Mediated Tonic Inhibition in Mouse Neocortex

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Vardy I, Drasbek KR, Dósa Z, Jensen K. Cell type–specific GABA$_A$ receptor–mediated tonic inhibition in mouse neocortex. J Neurophysiol 100: 526–532, 2008. First published May 7, 2008; doi:10.1152/jn.01224.2007. Activity of extrasynaptic GABA$_A$ receptors mediating tonic inhibition is thought to play an important role for the excitability of the mammalian cerebral cortex. However, little is known about the cell type–specific expression of tonic inhibition in particular types of cortical interneurons. Here, we used transgenic mice expressing green fluorescent protein (GFP) in somatostatin–positive (SOM) interneurons and investigated tonic inhibition in SOM interneurons versus pyramidal cells in neocortical layers 2/3. In brain slices, pyramidal cells showed a tonic current of 66 ± 19 pA in response to the $\delta$-subunit selective GABA$_A$ agonist THIP (1 $\mu$M). On the other hand, tonic inhibition was absent in SOM interneurons (8 ± 1 pA) in response to THIP. As opposed to pyramidal cells, SOM interneurons were also insensitive to the $\delta$-subunit preferring neurosteroid allotetrahydroidoxy corticosterone (THDOC) (100 nM) and elevated endogenous GABA levels in the slice. Finally, SOM interneurons received only 45% of the phasic charge transfer during GABA$_A$ receptor–mediated synaptic activity compared with pyramidal cells.

Because tonic inhibition has not been studied in SOM-positive interneurons, we here used transgenic “GIN” mice that express enhanced green fluorescent protein (EGFP) in SOM interneurons in the neocortex (Oliva et al. 2000). We found a cell type–specific tonic inhibition in layer 2/3 neurons, which may have implications for the control of the excitability of this brain region.

METHODS

Preparation of brain slices

Mice were kept in a university animal facility with a 12/12-h light/dark cycle with unrestricted access to food and water. Postnatal day 14–24 (P14–P24) male somatostatin-EGFP “GIN” mice (Oliva et al. 2000) [strain FVB-TgN(GadGFP)45704Swn, Jackson Laboratories] were anesthetized with isoflurane, in accordance with Danish and European legislation regarding laboratory animals. The mice were decapitated, and the brains were dissected out and transferred to ice-cold artificial cerebrospinal fluid (ACSF) composed of (in mM) 126 NaCl, 2.5 KCl, 2 CaCl$_2$, 2 MgCl$_2$, 1.25 NaH$_2$PO$_4$, 26 NaHCO$_3$, and 10 d-glucose (osmolality 305–315 mosmol/kg), pH 7.4, when bubbled with carbogen (5% CO$_2$, 95% O$_2$). Three hundred fifty-micrometer-thick coronal slices were cut on a Vibratome 3000 Plus (Vibratome, St. Louis, MO), and slices rested for 1 h before recording. To improve slice quality, 3 mM kynurenic acid, 0.2 mM ascorbic acid, and 0.2 mM pyruvic acid were added during slicing and storage.

Electrophysiology

Slices were placed in a recording chamber (33 ± 1°C) and perfused with bubbled ACSF at 2–3 ml/min. Layer 2/3 neurons of the frontoparietal cortex were visualized by a custom-built infrared microscope (Versascope, E. Marton Electronics, Cacoga Park, CA) equipped with a ×40 water-immersion objective (Olympus, Ballerup, Denmark) and a CCD100 camera (DAGE-MTI, Michigan City, IN). Whole cell patchclamp recordings were carried out using a MultiClamp 700B amplifier (Molecular Devices, Union City, CA). For current-clamp recordings, the patch-pipettes (resistances 3–5 MΩ) contained (in mM) 135 K-methylsulfate, 10 KCl, 0.3 Na-GTP, 2 Mg-ATP, and 10 HEPES, pH 7.2, with KOH, osmolality 280–290 mosmol/kg adjusted with sucrose. Neurons with a resting membrane potential more negative than −50 mV were included. For voltage-clamp recordings, the patch-pipettes were filled with (in mM) 140 CsCl, 2 MgCl$_2$, 0.05 EGTA, and 10 HEPES, adjusted to pH 7.2 with CsOH (280–290 mosmol/kg). Giga seals (>1 GΩ) were always obtained before break-in. SOM interneurons were identified by GFP fluorescence from the soma clearly observed under epifluorescence. Throughout the voltage-clamp recordings, the whole cell capacitance and series resistance were noted, and resistances were compensated by 70% (lag 10 μs). Recordings were discontinued if series...
FIG. 1. Phasic inhibition in somatostatin-positive interneurons in neocortex is smaller, slower, and less frequent than in pyramidal cells. A: representative current-clamp recording from a layer 2/3 pyramidal (PYR) cell. The neuron was regular spiking and showed frequency adaptation in response to a 1-s-long depolarization. Current injections were +160 or −160 pA. B: representative current-clamp recording from a green fluorescent protein (GFP)-positive somatostatin (SOM) interneuron in layer 2/3, which showed frequency adaptation and a sag when hyperpolarized. Current injections were +160 or −160 pA. C: the input resistance of SOM interneurons was higher (214 ± 12.2 MΩ, n = 5) than of PYR cells (122 ± 12.5 MΩ, n = 6). D and E: spontaneous inhibitory postsynaptic currents (sIPSCs) recorded from layer 2/3 PYR cells and SOM interneurons. sIPSCs were smaller, slower, and less frequent in SOM interneurons compared with pyramidal cells. Averages of sIPSCs from these cells show the slower sIPSC decay in SOM interneurons.
resistances increased by >50% or exceeded 20 MΩ. GABA_A receptor agonists and GAT1 inhibitors were perfused for 5–10 min, whereas the neurosteroid allopregnanolone (THDOC) was perfused for 5–15 min before tonic currents were assessed to ensure a comparable exposure of drugs to the slices.

Data acquisition and analysis

Currents were low-pass filtered (8-pole Bessel) at 3 kHz, digitized at 20 kHz, and acquired using a BNC-2110 D/A converter and a PCI-6014 board (National Instruments, Austin, TX) and custom-written LabVIEW 6.1–based software (EVAN v. 1.4, courtesy of Istvan Mody), which was also used to detect and analyze spontaneous inhibitory postsynaptic currents (sIPSCs) with typical amplitude detection thresholds of 7–8 pA. All events were inspected before an average of 50–100 events was made. Event amplitude, 10–90% rise time, and frequency were measured, whereas the IPSC weighted decay-time constant (τ_w) was calculated using double-exponential fits. In most experiments, injection of the GABA_A receptor antagonist 2-(3-carboxypropyl)-3-amino-6-methoxy-phenyl-pyridazinium bromide (SR95531 >100 μM) into the slice chamber was used to show a GABA_A receptor–mediated tonic current (15 μl of a 6 mM SR95531 solution injected into a 0.80 to 0.85 ml slice chamber yielding a final concentration of 100–110 μM). When the more slowly acting GABA_A antagonist picrotoxin (PTX) was used, it was bath perfused at 100 μM. Current samples (length 5 ms) were obtained every 100 ms and plotted against time to estimate the tonic current (Fig. 2A) (Nusser and Mody 2002). The mean tonic current was calculated in 4-s-long segments at three time points: just before SR95531 injection (denoted b) and 20 s before (a) and after (c) this time point. The tonic current was taken as c − b, whereas the variations in the baseline (b − a) were used to assess the stability of the recording (typically ~6 pA). Because small variations in cell size between pyramidal cells and SOM interneurons were seen (20.6 ± 1.0 pF, n = 20 and 18.6 ± 0.54 pF, n = 18, respectively), the tonic currents were normalized to the cell capacitance (pA/pF) in histograms. Unpaired Student’s t-test was used to compare means with two-tailed P < 0.05 as the significance level. Data are presented as means ± SE, with n indicating the number of neurons.

Solutions and drugs

All drugs were from Sigma (St. Louis, MO) except pyruvic acid, which was purchased from MP Biomedicals (Irvine, CA). Stock solution of THDOC (100 μM) was prepared in ACSF containing 70% DMSO, whereas SR95531 stock (6 mM) was prepared in ACSF containing 50% DMSO. The final DMSO concentrations (~1%) had no effect on the tonic currents (Drasbek et al. 2007).

RESULTS

To examine distinct cells types with respect to phasic and tonic GABAergic inhibition in the mouse neocortex, we used transgenic “GIN” mice expressing EGFP in SOM interneurons (Oliva et al. 2000). Because phasic and tonic inhibition has previously been studied in pyramidal (PYR) cells, we used these cells for comparison (Drasbek and Jensen 2006). PYR cells were identified under infrared videomicroscopy in layer 2/3 displaying a large pyramidal-shaped soma and a prominent apical dendrite projecting >100 μm toward layer 1 (Drasbek et al. 2007), whereas SOM interneurons were identified by their green fluorescence. First, we performed current-clamp recordings from both cell types, showing that pyramidal cells were regular spiking (Fig. 1A) and had a relatively low input resistance (122 ± 12.5 MΩ, n = 6; Fig. 1C). SOM interneurons showed frequency adaptation (Fig. 1B), were never fast-spiking, displayed a sag in response to hyperpolarizing current injection, and had a higher input resistance (214 ± 12.2 MΩ, n = 5).

Phasic inhibition in pyramidal cells versus SOM interneurons

When PYR cells were voltage-clamped at a V_h hold of −70 mV using a CsCl-based pipette solution, sIPSCs appeared as fast inward currents (E_Cl ~ 0 mV; Fig. 1D) and had mean amplitudes of 43.7 ± 2.6 pA (n = 11), weighted decay time constants of 20.6–100 ms and plotted against time to estimate the tonic current (Fig. 2A) (Nusser and Mody 2002). The mean tonic current was calculated in 4-s-long segments at three time points: just before SR95531 injection (denoted b) and 20 s before (a) and after (c) this time point. The tonic current was taken as c − b, whereas the variations in the baseline (b − a) were used to assess the stability of the recording (typically ~6 pA). Because small variations in cell size between pyramidal cells and SOM interneurons were seen (20.6 ± 1.0 pF, n = 20 and 18.6 ± 0.54 pF, n = 18, respectively), the tonic currents were normalized to the cell capacitance (pA/pF) in histograms. Unpaired Student’s t-test was used to compare means with two-tailed P < 0.05 as the significance level. Data are presented as means ± SE, with n indicating the number of neurons.

FIG. 2. Somatostatin-positive interneurons in neocortex display no THIP-induced tonic inhibition. A: in the presence of the δ-subunit preferring GABA_A agonist THIP (1 μM), the PYR cell displayed a tonic current of 47 pA, which was shown by the GABA_A receptor antagonist SR95531 (>100 μM, applied at the horizontal bar above trace). B: the SOM interneuron showed no appreciable tonic GABA_A receptor–mediated tonic current in the presence of THIP. C: histogram showing the average tonic currents (normalized to the cell capacitance) in PYR and SOM cells. The THIP-induced tonic current was 2.9 ± 0.6 pA/pF in PYR (n = 6) but was basically absent in SOM interneurons (n = 7; **P < 0.01).
6.9 ± 0.5 ms, and mean frequencies of 9.9 ± 2.5 Hz. On the other hand, sIPSCs in SOM interneurons (Fig. 1E) were smaller (30.0 ± 2.4 pA, n = 10) with slower decay time constants (10.1 ± 0.7 ms) and lower frequencies (5.4 ± 2.0 Hz). The total charge transfer per average sIPSC was 83% in SOM interneurons compared with PYR cells. Subsequently, the lower sIPSC frequency in SOM neurons led to an overall low level of phasic inhibition in this cell type (45% charge transfer per time compared with PYR cells).

**Tonic inhibition induced by THIP in layer 2/3 neurons**

To examine whether the relatively weak phasic inhibition in SOM interneurons was counterbalanced by tonic inhibition, we

![Graphs showing tonic inhibition](http://jn.physiology.org/)

**Fig. 3.** Physiological levels of GABA do not induce tonic currents in SOM interneurons. A: when ambient GABA levels were elevated to physiological levels by perfusion of 0.8 μM GABA and 10 μM NO-711, PYR neurons displayed a clear tonic current after application of SR95531 (>100 μM). The holding current was measured every 100 ms and plotted against time and used for estimation of the tonic current. Horizontal bars indicate the application of SR95531. B: in contrast, no tonic current was found in the SOM interneuron in the presence of 0.8 μM GABA and 10 μM NO-711. C: using another GABAA receptor antagonist picrotoxin (PTX), PYR cells showed a tonic current of 22 pA in the presence of 0.8 μM GABA and NO-711. Traces were obtained before and after bath perfusion of PTX (100 μM). The plot shows the holding current plotted every 100 ms during the PTX perfusion. D: SOM interneuron showed still no tonic current using PTX as an antagonist. E (left): histogram of the averages of the normalized tonic currents in PYR cells (n = 6) and SOM (n = 5) interneurons using SR95531 (>100 μM) as an antagonist. Tonic currents were essentially absent in SOM neurons (***P < 0.01), showing that physiological levels of GABA were not capable of inducing tonic currents in these cells. Right: similar results were obtained when PTX (100 μM) was used as an antagonist in PYR (n = 5) PYR cells and SOM interneurons (n = 5).
perfused the δ-subunit selective agonist THIP at 1 μM, which exclusively activates extrasynaptic GABA<sub>δ</sub> receptors (Chandra et al. 2006; Drasbek and Jensen 2006; Maguire et al. 2005). When the GABA<sub>δ</sub>-antagonist SR95531 (>100 μM) was injected into the slice chamber (Fig. 2A), the tonic current appeared in PYR cells as an outward shift in the holding current of 66.2 ± 19.0 pA (n = 6). However, in SOM interneurons, little or no tonic current was observed (7.8 ± 0.8 pA, n = 7; Fig. 2B). These data indicate that SOM interneurons lack functional δ-subunit containing extrasynaptic GABA<sub>δ</sub> receptors, which can mediate a tonic current (Fig. 2C).

**Tonic inhibition induced by GABA in layer 2/3 neurons**

We hypothesized that SOM interneurons could express other extrasynaptic GABA<sub>δ</sub> receptor subtypes insensitive to THIP, and we therefore used the natural agonist GABA. The ambient extracellular GABA level was raised to presumed physiological levels by perfusing 0.8 μM GABA and the GABA-uptake inhibitor NO-711 (10 μM). In PYR cells, this induced a SR95531-sensitive tonic current of 23.3 ± 3.5 pA (n = 6; Fig. 3A), but still no tonic current was seen in SOM interneurons (Fig. 3B; 4.2 ± 1.5 pA, n = 5). Earlier, it was shown that tonic currents in some interneurons can only be blocked by PTX (Bieda and MacIver 2004). Therefore, in the presence of GABA and NO-711 we bath-perfused PTX (100 μM) to PYR cells (n = 5) and SOM interneurons (n = 5; Fig. 3, C and D), still showing no tonic current in the SOM neurons (26.5 ± 3.5 pA in PYR vs. 5.6 ± 2.3 pA in SOM). The normalized tonic currents are summarized in Fig. 3E.

**Tonic inhibition in SOM interneurons is not enhanced by the neurosteroid THDOC**

Finally, to substantiate the finding that THIP did not induce a tonic current in SOM interneurons, we also used the δ-subunit preferring modulator and neurosteroid THDOC in combination with GABA and NO-711. As δ-subunit containing GABA<sub>δ</sub> receptors are expressed in PYR cells (Drasbek and Jensen 2006), THDOC (100 nM) was expected to increase the GABA/NO-711 induced tonic current in these cells. Indeed, a significant enhancement of the tonic current on THDOC treatment was observed (by 178% to 64.6 ± 18.9 pA, n = 9; Fig. 4A). On the other hand, THDOC did not influence the GABA/NO-711 tonic current in SOM interneurons (Fig. 4B; 6.0 ± 1.1 pA, n = 6). Even when THDOC was incubated in the slices for longer periods (60–120 min, n = 2), which is thought to cause rapid insertion of δ-containing receptors into the membranes (Maguire and Mody 2007), no tonic current could be shown in SOM interneurons (data not shown). Again, this indicates that δ-containing receptors are not expressed in SOM interneurons.

**Prolongation of phasic inhibitory currents by THDOC**

In PYR cells, THDOC (100 nM) prolonged the decay time constant of sIPSCs from 6.9 ± 0.5 to 11.6 ± 0.5 ms (by 68%; Fig. 4C). This prolongation could be related to enhanced GABA affinity of δ-containing receptors activated by synapticly released GABA (Wei et al. 2003). Interestingly, this prolongation by THDOC was also absent in SOM interneurons, again suggesting that δ-containing receptors are absent in

![FIG. 4. THDOC does not enhance tonic currents in SOM interneurons. A: application of the neurosteroid THDOC (100 nM) for 10 min in the presence of GABA (0.8 μM) and NO-711 (10 μM) increased the tonic current in PYR cells to 64 pA. B: in contrast, THDOC did not affect the tonic current in SOM interneurons. C: THDOC prolonged the sIPSC decay in PYR cells but not in SOM interneurons. D: histogram showing the average normalized tonic currents in PYR cells and SOM interneurons. A negligible tonic current was observed in SOM neurons (n = 9; **P < 0.01) compared with PYR cells (n = 6).]
SOM interneurons. A summary of sIPSC properties in all drugs combinations is found in Table 1.

**DISCUSSION**

Using transgenic mice expressing GFP in SOM interneurons, we studied GABAergic inhibition in two cell types of the mouse neocortex. Although PYR cells in layer 2/3 of these mice exhibited phasic and tonic currents similar to those found in wild-type mice (Drasbek and Jensen 2006), we found that SOM interneurons displayed no tonic inhibition, in combination with a relatively low frequency of phasic inhibition. The inability of GABA, THIP, and THDOC to enhance a tonic current indicated that SOM interneurons lack the typical extrasynaptic δ-containing GABA_$$\text{A}$$_$$\text{a}$$ receptors, and possibly other extrasynaptic GABA_$$\text{A}$$_$$\text{a}$$ receptors. The implications of these findings are that ambient GABA will have little or no influence on the activity of these SOM interneurons and that they cannot be tonically influenced by the sleep drug THIP or neurosteroids such as THDOC.

**Tonic inhibition in interneurons**

Only few reports have previously described tonic inhibition in defined sets of cortical interneurons. In rat neocortical layer I interneurons, tonic inhibition could be induced by increasing endogenous GABA in the slice using GABA uptake inhibitors (Keros and Hablitz 2005). In the molecular layer of the dentate gyrus, interneurons expressing an unusual ($$\text{a}$$_$$\text{i}$$,$$\text{b}$$) GABA_$$\text{A}$$_$$\text{a}$$ receptor composition display a tonic current comparable with that of granule cells (Glykys et al. 2007). Furthermore, in stratum radiatum of CA1 hippocampus in guinea pigs, a strong tonic inhibition was observed in interneurons, which under some circumstances, superseded that of pyramidal cells (Semyanov et al. 2003). These observations have led to the paradigm that interneurons are generally under a strong tonic inhibitory influence. However, our study showed that certain types of identified interneurons exhibit no tonic inhibition in response to a range of pharmacological treatments, such as raising ambient GABA or applying selective agonists for typical extrasynaptic δ-subunit containing receptors. Thus we suggest that tonic inhibition in cortical interneurons is cell specific and more complex than previously assumed.

**Somatostatin-positive interneurons in neocortex**

Somatostatin-positive interneurons in the hippocampus and neocortex share several features and are generally thought to be low-threshold or regular-spiking (Halabisky et al. 2006). Classical examples of SOM interneurons include the dendritically targeting oriens lacunosum-molecular cell of the hippocampus, and the neocortical Martinotti cell. SOM interneurons have caught special attention, as they seem to be vulnerable in disorders such as epilepsy and brain trauma (Lowenstein et al. 1992). To facilitate the study of these neurons, "GIN" mice expressing GFP in SOM interneurons were generated, which express GFP in a relatively large subset of SOM-positive cells (Oliva et al. 2000). Although some GFP-positive SOM cells co-express calretinin, they are never positive for parvalbumin, neuropeptide y (NPY), or nitric oxide synthase (Xu et al. 2006). Although a certain diversity of GFP neurons in GIN mice has been reported (Halabisky et al. 2006), we found a very homogeneous (always absent) response to extrasynaptic GABA_$$\text{A}$$_$$\text{a}$$ receptor agonists.

**Lack of tonic inhibition in somatostatin-positive interneurons**

Typical extrasynaptic GABA_$$\text{A}$$_$$\text{a}$$ receptors contain $$\text{a}$$_$$\text{b}$$ or $$\text{a}$$_$$\text{b}$$δ-subunit combinations. Since a recent study found no contribution from $$\text{a}$$_$$\text{s}$$ subunits to GABA responses in deep neocortical interneurons (Scimemi et al. 2006), we primarily focused on δ-subunits. The lack of effect of THIP and THDOC points to the absence of δ-subunits, and perhaps of presumed extrasynaptic receptors able of mediating a tonic current in general, because elevated levels of endogenous GABA did not elicit a tonic current. The inability of THDOC to prolong sIPSCs corroborates the absence of δ-containing receptors, which in other brain regions are activated by spill-over of synaptically released GABA (Wei et al. 2003). Finally, the relatively low frequency of sIPSCs recorded in SOM interneurons was also recently found by Yuste and coworkers, because SOM cells received only one third of inhibitory events per time compared with parvalbumin- or NPY-expressing interneurons (Dumitriu et al. 2006). Altogether, this points to an overall weak GABAergic inhibitory influence on SOM interneurons in neocortex.

**TABLE 1. sIPSC properties in the different drug combinations**

<table>
<thead>
<tr>
<th>Average sIPSCs</th>
<th>Amplitude, pA</th>
<th>RT (10–90%), ms</th>
<th>Decay $$\tau_m$$, ms</th>
<th>Frequency, Hz</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control sIPSCs Layer 2/3 PYR</td>
<td>43.7 ± 2.6</td>
<td>0.40 ± 0.04</td>
<td>6.9 ± 0.5</td>
<td>9.9 ± 2.5</td>
<td>11</td>
</tr>
<tr>
<td>THIP (1 μM)</td>
<td>41.4 ± 3.3</td>
<td>0.33 ± 0.04</td>
<td>8.2 ± 0.7</td>
<td>7.0 ± 2.5</td>
<td>5</td>
</tr>
<tr>
<td>GABA (0.8 μM) + NO-711 (10 μM)</td>
<td>42.9 ± 4.4</td>
<td>0.41 ± 0.05</td>
<td>7.4 ± 0.8</td>
<td>9.4 ± 2.8</td>
<td>6</td>
</tr>
<tr>
<td>GABA (0.8 μM) + NO-711 (10 μM) + THDOC (100 nM)</td>
<td>36.8 ± 5.2</td>
<td>0.48 ± 0.06</td>
<td>11.6 ± 0.5* P = 3.0 × 10^{-6}</td>
<td>12.2 ± 3.0</td>
<td>7</td>
</tr>
<tr>
<td>Control sIPSCs SOM</td>
<td>30.0 ± 2.4* P = 0.003</td>
<td>0.39 ± 0.05 NS P = 0.69</td>
<td>10.1 ± 1.2* P = 0.024</td>
<td>5.4 ± 2.0 NS P = 0.19</td>
<td>10</td>
</tr>
<tr>
<td>THIP (1 μM)</td>
<td>29.8 ± 2.0</td>
<td>0.31 ± 0.03</td>
<td>11.8 ± 0.9</td>
<td>5.9 ± 0.9</td>
<td>7</td>
</tr>
<tr>
<td>GABA (0.8 μM) + NO-711 (10 μM)</td>
<td>30.8 ± 3.0</td>
<td>0.40 ± 0.04</td>
<td>10.0 ± 0.4</td>
<td>5.4 ± 1.0</td>
<td>7</td>
</tr>
<tr>
<td>GABA (0.8 μM) + NO-711 (10 μM) + THDOC (100 nM)</td>
<td>26.8 ± 1.7</td>
<td>0.34 ± 0.04</td>
<td>10.1 ± 1 NS P = 0.97</td>
<td>9.7 ± 1.8</td>
<td>5</td>
</tr>
</tbody>
</table>

sIPSCs recorded from 2 different types of neurons in layer 2/3 of neocortex: PYR and SOM. Values are mean ± SE with respect to sIPSC amplitude, RT, decay kinetics, and frequency. Data were obtained from averages of 50–100 consecutive sIPSCs for each cell and values were pooled. Number of cells (n) is shown to the right. *P < 0.001. †P < 0.01. ‡P < 0.05. sIPSCs, spontaneous inhibitory postsynaptic potentials; RT, rise time; PYR, pyramidal cells; THIP, 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol; THDOC, allotetrahydrodeoxycorticosterone; SOM, somatostatin; NS, not significant.
**Functional consequences**

Scanziani and coworkers recently found that the activity of a single layer 2/3 pyramidal cells can elicit widespread feedback inhibition via SOM interneurons and that these neurons could be recruited supralinearly (Kapfer et al. 2007). Although GABAergic inhibition is only one of several mechanisms to set the excitability of an interneuron, our findings support the concept of an inhibitory system involving SOM interneurons, which receive relatively infrequent inhibitory input and cannot be brought under the influence by tonic inhibition. The lack of tonic inhibition may provide a more “fail-safe” inhibitory feedback system in the neocortex.

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