Exp Brain Res (2003) 153: 118–122
DOI 10.1007/s00221-003-1634-y

RESEARCH NOTE

Charles Capaday · Douglas D. Rasmusson

Expansion of receptive fields in motor cortex by local blockade of $GABA_A$ receptors

Received: 28 May 2003 / Accepted: 26 June 2003 / Published online: 18 September 2003

Abstract Experiments were done in α-choralose anesthetized cats to determine whether local disinhibition would expand the sensory receptive field (RF) of motor cortical neurons. Most of the neurons (n = 17) responded only to a rapid high velocity tap of the paw or forearm, often requiring movement of a joint, while four cells responded to light touch of the skin. The receptive field of single neurons was re-examined after microiontophoretic ejection of bicuculline (BIC). In all 21 neurons examined, BIC produced an expansion of the RF (mean 4 times before drug). Expansion was seen most often in the proximal-distal axis (17 neurons) but was also commonly seen in the mediolateral axis (9 neurons). The expansion was usually restricted to the dorsal or ventral surface that the original RF was on; in only three neurons in which the pre-drug RF was on the dorsal surface of the paw did the expansion include part or the entire ventral surface. Response thresholds could only be tested in those neurons with touch RFs and showed no evidence of a change within the original RF of these cells. Local disinhibition has previously been shown to allow for the functional linking of motor cortical points, a mechanism that may be involved in the recruitment of movement related muscle synergies. The present results suggest that this may be also accompanied by expansion of the receptive fields. Such a receptive field expansion may be of functional value since motor cortical output neurons would receive sensory input integrated over a larger area of the limb. The role of local inhibitory control of sensory inputs to motor cortex neurons may thus be different than that in sensory cortex where it is thought to restrict receptive field size.

Keywords Intracortical inhibition · Bicuculline · Cortical circuitry · Receptive field · Motor cortex

C. Capaday · D. D. Rasmusson
Department of Anatomy and Physiology, CRULRG Brain and Movement Laboratory and Department of Physiology and Biophysics, Dalhousie University,
Halifax, NS, B3H 4H7, Canada

C. Capaday (✉)
CRULRG Brain and Movement Laboratory2601 de la Canardière,
F-6500, Québec, G1J 2G3, Canada
e-mail: charles.capaday@anm.ulaval.ca
Tel.: +1-418-6635747
Fax: +1-418-6638756

Introduction

Normally local inhibitory connections restrict the spatial extent of cutaneous receptive fields (RFs) of somatosensory cortical neurons as demonstrated by microiontophoretic administration of $GABA_A$ or $GABA_B$ receptor antagonists, which can produce RF expansion (Hicks and Dykes 1983; Alloway et al. 1989; Tremere et al. 2001; Chowdhury and Rasmusson 2002). This indicates that these neurons receive excitatory inputs from a larger region than is apparent when inhibition is intact. Dynamic modulation of this inhibition provides one means of regulating RF size and consequently sensory acuity, while long-term modulation of local inhibition could enable mechanisms of plasticity following increased or decreased sensory input (Jones 1993; Capaday et al. 2000; Tremere et al. 2001). Similarly, local disinhibition has recently been shown to permit functional linking of separate motor cortical points (Schneider et al. 2002), a mechanism that may be involved in the recruitment of movement related muscle synergies. Since most neurons in motor cortex also receive sensory inputs that contribute to the control of motor outputs (Welt et al. 1967; Asanuma et al. 1968), we thought it of interest to determine if the sensory inputs to neurons in motor cortex are also under local inhibitory control. To test this we examined the effect of $GABA_A$ receptor blockade on sensory RFs in motor cortex.

Materials and methods

Data were obtained from seven male cats (3–5 kg). The methods used were approved by the local ethics committee and conformed to

the procedures outlined in the Guide for the Care and Use of Laboratory Animals, published by the Canadian Council for Animal Protection. Detailed experimental procedures are presented in Schneider et al. (2002). Briefly, anesthesia was induced using 2% halothane and catheters were inserted into the femoral artery and vein to monitor blood pressure and administer drugs and glucose solution. Rectal temperature was monitored and maintained at 38°C. A pair of stainless steel EMG electrodes was inserted into each of the following muscles: extensor carpi radialis (ECR), biceps (Bi), flexor carpi radialis (FCR) or palmarus longus (PL), spinodeltoid (SpD) and latissimus dorsi (LD). The head was positioned in a Kopf stereotaxic frame, the cisterna magna was opened to reduce pulsations and the right motor cortex was exposed. Following the surgical procedures, gas anesthesia was discontinued and the animal was maintained under α-chloralose anesthesia (5% in propylene glycol; 50 mg/kg, i.v.). This dose was supplemented as needed for the duration of the experiment by monitoring blood pressure and responses to pinching the paw.

Single neuron recordings were obtained using stainless steel electrodes (FHC, Bowdoinham, ME) having impedance about 1 MΩ. The signal was amplified, filtered (500–5000 Hz), sampled at 10 kHz and saved on microcomputer using Spike2 (CED, Cambridge, UK). The units RF was defined as the region of skin from which a clear response could be evoked by stroking or tapping the skin manually. Receptive field threshold was determined with Von Frey hairs. The RF was drawn directly on the forepaw with a water soluble ink marker and on a schematic of the forepaw. The RFs mediolateral and distal-proximal extent were measured with a vernier. In five animals, bicuculline methochloride (BIC, 10 mM in 0.9% NaCl; Tocris) was delivered iontophoretically (NeuroData Instruments) via a micropipette inserted 50–100 μm adjacent to the recording electrode at the same depth. In two animals, BIC was delivered via one barrel of a three barrel micropipette while recordings were obtained via another barrel containing a carbon-fiber (Armstrong-James and Millar 1979). BIC was administered using continuous positive currents ranging from 45 to 150 nA, with a negative 30–50 nA retention current before delivery. Iontophoresis was terminated when spontaneous bursting was first observed, usually within10 min. The RF was repeatedly monitored during and after administration of BIC.

The motor effects of intracortical microstimulation (ICMS) at the recording site were tested by delivering stimuli through the recording electrode (10–60 μA, 200 μs cathodal square pulses delivered at 333 Hz in 30–50 ms trains, i.e. 11–15 pulses). EMG signals were monitored on an oscilloscope, digitized at 2 kHz, averaged over eight trials in real-time, and stored on a micro-computer.

Results

The effect of BIC was determined on 21 motor cortical neurons. These neurons were located anterior, lateral and posterior to the cruciate sulcus within area 4γ as described by Hassler and Muhs-Clement (1964). The neurons sampled were located at depths ranging from 564 to 1300 μm below the cortical surface (mean = 1087 μm). ICMS at 16 of 21 recording sites produced movement of the forelimb about the shoulder, elbow and/or wrist.

Most of the neurons (n = 17) responded only to a rapid, high velocity, tap of the paw or forearm often requiring movement of a joint. In four cases the cells responded to light touch of the skin. In all cases, the responses to stimulation were rapidly adapting. The tap RFs tended to be quite large and had indistinct borders, whereas the touch RFs were smaller and had more distinct borders. A large proportion of the neurons (73%) had receptive fields whose major aspect was on the dorsal part of the paw or forearm.

BIC produced a rapid increase in RF size in all cells tested. The expansion was often evident within 1 min and continued over several minutes. An example is shown in Fig. 1. The original RF for this neuron was on the radial

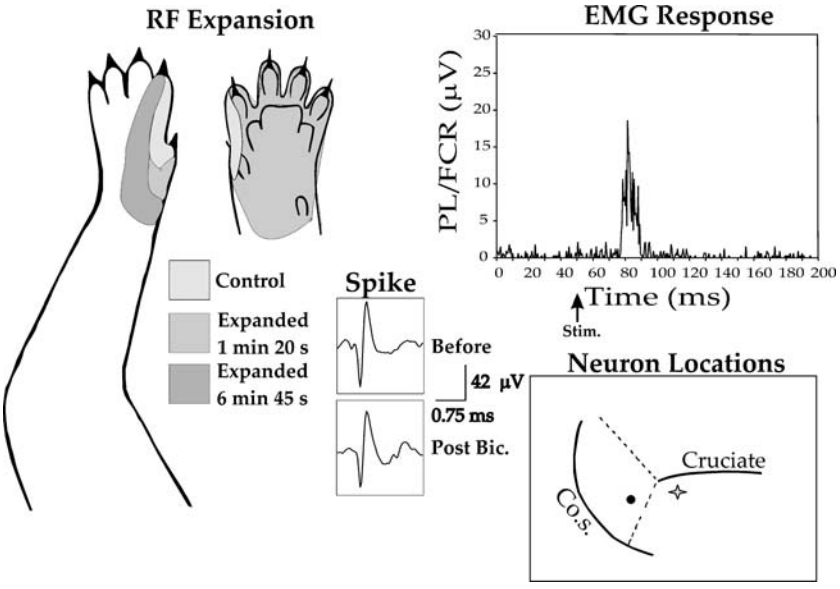

Fig. 1 Example of the progressive receptive field (*RF*) expansion, up to 6 min and 45 s, of a motor cortical neuron following iontophoretic ejection of bicuculline. The location of the neuron (●) relative to the surface of the cat motor cortex (area 4γ), bounded laterally by the coronal sulcus (*Co.s.*), is shown in the *inset* in the lower portion of the figure (adapted from Armstrong and Drew 1984). The *dashed lines* delineate the coronal gyrus. The location of the neuron that is the subject of Fig. 2 is indicated by the *star symbol*. Threshold microstimulation (40 μA) at the point where the neurons spike activity was recorded elicited an EMG response in the wrist flexors PL/FCR. The onset of the stimulus train is indicated in the figure. The neurons spike waveform is shown before and 8 min after the onset of iontophoresis

side of the paw, extending over digits 1 and 2. Within 2 min the RF approximately doubled in size, extending proximally on the side of the paw. Over the next 5 min the RF expanded across the entire ventral surface of the forepaw and across the radial half of the dorsal forepaw. A second example (Fig. 2) had a pre-BIC RF that was centered on the dorsum of the wrist. After BIC iontophoresis the field expanded in both distal and proximal directions on the dorsal surface and also included the carpal and digit pads on the ventral surface.

RF expansion was seen most often in the proximal-distal axis (17 neurons) but was also commonly seen in the mediolateral axis (9 neurons). The expansion was usually restricted to the dorsal or ventral surface that the original RF was on; in only three neurons in which the pre-BIC RF was on the dorsal surface of the paw did the expansion include part or the entire ventral surface of the paw. While accurate measurement of RF size could not usually be carried out because of the nature of the effective stimulus and the imprecise borders between responsive and non-responsive areas, estimates of RF size indicated at least a doubling of the RF in 14 of the neurons. For example, the two RFs shown in Figs. 1 and 2 had a four and twelve-fold increase in RF size, respectively, following BIC iontophoresis. The average increase in size was fourfold. Response thresholds could only be tested in those neurons with touch RFs. There was no evidence of a decrease in threshold within the original RF of these cells. BIC did not produce a change in modality of the effective sensory input in any of the recorded neurons.

ICMS produced a variety of muscle responses ranging from shoulder retraction to wrist flexion. There was no relationship between the control or expanded RF location and the muscle response(s) to ICMS. Only a few sites (n = 5) did not yield any movement with ICMS. A detailed summary of the pre- and post-BIC RF characteristics, cell depth, modality and response to ICMS is provided in Table 1.

Discussion

The interplay of excitatory and inhibitory connections within any brain region determines the moment-to-moment output of the region. In somatosensory cortex, the GABAergic neurons clearly restrict the spatial extent of various inputs, resulting in smaller RFs than would be expected from the connections that are anatomically present (Hicks and Dykes 1983; Alloway et al. 1989; Tremere et al. 2001; Chowdhury and Rasmusson 2002). Modulation of GABAergic strength provides one mechanism for selection of different inputs following impairment of sensory input (Warren et al. 1989; Skangiel-Kramska et al. 1994; Land et al. 1995) or increased stimulation (Welker et al. 1989; Siucinska et al. 1999; Knott et al. 2002).

The sensory responses of neurons in motor cortex have been recognized for many years (e.g., Welt et al. 1967; Asanuma et al. 1968). These responses arise directly from thalamocortical pathways (Asanuma et al. 1980) and indirectly via somatosensory cortex (Zarzecki et al. 1978). Numerous studies have shown that during active movement sensory information can be modulated within the sensory pathways (Ghez and Pisa 1972; Lamarre et al. 1985; Chapman et al. 1988). It is therefore not surprising that the effectiveness of sensory inputs to the motor cortex is also under local control, as demonstrated here. The ability of motor cortex to modulate different sensory inputs could contribute to normal motor behavior and facilitate changes in behavior in response to sensory feedback. The role of local inhibitory control of sensory inputs to motor cortex neurons may thus be different than that in sensory cortex where it is thought to restrict receptive field size in the presence of what appear to be a large number of unwanted inputs (Hicks and Dykes 1983; Alloway et al. 1989; Tremere et al. 2001; Chowdhury and Rasmusson 2002).

It is interesting to note that BIC did not produce a change in modality of the effective sensory input in any of

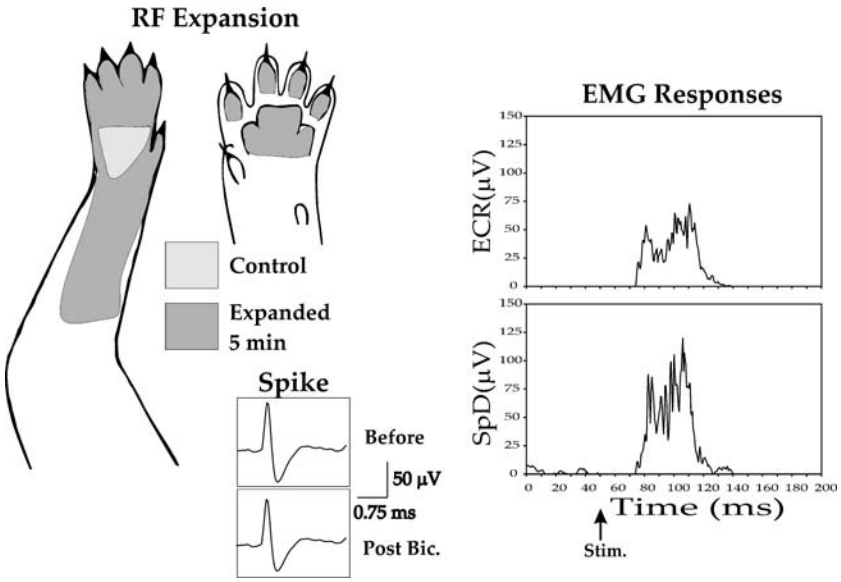

Fig. 2 A second example of RF expansion of a motor cortical neuron following iontophoretic ejection of bicuculline. Threshold microstimulation (18 μV) at the point where the neurons spike activity was recorded elicited EMG responses in the ECR and the SpD muscles. The onset of the stimulus train is indicated in the figure. The location of the neuron (*star symbol*) relative to the surface of the cat motor cortex (area 4γ) is shown in the *inset* of Fig. 1. The neurons spike waveform is shown before and 10 min after the onset of iontophoresis

Table 1 Summary table of the experimental results. Note particularly the post/pre RF expansion

Cell #	Depth (μm)	Modality	RF location[a]	Post BIC location	Pre BIC size (cm^2)	Post BIC size (cm^2)	Ratio post/pre	ICMS[b] response
1	1190	Tap	23d	Pdr	0.5	4	8.0	ECR/Bi
2	-	Tap	Wdr	Wr/FAr	1.6	3.2	2.0	ECR/Bi/SpD
3	1200	Tap	FAd	FA UAd	9.7	100	10.3	LD/FCR
4	1247	Touch	3d	Pd	1.2	5	4.0	FCR
5	-	Tap	Wd/FAd	Wd/FAd	15.5	18.2	1.2	Bi
6	-	Tap	Wd/FAd	Wd/FAd/UAd	30.5	79.7	2.6	None
7	1220	Tap	WPd	FAd/Pv	14.4	30.3	2.1	None
8	1200	Tap	Wd/2v	FAd/Pv	15.8	30.7	1.9	ECR/FCR
9	1175	Tap	Wd	FAd/Pv	3.6	10.8	3.0	SpD
10	1200	Tap	Pd/345d	Pd	6.1	11.1	1.8	SpD/ECR
11	1300	Tap	WPd	FAd/Pv	29	43.5	1.5	Bi
12	783	Tap	Pdv	FAd	15.1	39.1	2.6	Bi/ECR
13	714	Tap	Pd/5vCv	FAd/Pv	15.7	49.5	3.2	ECR/SpD
14	564	Tap	Pd	Pd/Pv	18.4	24.6	1.3	ECR/Bi/SpD
15	1293	Tap	45v	Wv/Cv	0.5	1.6	3.2	ECR
16	1293	Tap	Wdu	FAu	7.5	20	2.7	ECR
17	1291	Tap	34FAd	PFAd	5.5	7	1.3	Bi/SpD
18	992	Tap	12d	Pd/Pv	1.2	15	12.0	FCR
19	850	Touch	4v	Cv	0.5	3	6.0	None
20	833	Touch	4v	34vCv	0.3	3	10.7	None
21	1221	Touch	Pv	Wv	3.7	12	3.2	None
							Mean	
							4.0	

[a]RF locations: *C* carpal pad; *FA* forearm; *P* forepaw; *W* wrist; *1, 2, 3, 4, 5* digits; *d* dorsal; *r* radial; *u* ulnar; *v* ventral
[b]Muscles: *Bi* biceps; *ECR* extensor carpi radialis; *FCR* flexor carpi radialis; *LD* latissimus dorsi; *SpD* spinodeltoid

the recorded neurons. The similarity in response properties (tap vs. touch) in the expanded and the original RF in each case suggests that the inhibition produces a spatial restriction, but does not selectively remove a functional type of inputs. The striking preponderance of tap units having receptive fields on the dorsum of the paw observed in our choralose anaesthetized preparations may reflect the fact that an important role of sensory inputs to the cat motor cortex is the initiation of placing reactions (Amassian 1979).

GABAergic modulation of interactions within motor cortex appears to be important for producing its output (Schneider et al. 2002). Specifically, local disinhibition has been shown to allow for the functional linking of motor cortical points and thus the recruitment of movement related muscle synergies. The relative importance of inhibition of sensory inputs vs. motor interconnections is not known, nor is it clear whether the same interneurons can contribute to both types of inhibition. Nonetheless, the present results suggest that the functional linking of motor cortical points may also be accompanied by expansion of the receptive fields of the neurons involved. Receptive field expansion may be of functional value since motor cortical output neurons would receive sensory input integrated over a larger area of the limb. If this occurs, the movement related increase of neural and psychophysical (Chapman and Bushnell 1987; Chapman et al. 1988; Feine et al. 1990) sensory thresholds may be related to the receptive field expansion. One may suggest that an increased threshold reduces the neurons firing rate despite greater spatial summation of synaptic inputs.

In conclusion, the present study shows that a mechanism exists within the motor cortex that may allow for the dynamic modulation of a neurons receptive field size without affecting the sensory modality. To what extent receptive fields expand during natural behaviour and whether this affords a functional advantage to motor control remain to be elucidated.

Acknowledgements This work was funded by NSERC and CIHR. Charles Capaday is a senior scholar of the FRSQ. We thank Dr. Allan Smith for his comments and suggestions on a draft of this manuscript. We also thank France Roy and Pierre Vachon for expert and dedicated technical assistance, and Mr. Simon Lecomte for help with photography and graphics.

References

Alloway KD, Rosenthal P, Burton H (1989) Quantitative measurements of receptive field changes during antagonism of GABAergic transmission in primary somatosensory cortex of cats. Exp Brain Res 78:514–532

Amassian VE (1979) The use of contact placing in analytical and synthetic studies of the higher sensory motor control system. In: Asanuma H, Wilson VJ (eds) Integration in the nervous system. Igaku-Shoin, New York, pp 279–304

Armstrong DM, Drew T (1984) Topographical localization in the motor cortex of the cat for somatic afferent responses and evoked movements. J Physiol 350:33–54

Armstrong-James M, Millar J (1979) Carbon fiber microelectrodes. J. Neurosci Methods 1:279–287

Asanuma H, Stoney SD, Abzug C (1968) Relationship between afferent input and motor outflow in cat motor sensory cortex. J Neurophysiol 31:670–681

Asanuma H, Larsen K, Yumiya H (1980) Peripheral input pathways to the monkey motor cortex. Exp Brain Res 38:349–355

Capaday C, Richardson MP, Rothwell JC, Brooks DJ (2000) Long-term changes of GABAergic function in the sensorimotor cortex of amputees. A combined magnetic stimulation and 11C-flumazenil PET study [in process citation]. Exp Brain Res 133:552–556

Chapman CE, Bushnell MC (1987) Sensory perception during movement in man. Exp Brain Res 68:516–524

Chapman CE, Jiang W, Lamarre Y (1988) Modulation of lemniscal input during conditioned arm movements in the monkey. Exp Brain Res 72:316–334

Chowdhury SA, Rasmusson DD (2002) Comparison of receptive field expansion produced by $GABA_B$ and $GABA_A$ receptor antagonists in raccoon primary somatosensory cortex. Exp Brain Res 144:114–121

Feine JS, Chapman CE, Lund JP, Duncan GH, Bushnell MC (1990) The perception of painful and nonpainful stimuli during voluntary motor activity in man. Somatosens Mot Res 7:113–124

Ghez C, Pisa M (1972) Inhibition of afferent transmission in cuneate nucleus during voluntary movement in the cat. Brain Res 40:145–155

Hassler R, Muhs-Clement K (1964) Architektonischer Aufbau des sensomotorishen und parietalen Cortex der Katze. J Hirnforschung 6:377–420

Hicks TP, Dykes RW (1983) Receptive field size for certain neurons in primary somatosensory cortex is determined by GABA-mediated intracortical inhibition. Brain Res 274:160–164

Jones EG (1993) GABAergic neurons and their role in cortical plasticity in primates. Cereb Cortex 3:361–372

Knott GW, Quairiaux C, Genoud C, Welker E (2002) Formation of dendritic spines with GABAergic synapses induced by whisker stimulation in adult mice. Neuron 34:265–273

Lamarre Y, Spidalieri G, Chapman CE (1985) Activity of areas 4 and 7 neurons during movements triggered by visual, auditory, and somesthetic stimuli in the monkey: movement-related versus stimulus-related responses. Exp Brain Res 10:196–210

Land PW, de Blas AL, Reddy N (1995) Immunocytochemical localization of $GABA_A$ receptors in rat somatosensory cortex and effects of tactile deprivation. Somatosens Mot Res 12:127–141

Schneider C, Devanne H, Lavoie BA, Capaday C (2002) Neural mechanisms involved in the functional linking of motor cortical points. Exp Brain Res 146:86–94

Siucinska E, Kossut M, Stewart MG (1999) GABA immunoreactivity in mouse barrel field after aversive and appetitive classical conditioning training involving facial vibrissae. Brain Res 843:62–70

Skangiel-Kramska J, Glazewski S, Jablonska B, Siucinska B, Kossut M (1994) Reduction of $GABA_A$ receptor binding of [^{3}H]muscimol in the barrel field of mice after peripheral denervation: transient and long-lasting effects. Exp Brain Res 100:39–46

Tremere L, Hicks TP, Rasmusson DD (2001) Expansion of receptive fields in raccoon somatosensory cortex in vivo by $GABA_A$ receptor antagonism: implications for cortical reorganization. Exp Brain Res 135:447–455. DOI 410.1007/s002210000612

Warren R, Tremblay N, Dykes RW (1989) Quantitative study of glutamic acid decarboxylase-immunoreactive neurons and cytochrome oxidase activity in normal and partially deafferented rat hindlimb somatosensory cortex. J Comp Neurol 288:583–592

Welker E, Soriano E, Dorfl J, van der Loos H (1989) Plasticity in the barrel cortex of the adult mouse: transient increase of GAD-immunoreactivity following sensory stimulation. Exp Brain Res 78:659–664

Welt C, Aschoff JC, Kameda K, Brooks VB (1967) Intracortical organization of cats motorsensory neurons. In: Purpura DP (ed) Neurophysiological basis of normal and abnormal motor activities. Raven Press, Hewlett, NY, pp 255–293

Zarzecki P, Shinoda Y, Asanuma H (1978) Projection from area 3a to the motor cortex by neurons activated from group I muscle afferents. Exp Brain Res 33:269–282