Layer-specific regulation of cortical neurons by interhemispheric inhibition

Lucy M. Palmer,1,† Jan M. Schulz2,† and Matthew E. Larkum3

1Physiologisches Institut; Universität Bern; Bern, Switzerland; 2Department of Biomedicine; Physiological Institute; University of Basel; Basel, Switzerland; 3Neurocure Cluster of Excellence; Humboldt University; Berlin, Germany

†These authors contributed equally to this article.

Processing of sensory information from both sides of the body requires coordination of sensory input between the two hemispheres. This coordination is achieved by transcallosal (interhemispheric) fibers that course through the upper corticals layers. In a recent study by Palmer et al. (2012), we investigated the role of this interhemispheric input on the dendritic and somatic activity of cortical pyramidal neurons. This study showed that interhemispheric input evokes GABA(B)-mediated inhibition in the distal dendrites of layer 5 pyramidal neurons, decreasing the action potential output when paired with contralateral sensory stimulation. In contrast, layer 2/3 pyramidal neurons were not inhibited by interhemispheric input possibly due to transcallosal fibers evoking more excitation in these neurons than layer 5 neurons. These results highlight both the precise nature of the microcircuitry of interhemispheric inhibition and how the balance between excitation and inhibition is different in the different layers of the cortex. Identifying the cellular and molecular elements involved in interhemispheric inhibition is crucial not only for understanding higher brain function but also dysfunction in the diseased brain.

One of the complexities of sensory processing is the coordination of information across both hemispheres of the cerebral cortex. This is achieved mostly via a huge bundle of fibers called the corpus callosum. It has long been known that an important action of these transcallosal fibers is to mediate interhemispheric inhibition1,2 which influences fine motor control,3,4 visuospatial attention5,6 and somatosensory processing7,8 and might contribute to or even underlie behavioral laterality.9 Furthermore, transcallosal fibers have been shown to regulate the efficacy, or gain, of sensory input, for example, during sensory perception.10 Gain modulation can be measured at the level of single neurons11 and may play a fundamental role in the control of numerous behaviors (for a review see Salinas and Sejnowski, 2001).12 In a recent study by Palmer et al. (2012), we identified the cellular basis of slow interhemispheric inhibition that may be principally involved in regulating the gain in the principle output neurons of the cortex.

In this study,13 sensory stimulation of the contralateral hindpaw increased the firing rate in layer 5 (L5) pyramidal neurons of the primary somatosensory cortex by approximately 3-fold, while stimulation of the hindpaw on the ipsilateral side had little influence on the firing rate. However, an inhibitory influence on evoked firing was revealed when the ipsilateral hindpaw was stimulated just before (200–400 ms) the contralateral hindpaw (Fig. 1A–C). This observation was surprising in two ways. First, ipsilateral stimulation had no apparent effect on the postsynaptic membrane potential of the L5 neuron. Hence, inhibition was “silent” in the absence of action potential output (Figs. 1 and 2). This suggests that the decrease in action potentials during
approach using light to specifically activate axons from the opposite cerebral hemisphere. This was achieved by prior injection of a virus expressing channelrhodopsin (a light-activatable protein channel) in the opposite hemisphere which allowed us to investigate interhemispheric information transfer very precisely in vivo and in vitro.

In vivo, optogenetic activation of callosal fibers evoked the same effect on contralateral hindpaw stimulation as ipsilateral hindpaw stimulation, i.e., it decreased the evoked firing. In vitro, activation of callosal fibers indicated that interneurons in the upper cortical layers received much more excitatory inputs from the contralateral hemisphere than L5 neurons. Thus, inhibitory interneurons in the upper cortical layers were the most likely candidates to mediate the observed interhemispheric inhibition. Having narrowed the focus to glutamatergic activation of upper-layer interneurons, we injected small amounts of the glutamate channel-blocker, CNQX, layer 1 (L1) and layer 2/3 (L2/3) separately which revealed that the source of interhemispheric inhibition dual current injections of in vivo waveform into the dendrite and soma had little effect on somatic depolarization but dramatically reduced the spiking output (Fig. 1E and F). Direct block of dendritic calcium channels by local application of the calcium channel blocker Cadmium/Nickel accounted for the majority of the decrease in firing induced previously by GABA B receptor activation. The effects on L5 pyramidal neuron activity by direct dendritic GABA B receptor activation was similar to interhemispheric inhibition and suggests that dendritic depolarization during hindpaw stimulation increases the gain of the conversion of synaptic inputs into action potential output and that GABA B receptor activation counteracts this gain increase.

The specific activation of GABA B receptors was puzzling on two levels. First, the vast majority of fibers crossing the corpus callosum are glutamatergic, and second, it is a priori difficult to understand why the influence of the release of the neurotransmitter GABA was mainly confined to one inhibitory receptor type. To investigate this we used an optogenetic approach using light to specifically activate axons from the opposite cerebral hemisphere. This was achieved by prior injection of a virus expressing channelrhodopsin (a light-activatable protein channel) in the opposite hemisphere which allowed us to investigate interhemispheric information transfer very precisely in vivo and in vitro.

In vivo, optogenetic activation of callosal fibers evoked the same effect on contralateral hindpaw stimulation as ipsilateral hindpaw stimulation, i.e., it decreased the evoked firing. In vitro, activation of callosal fibers indicated that interneurons in the upper cortical layers received much more excitatory inputs from the contralateral hemisphere than L5 neurons. Thus, inhibitory interneurons in the upper cortical layers were the most likely candidates to mediate the observed interhemispheric inhibition. Having narrowed the focus to glutamatergic activation of upper-layer interneurons, we injected small amounts of the glutamate channel-blocker, CNQX, layer 1 (L1) and layer 2/3 (L2/3) separately which revealed that the source of interhemispheric inhibition
In summary, we have described a form of interhemispheric inhibition that specifically affects deep cortical output neurons and is only evident during periods of increased dendritic activity, e.g., after paired hindpaw stimulation (Fig. 3). This form of inhibition may mediate the competition between the two hemispheres and result in an interhemispheric balance in L5 pyramidal neurons. Identifying the cellular and molecular elements involved in interhemispheric inhibition is crucial not only for understanding higher brain function and but reveals potential targets for direct therapeutic intervention in the diseased brain. In patients with a unilateral stroke for example, interhemispheric balance is thought to be disrupted and the affected hemisphere can become over-inhibited. The investigation of the roles of the upper layer of the cortex for network functions have just begun and this area of research likely remains a hot topic for years to come.

The projection pattern of the nucleus basalis indicates that this disinhibition is not restricted to a specific cortical area, but is a non-specific neuromodulatory phenomenon. In contrast, the interhemispheric inhibition that we observed was highly specific to the stimulation of matching body parts, i.e., stimulation of other areas on the ipsilateral hindlimb did not result in inhibition. Furthermore, interhemispheric inhibition of neuronal activity was only found in pyramidal neurons from deep cortical L5, the principal output neurons of the cortex, but not in pyramidal neurons in L2/3 (Fig. 2A–C). This may be simply due to these neurons receiving more excitation from interhemispheric input than L5 pyramidal neurons (Fig. 2D–F). These results highlight the possibility that, besides global modulatory signals, L1 neurons convey specific information from the contralateral hemisphere to a particular layer of the cortical microcircuitry.

In summary, we have described a form of interhemispheric inhibition that specifically affects deep cortical output neurons and is only evident during periods of increased dendritic activity, e.g., after paired hindpaw stimulation (Fig. 3). This form of inhibition may mediate the competition between the two hemispheres and result in an interhemispheric balance in L5 pyramidal neurons. Identifying the cellular and molecular elements involved in interhemispheric inhibition is crucial not only for understanding higher brain function and but reveals potential targets for direct therapeutic intervention in the diseased brain. In patients with a unilateral stroke for example, interhemispheric balance is thought to be disrupted and the affected hemisphere can become over-inhibited. The investigation of the roles of the upper layer of the cortex for network functions have just begun and this area of research likely remains a hot topic for years to come.
Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References
1. Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD. Interhemispheric inhibition of the human motor cortex. J Physiol 1992; 453:525-46; PMID:1464845.
2. Asanuma H, Okuda O. Effects of transcallosal volleys on pyramidal tract cell activity of cat. J Neurophysiol 1962; 25:198-208; PMID:13862744.
3. Geffen GM, Jones DL, Geffen LB. Interhemispheric control of manual motor activity. Behav Brain Res 1994; 64:131-40; PMID:7840879; http://dx.doi.org/10.1016/0166-4328(94)90125-2.
4. Kobayashi M, Hutchinson S, Théorêt H, Schlaug G, Pascual-Leone A. Repetitive TMS of the motor cortex improves ipsilateral sequential simple finger movements. Neurology 2004; 62:21-30; PMID:14718704; http://dx.doi.org/10.1212/01.WNL.0000110622.00008.00.
5. Heilman KM, Valenstein E. Frontal lobe neglect in man. Neurology 1972; 22:660-4; PMID:4673341; http://dx.doi.org/10.1212/01.WNL.22.6.660.
6. Hilgetag CC, Théorêt H, Pascual-Leone A. Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. Nat Neurosci 2001; 4:953-7; PMID:11528429; http://dx.doi.org/10.1038/nn0901-953.
7. Forss N, Hietanen M, Salonen O, Hari R. Modifed activation of somatosensory cortical network in patients with right-hemisphere stroke. Brain 1999; 122:1889-99; PMID:10560691; http://dx.doi.org/10.1093/brain/122.10.1889.
8. Seyl M, Ro T, Ralaf R. Increased sensitivity to ipsilateral cutaneous stimuli following transcranial magnetic stimulation of the parietal lobe. Ann Neurol 1995; 38:264-7; PMID:7654076; http://dx.doi.org/10.1002/ana.410380221.
9. Yagán MY, Wester BE, Kinsbourne M, Peterson B, Leckman JF. Functional significance of individual variations in callosal area. Neuropsychologia 1995; 33:709-79; PMID:76751166; http://dx.doi.org/10.1016/0028-3932(95)00018-X.
10. Schnitzler A, Kessler KR, Benecke R. Transcallosally mediated inhibition of interneurons within human primary motor cortex. Exp Brain Res 1996; 112:381-91; PMID:9007540; http://dx.doi.org/10.1007/BF0027944.
11. Larkum ME, Senn W, Lüchter HR. Top-down dendritic input increases the gain of layer 5 pyramidal neurons. Cereb Cortex 2004; 14:1059-70; PMID:15157547; http://dx.doi.org/10.1093/cercor/bhh065.
12. Salinas E, Sejnowski TJ. Correlated neuronal activity and the flow of neural information. Nat Rev Neurosci 2001; 2:539-50; PMID:11483997; http://dx.doi.org/10.1038/35086012.
13. Palmer LM, Schulz JM, Murphy SC, Ledergerber D, Murayama M, Larkum ME. The cellular basis of GABA(B)-mediated interhemispheric inhibition. Science 2012; 335:989-93; PMID:22363012; http://dx.doi.org/10.1126/science.1217276.
14. Pérez-Garcia E, Gassmann M, Bettler B, Larkum ME. The GABAB1b isoform mediates long-lasting inhibition of dendritic Ca2+ spikes in layer 5 somatosensory pyramidal neurons. Neuron 2006; 50:603-16; PMID:16701210; http://dx.doi.org/10.1016/j.neuron.2006.04.019.
15. Bettler B, Kaupmann K, Mosbacher J, Gassmann M. Molecular structure and physiological functions of GABA(B) receptors. Physiol Rev 2004; 84:835-67; PMID:15269338; http://dx.doi.org/10.1152/physrev.00036.2003.
16. Innocenti GM. General organization of callosal connections in the cerebral cortex In: Jones EG, Peters A, eds. Cerebral Cortex. New York: Plenum Press, 1986:291-353.
17. Zhang F, Wang LP, Boyden ES, Deisseroth K. Channelrhodopsin-2 and optical control of excitable cells. Nat Methods 2006; 3:785-92; PMID:16990810; http://dx.doi.org/10.1038/nmeth936.
18. Olah S, Komlosi G, Szabadics J, Varga C, Toth E, Barzo P, et al. Output of neurogliaform cells to various neuron types in the human and rat cerebral cortex. Frontiers in Neural Circuits 2007; 1.
19. Oláh S, Füle M, Komlósi G, Varga C, Báldi R, Barzó P, et al. Regulation of cortical microcircuits by unitary GABA-mediated volume transmission. Nature 2009; 461:1278-81; PMID:19865171; http://dx.doi.org/10.1038/nature08503

20. Wozny C, Williams SR. Specificity of synaptic connectivity between layer 1 inhibitory interneurons and layer 2/3 pyramidal neurons in the rat neocortex. Cereb Cortex 2011; 21:1818-26; PMID:21220765; http://dx.doi.org/10.1093/cercor/bhq257.

21. Letkus JJ, Wolff SBE, Meyer EMM, Tovote P, Courtin J, Herry C, et al. A disinhibitory microcircuit for associative fear learning in the auditory cortex. Nature 2011; 480:331-5; PMID:22158104; http://dx.doi.org/10.1038/nature10674.
Author/s:
Palmer, LM; Schulz, JM; Larkum, ME

Title:
Layer-specific regulation of cortical neurons by interhemispheric inhibition.

Date:
2013-05-01

Citation:
Palmer, L. M., Schulz, J. M. & Larkum, M. E. (2013). Layer-specific regulation of cortical neurons by interhemispheric inhibition.. Commun Integr Biol, 6 (3), pp.e23545-.
https://doi.org/10.4161/cib.23545.

Persistent Link:
http://hdl.handle.net/11343/261809

File Description:
Published version

License:
CC BY-NC