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Interhemispheric Modulation on Afferent Sensory Transmission to the Ventral Posterior Medial Thalamus by Contralateral Primary Somatosensory Cortex

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Single unit responses of the ventral posterior medial (VPM) thalamic neurons to stimulation were monitored in anesthetized rats during activation of contralateral primary somatosensory (SI) cortex by GABA antagonist. The temporal changes of afferent sensory transmission were quantitatively analyzed by poststimulus time histogram (PSTH). Mainly, afferent sensory transmission to VPM thalamus was facilitated (15 neurons of total 23) by GABA antagonist (bicuculline) applied to contralateral cortex, while 7 neurons were suppressed. However, when ipsilateral cortex was inactivated by GABA agonist, musimol, there was significant suppression of afferent sensory transmission of VPM thalamus. This suppressed responsiveness by ipsilateral musimol was not affected by bicuculline applied to contralateral cortex. These results suggest that afferent transmission to VPM thalamus may be subjected to the interhemispheric modulation via ipsilateral cortex during inactivation of GABAergic neurons in contralateral SI cortex.

Key Words: Somatosensory, VPM thalamus, SI cortex, Interhemispheric modulation, GABA, Bicuculline, Callosal projection

INTRODUCTION

The callosal projection plays a crucial role in sensory-motor integrative functions of the two hemispheres (Berlucchi et al, 1995; Innocenti et al, 1995). A study by Shin et al (1997) suggested that temporary absence of afferent flow from the digit to the SI cortex exerts interhemispheric modulation of afferent transmission in the opposite somatosensory cortex of anesthetized rats. Furthermore, systemic plasticity of the cortex has been reported to alter the sensory processing and transmission of thalamus via corticofugal projections (Krupa et al, 1999; Jung & Shin, 2002a). These reports suggest the possibility that information processing of thalamus in somatosensory system may be involved in the interhemispheric modulation of the contralateral cortex Unfortunately, however the actual experimental evidence for this suggestion has not yet been provided.

Recently, corticothalamic projection has been reported to be connected with callosal projection in infragranular layers of the neocortical area (Matsubara et al, 1996; Cisse et al, 2003), and presumably gamma-aminobutyric acidergic (GABAergic) neurons in these areas, which require a source of excitatory synaptic drivers from thalamic nuclei, are also the targets of callosal pathway (Cisse et al, 2003). Therefore, in the present study we have recorded the evoked responses of ventral posterior medial (VPM) thalamic neurons to peripheral electrical stimulation, using the extracellular single unit recording during inactivation of the contralateral cortical GABAergic system, and characterized the GABAergic modulatory function of the contralateral cortex on sensory information processing of the VPM thalamus in the other side.

METHODS

Animals and electrophysiological recording

Sprague-Dawley rats (250~300 g body weight, n=52) were anesthetized with urethane (Sigma, 1 g Kg^{-1} body weight, i.p.). Animals were mounted in a stereotaxic frame and a relatively large (2~3 mm diameter) craniotomy was performed over the VPM thalamus for single unit recording and over both ipsilateral and contralateral SI cortex for microinjection of drugs. A tungsten microelectrode (5

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ABBREVIATIONS: VPM, ventral posterior medial; SI primary, somatosensory; PSTH, poststimulus time histogram; GABA, gamma-aminobutyric acid; EUR, evoked unit response

MOhm at 1 KHz, 125 μm diameter, A-M system, USA) was inserted to the VPM thalamus, and then, the receptive field was identified by listening to the recorded signal through an audio speaker while using a fine tipped probe to tap the vibrissae area lightly, until zone responding most intensely and reliably was defined. A bipolar concentric stimulating electrode (50 μm tip, 100 μm o.d., 0.5 mm tip separation, David Kopf, Tujunga, CA, USA) was inserted under the center of the receptive field, and the electrode was firmly fixed to prevent any movement. Responses of individual cells to electrical stimulation (single 1 ms pulses, 1.0 Hz, 1.5 times above threshold) of the receptive field were characterized by poststimulus time histograms (PSTHs) using the data acquisition system (CED 1401 & Spike3 software, CED, UK). The stimulating current necessary to produce a minimal response in the units was generally in the range of 100~150 μA.

Drugs and experimental protocol

The detailed methods for microinjection of drugs to SI cortex were described in our previous paper (Jung and Shin, 2002b). Briefly, after verifying the stability of the evoked responses for 10~30 min of control period, drugs were microinjected to both contralateral and ipsilateral cortex via two 28 G needles, which were individually inserted in layer 4 or 5 of two cortices before recording. GABA agonist (musimol, 100 μM, 10 μl, BIOMOL, USA) and antagonist (bicuculline, 50 μM, 10 μl, SIGMA, USA) diluted with saline or saline for control group were slowly infused via needles for 5 min. In the present study, the animals were divided into two groups: One was the ipsilateral-saline group (IS group) that was treated with saline in ipsilateral cortex, and the other was the ipsilateral-musimol group (IM group) with musimol in ipsilateral cortex. In all groups, either bicuculline (contralateral-bicuculline, CB) or saline (contralateral-saline, CS) was simultaneously microinjected to the contralateral cortex with microinjection of drugs to ipsilateral cortex (Table 1).

Table 1. Drug application and the number of neurons in each group

		IS group		IM group	
		IS-CS	IS-CB	IM-CS	IM-CB
Drug	Ipsilateral contralateral	Saline saline	Saline bicuculline	Musimol musimol	Saline bicuculline
Total neurons		8	23	9	24
Facilitated		0	15	1	1
Suppressed		0	7	7	20
NS		8	1	1	3

(NS: no significance)

Data analysis

PSTHs were constructed for quantitative measurement of intensity of evoked unit responses (EURs). The firing rates (spikes s^{-1}) were determined during the epochs defined as: (No. of spikes/No. of sweeps) × (1000/No. of ms in epoch). The changes of sensory transmission to the VPM thalamus by drugs were expressed in terms of percentage change from averaged EUR value calculated during 15 min of the control period. Statistical analysis was performed with the Students t-test. All results are presented as mean ±SEM.

RESULTS

Fig. 1A shows the PSTHs obtained from four VPM thalamic neurons before (CON) and after (60 min, 120 min) application of the drugs. Stability of the afferent sensory transmission to these neurons was ensured by monitoring short latency EURs of three poststimulus time histograms

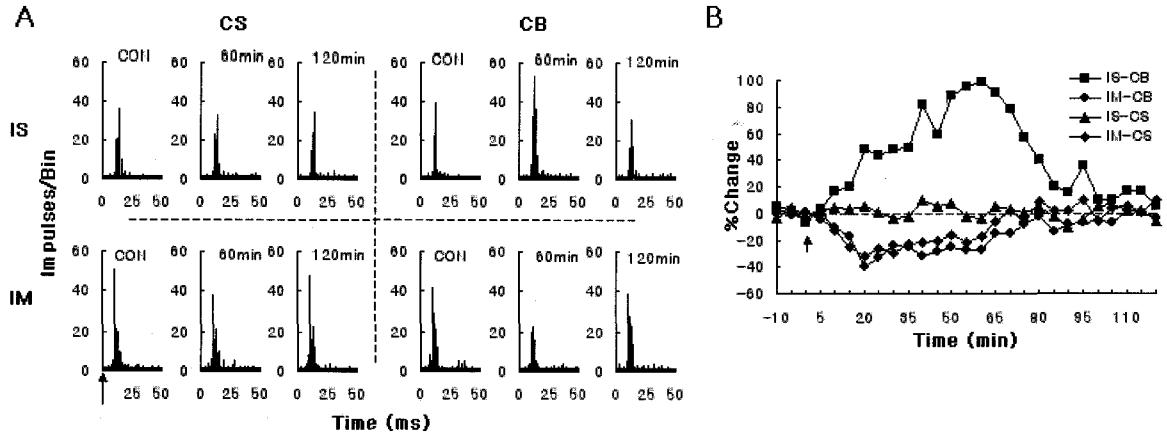

Fig. 1. Effects of bicuculline applied to contralateral cortex on the afferent transmission to VPM thalamus. A. Post-stimulus time histograms (PSTHs) under different conditions, IS-CS: ipsilateral-saline and contralateral-saline, IS-CB: ipsilateral-saline and contralateral-bicuculline, IM-CS: ipsilateral-musimol and contralateral saline, IM-CB: ipsilateral-musimol and contralateral-bicuculline. These histograms show the EUR triggered by s.c. electrical stimulation (arrow in histogram indicates the stimulation time) under the receptive field (vibrissae) during 5 min of control period at 0 min (CON), at 60 min post-drug (60 min) and at 120 min post-drug (120 min). B. Percentage changes of afferent sensory transmission to four VPM neurons in A during 15 min of control period and 120 min following drug administration. Arrow: drug application time.

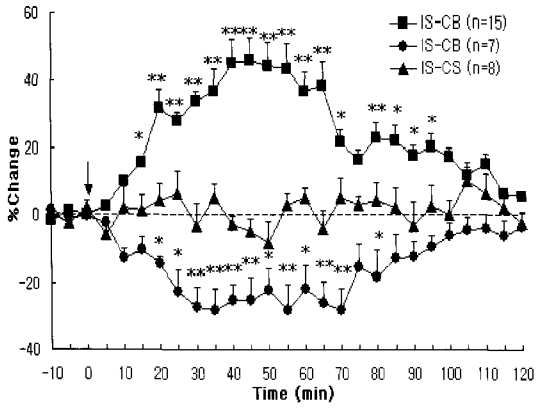

Fig. 2. Averaged percentage changes of afferent sensory transmission to VPM thalamic neurons of IS group before and after drug administration. In the IS-CB group, fifteen of total neurons were reversibly facilitated, while 7 neurons were suppressed. Eight thalamic neurons in IS-CS group did not show significant change of evoked responses. All results are expressed as mean±SEM. **p<0.01, *p<0.05 (compared with control period). Arrow indicates the drug administration. Dotted line, averaged control value.

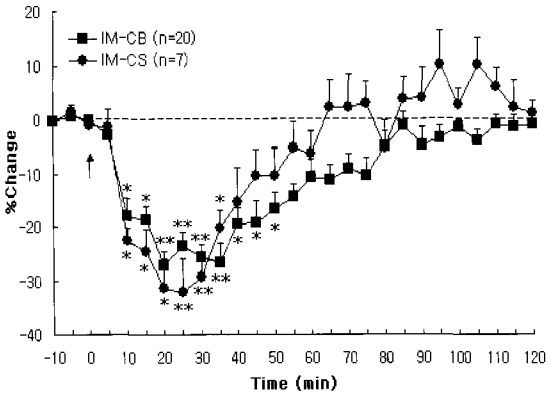

Fig. 3. Averaged percentage changes of afferent sensory transmission to VPM thalamic neurons of IM group before and after drug administration. All results are expressed as mean±SEM. **p< 0.01, *p<0.05 (compared with control period). There was no statistical significance between IM-CS (n=7) and IM-CB (n=20) groups. Arrow indicates the drug administration. Dotted line, control value.

(5 min duration for each histogram) generated during 15 min control period before the drug administration. Reversible facilitation of evoked responses was observed in a VPM neuron of the IS group after microinjection of bicuculline to contralateral cortex (Fig. 1A, IS-CB, Con: 86, 60 min : 169 impulses/bin), and they were then gradually restored to the control value until 120min post-drug (120 min : 91 impulses/bin). However, the afferent transmission to a neuron of the IS group was not altered under the condition of contralateral-saline (Fig. 1A, IS-CS, CON : 114, 60 min : 111, 120 min : 104 impulses/bin). In the IM group, musimol applied to ipsilateral cortex induced reversible suppression of evoked response of a VPM thalamic neuron to peripheral stimulation under the condition of contralateral-saline (Fig. 1A, IM-CS, CON : 145, 60 min : 109, 120 min : 139 impulses/bin), and this suppressed response was not affected by bicuculline applied to contralateral cortex (Fig. 1A, IM-CB, CON : 145, 60 min : 96, 120 min : 132 impulses/bin). Fig. 1B shows percentage changes of sensory responses of four VPM thalamic neurons in fig. 1A during 15 min of control period and 120 min following drug administration. The overall effects of bicuculline applied to the contralateral cortex in each group during the 120 min post-drug period are shown in Fig. 2 and Fig. 3, respectively.

In 15 of total 23 VPM thalamic neurons of the IS-CB group, afferent sensory transmission was reversibly facilitated after microinjection of bicuculline to the contralateral cortex, and they were then gradually restored to the control values until 120min post-drug (Fig. 2, 0 min : 0.19±2.63, 50 min : 44.45±7.00, $p<0.01$, 120 min : 5.40 ±0.74%). However, seven of 23 neurons in the IS group were suppressed and their gradual recovery to the control value was observed after 70 min post-drug (Fig. 2, 0 min : −0.54±1.13, 50 min : −22.18±6.25, $p<0.01$, 120 min : −3.60±4.19%). Significant change of afferent sensory transmission to VPM neurons (n=8) was not observed in the IS-CS group (IS-CS in Fig. 2, 0 min : 2.11±2.01, 50 min : −8.26±6.28, 120 min : −2.37±3.44%). Fig. 3 shows averaged percentage changes of 27 VPM thalamic neurons of the IM group (total 33 neurons, Table 1). In the IM-CS group, afferent sensory transmission to the VPM thalamus was reversible suppressed by musimol microinjected to ipsilateral cortex (Fig. 3, IM-CS, 0 min : −1.12±0.41, 30 min : −29.15±4.18%, n=7, $p<0.01$). This suppressed responsiveness of IM thalamic neurons was gradually restored to the control value forl 80 min post-drug (80 min : −5.22±5.26%). Suppression of afferent transmission to thalamic neurons by ipsilateral-musimol was not altered by bicuculline applied to contralateral cortex (Fig. 3, IM-CB, 0 min : −0.13±0.47, 30 min : −25.59±2.42, 80 min : −5.06±2.80%, n=20).

DISCUSSION

The results of this study clearly demonstrate that afferent sensory transmission to the VPM thalamus in one brain may be subjected to interhemispheric modulation from the opposite brain following the inactivation of GABAergic neurons in the contralateral SI cortex. This is evidenced by the facilitation of sensory transmission to 15 (65.2%) of the total 23 VPM neurons of the IS group. It is well known that callosal connection between cortices is mainly excitatory (Schnitzler et al, 1995). This observation together with our results suggest that callosal excitatory connections between two SI cortices may be enhanced by inactivation of the contralateral intracortical GABAergic system. In the IM group, suppressed changes of EURs in thalamus (20 of total 24 neurons, 83.3%) were mainly observed after microinjection of musimol to the ipsilateral cortical area. And, there was no significant difference in their responsiveness between IM-CS and IM-CB. Suppression of thalamic EURs in the IM group was quite similar to the suppressed thalamic reorganization by inactivation of the ipsilateral cortex (Krupa et al, 1999). Also, in seven neurons of IS-CB group (total 23 neurons), we observed

suppressed responses of the VPM thalamus. These results may include a tonic inhibition, which was generated primarily by cortically driven excitation of GABAergic neurons located in reticular nucleus of the thalamus and probably also in the trigeminal brainstem complex (Jacquin et al, 1990; Lee et al, 1994). Therefore, these observation together with our results indicate that both excitatory and inhibitory pathways from cortex to subcortical nuclei may participate in corticofugal modulation.

In the current study, inactivation of GABAergic neurons in the contralateral cortex of IS-CB group was found to facilitate mainly afferent sensory transmission to the VPM thalamus evoked by vibrissae area stimulation, while there were no significant changes in IS-CS group. We have previously reported that corticothalamic connectivities was enhanced by peripheral temporary deafferentation (Jung & Shin, 2002a), and that cortical reorganization during temporary deafferentation might be due to disinhibition of intracortical GABAergic system (Jung & Shin, 2002b). These and present results strongly suggest that callosal to thalamic pathway may be activated by inactivation of contralateral GABAergic system. Cisse et al (2003) identified cortical neurons located in layer V to callosally eicite the activities to be spread across contralateral cortical and corticothalamic network. They have suggested that descending influences may be induced by direct stimulation, which may be led by inactivation of contralateral cortical layer III. The current study that the corticothalamic modulation may be induced by inactivation of contralateral intracortical GABAergic system is different from excitatory activation of the callosal pathway reported by Cisse et al. In the IM group, thalamic EURs of IM-CS were suppressed after microinjection of musimol to ipsilateral cortex and these responses were not directly affected by bicuculline microinjected to contralateral cortex (IM-CB). This result suggests that corticothalamic modulation originates from the ipsilateral cortex, and that callosal modulation of the contralateral cortex may have an influence on the thalamus in the other side via callosal pathway between two cortices. Yuan et al (1985, 1986) reported that inactivation of the SI cortex results in reduced thalamic response to electrocutaneous stimulation.

In the current study, we recorded the suppressed responses of afferent sensory transmission in 30.4% thalamic neurons, and no changes in 4.3% neurons in the IS group (not shown). Previous report suggested that descending dual influences of excitation and inhibition in corticofugal modulation may involve both the GABAergic neurons in the thalamic reticular nucleus and the direct glutamatergic projections from the SI cortex (Krupa et al, 1999). However, in the present study, we did not focus on this suggestion in the present study.

In conclusion, we examined in the present study the changes of afferent sensory transmission to the VPM thalamus during the inactivation of the intracortical GABAergic system in the contralateral cortex. Although we did not observe the changes of direct connectivities between two cortices and of corticothalamic projection, our results may provide clear evidence for changes of the thalamic information processing induced by interhemispheric modulation between cortices.

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