Role of the rostral agranular insular cortex in the modulation of neuropathic pain produced by stimulation of the motor cortex

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Directed by Professor Jin Woo Chang

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먼저 박사학위 연구 할 수 있는 기회와 다방면으로 지도를 해주신 장진우 지도교수님께 깊은 감사를 드립니다. 또한 부족한 저의 연구 실험에 많은 도움을 준 신재우, 김진형 연구원에게 고맙다는 말 전합니다.

돌이켜 보면 임상의로 바쁜 가운데 박사학위 취득까지 긴 시간이 흘러 주위 분들뿐만 아니라 제 개인적으로도 걱정이 많았었던 것이 사실입니다. 그 걱정에 마침표를 찍을 수 있게 되어 의미가 더욱 큰 것 같습니다.

연구를 하면서 부족한 저를 더욱 돌아 볼 수 있었던 것 같고, 이에 주위 동료들의 도움의 중요성을 다시 한 번 느끼게 되었습니다. 이번 기회를 이어 더욱 깊이 있는 연구와 학업에 매진해야겠다는 다짐을 할 수 있었습니다.

마지막으로, 지금까지 그리고 앞으로도 사랑으로 보살펴 주시는 부모님의 은혜에 감사를 드리며, 저의 고민과 근심을 덜어주는 아내에게도 감사 드립니다.

다시 한 번 저희 연세 정위기능신경외과 식구들과 연구원 모두 감사 드리며, 저도 여러분의 도움을 줄 수 있도록 더욱 노력하겠습니다.

감사합니다.

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<ABSTRACT>

Role of the rostral agranular insular cortex in the modulation of neuropathic pain produced by stimulation of the motor cortex

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Motor cortex stimulation (MCS) has been used to control various pain disorders in clinical field. Though functional imaging studies revealed that there were many other structures involved, the mechanisms of pain control by MCS are still poorly understood. To investigate the role of insular cortex on neuropathic pain modulation of MCS, we made unilateral lesion in rostral agranular insular cortex (RAIC) and compared with non-lesion model during MCS. We made 2 groups; Group A (n = 7); neuropathic pain (spared nerve injury model) + MCS, and Group B (n = 8); neuropathic pain + RAIC lesion + MCS. We measured the threshold and latency of pain in pre-stimulation and intra-stimulation phase using behavioral test. Pain threshold was increased in group A with “MCS on” and group B either “MCS off” or “MCS on”. Particularly, the threshold of group B with “MCS

on" was higher than that of group B with "MCS off" or group A. The latency of bearing painful stimulus was also increased in group A with "MCS on" and group B either "MCS off" or "MCS on". Also the latency was increased in group B with "MCS on" more than that of group B with "MCS off" or group A. Therefore, MCS and insular lesioning are possible participants in pain modulation. Compared with "MCS off", significant changes after "MCS on" were noted on electrophysiologic study using the percentage change in spontaneous activity from RAIC. So our results showed that the RAIC has its own pain modulation effect and its effect is influenced by MCS.

Key words : Motor Cortex Stimulation, Neuropathic pain, Insular

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Ⅰ. INTRODUCTION

Neuropathic pain is a neurodegenerative disease, caused by lesion or dysfunction of the central or peripheral nervous system, and it is one of the most difficult pains to control because it is a multidimensional clinical entity mediated by many different pathophysiological mechanisms [1-4]. So the medical refractory neuropathic pain was treated by invasive lesioning or stimulation therapy. Because of the advantage of stimulation, reversibility and adjustability, neuromodulation therapy became more popular.

In 1991, Tsubokawa first reported the effect of motor cortex stimulation

(MCS) in patient with chronic, drug-resistant neuropathic pain 5. MCS was initially applied to treat the central pain secondary to thalamic stroke, and it expanded to various other types of neuropathic pain. Chronic MCS showed about 45 to 75% of pain control rate in the literatures [6-11]. Thus MCS procedure was accepted as a promising therapy for patients with severe refractory neuropathic pain. But the mechanism of MCS for pain modulation is still not elucidated though clinical use in practice. From imaging and electrophysiological study, many other brain structures were activated after MCS. One of these structure, insular cortex is less evaluated though the imaging study from PET or fMR showed near straight forward involvement in pain process. The aim of this study is to evaluate the role of insular cortex in pain modulation during motor cortex stimulation.

Ⅱ. MATERIALS AND METHODS

1. Animals

All procedures were conducted according to the guidelines of the Ethical Committee of International Association for the Study of Pain [12] and approved by the Institution Animal Care and Use Committee (IACUC) of Yonsei University. Fifteen male Sprague-Dawley rats weighting 180 – 200 g were used in this study. Three animals were housed per laboratory cage with food and water available ad libitum. Light was controlled under a 12 hour light/dark (light on between 07:00 A.M. - 19:00 P.M.) cycle. The temperature was maintained at 22 ± 2 ℃ and relative humidity was at 55 ± 5%. Animals were allowed to acclimate for at least a week before surgery and behavioral testing. Behavioral study of MCS effect was observed in two animal groups: Group A, a neuropathic pain group (N=7); Group B, neuropathic pain + rostral agranular insular cortex (RAIC) lesion group (N=8). Furthermore, neuronal activity of MCS effect were measured electrophysiologically in neuropathic pain group (N=8).

2. Surgical procedures

A. Surgical procedures for pain model

To induce neuropathic pain, we used spared nerve injury (SNI) method [13]. Rats were deeply anesthetized with phentobarbital sodium (50 mg/kg, intraperitoneally). Under a surgical microscope (Olympus, Tokyo, Japan), the three major divisions of the left sciatic nerve was exposed, the common

peroneal and sural nerves were completely ligated and transected. Hemostasis was completed and the cut was closed with muscle and skin sutures.

B. MCS electrode implant

One week after the pain surgery, we measured the pain threshold to check whether the neuropathic pain was effectively induced or not. The detailed description of our behavior test for measuring pain threshold is at the section of behavior test. After behavior test, rats which did not show neuropathic pain response were excluded in this study. To implant the MCS electrode, rats were anesthetized by pentobarbital sodium (50 mg/kg, intraperitoneally) and fixed with a stereotaxic frame (Narishige, Tokyo, Japan). The scalp was opened and the skull was exposed. To place the electrode on the left hindlimb area of the primary motor cortex 14, we made a rectangular hole (2.0 mm x 2.0 mm) on right side. The coordination was -0.2 ~ +1.8 mm from bregma and +0.5 ~ +2.5 mm from midline. The electrode was placed on epidural space, and the electrode was firmly fixed using bolts and glue. The scalp finally was approximated.

C. RAIC lesion

In group B, prior to implant MCS electrode, we made a burr hole that allows to insert an electrode to target site (RAIC, AP: antero-posterior direction: +1.0 mm from bregma, ML: midline: +4.5mm right-side lateral from midline and DV: dorso-ventral direction: -6.0mm from dura) [15]. After inserting electrode to the target coordinate, we delivered an electrical pulse of 0.1mA for 10 seconds for the RAIC lesioning. Then the lesioning electrode was removed, and the MCS electrode was implanted.

3. Behavioral tests

The time table of SNI modeling and behavioral test in two groups are presented in Figure 1.

E. Measuring tactile threshold

Rats were placed inside acrylic cages (8 x 10 x 20 cm) on a wire mesh grid for measuring the mechanical allodynia. After 30 minute of adaptation, a series of von Frey filaments (0.4, 0.6, 1, 2, 4, 6, 8 and 15 g of bending force) were applied to the lateral edge of the left hind paw. By the 50% threshold up and down method [16], tactile threshold was calculated.

F. Measuring response latency

To measure the response latency, rats were placed the same acrylic cages (described above). After 30 minute of adaptation, we applied painful stimulation on left hindlimb using a Plantar test unit (model 37370, Ugo Basile Biological Instruments, Cemerio, VA, Italy). The strength of painful stimulation was gradually increased by time automatically. When the rat shows withdrawal response, the Plantar test unit records the duration of resistance from stimulation and the value of final force. We measured the latency three times, and averaged them.

G. Behavioral test schedule and MCS parameters

After 30 minute of adaptation in acryl cages, MCS was turned on (biphasic pulses of 65 Hz, 210 μs, 420 μA for 30 min) using a stimulator (Model3300, A-M systems, Sequim, WA, U.S.A). Behavioral tests was carried on at following time points; before stimulation; at 30 minutes after the start of

stimulation; immediate after ceasing stimulation and every 10 min by 5 times.

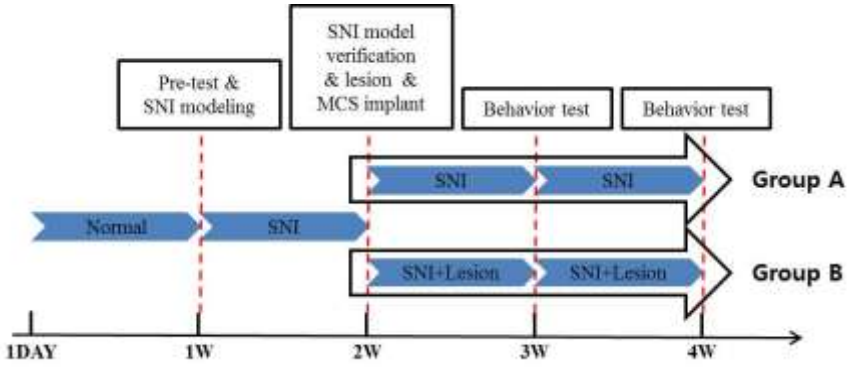

Figure 1. The timetable of SNI modeling and behavioral test in two group.

4. Electrophysiological measurement

Rats (SNI model; n = 8) were anesthetized with urethane (1.3 g/kg), and a microelectrode (573220, A-M systems, Sequim, WA, USA) was inserted into the ventroposterolateral nucleus of thalamus (VPL) and RAIC for extracellular recordings of single unit activities. Two channel array electrodes were positioned stereotactically in the VPL (ML: +2.8 mm; AP: -2.2 mm DV: -6.0 mm from bregma) and RAIC (AP: +1.0 mm, ML: +4.5mm, DV: -6.0mm from bregma). The neuronal activities were recorded for 5 minutes. During acquisition of neural signal, mechanical stimulation, using 300g of VonFrey hair, was applied on the rats' left hindpaw area. Signals from the microelectrode were amplified using an amplifier (model 1700, A-M systems, Sequim, WA, USA), and the signal was converted and transmitted to the recording system using an AD converter (Micro1401, Cambridge Electronic Design Limited, Milton Road, Cambridge, UK). The received signal data were stored by Spike 2 (Cambridge Electronic Design

Limited, Milton Road, Cambridge, UK). Recorded waveforms were analyzed using Offline Sorter (Plexon Inc., USA), NeuroExplorer (Neuroexplorer Inc., USA), and Matlab software (Mathworks, Natick, MA, USA).

Signal analysis was obtained for 20 seconds before and after MCS. Because of firing change of each region after MCS, the interval between the signal analyses was regulated. The time table of electrophysiological recordings at VPL and RAIC is illustrated in Figure 2.

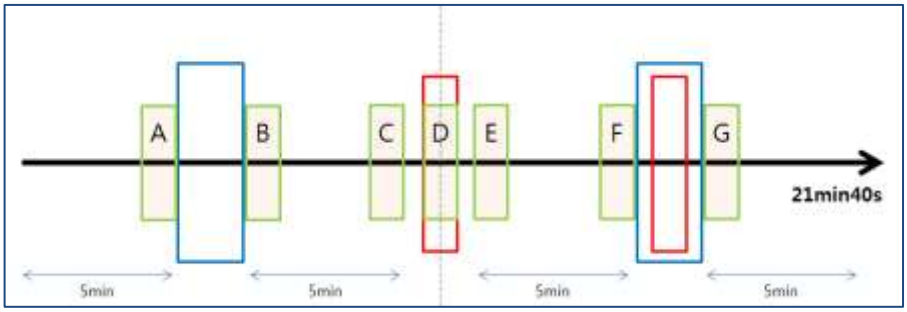

Figure 2. The timetable of electrophysiological recordings at ventroposterolateral thalamus (VPL) and rostral agranular insular cortex (RAIC).

Blue box; 40 sec for motor cortex stimulation

Red box; 20 sec for mechanical stimulation

Green box; 20 sec for signal analysis

A, C and F; resting period

B; resting period after MCS

D; mechanical stimulation with 300g von Frey hair period

E; resting period after mechanical stimulation without MCS

G; resting period after mechanical stimulation with MCS

5. Histological verification of RAIC lesion

To verify the RAIC lesioning, after termination of all experiments, rats were intracardiacly perfused with normal saline and fixed with 4% paraformaldehyde in PBS (pH 7.4). The brain was carefully removed and prepared for frozen section. Coronal sections of 30 um were obtained using a microtome with deep freezer (Fig. 3). The slices were dyed using cresyl violet. Microscopy images were obtained under a microscope (Olympus, Tokyo, Japan).

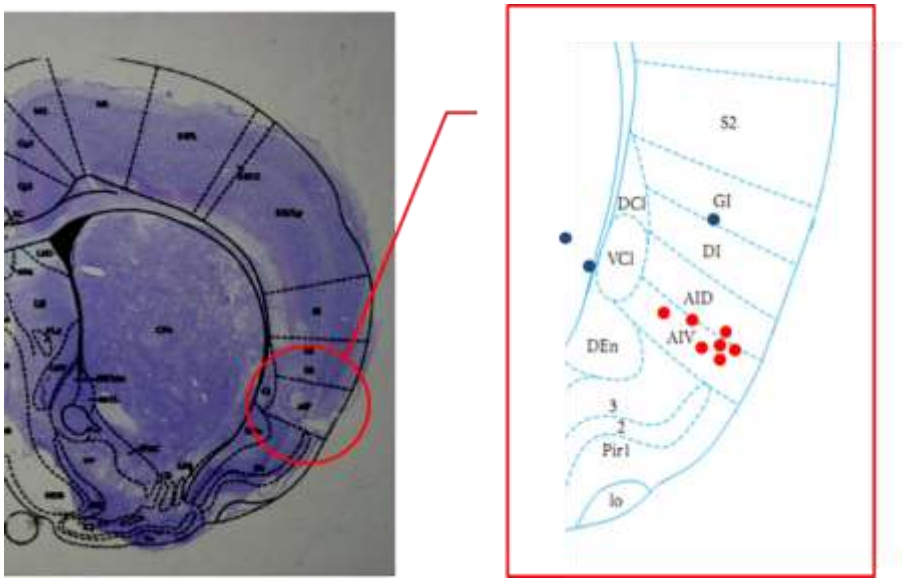

Figure 3. Histological verification of rostral agranular insular cortex.

After lesioning on rostral agranular insular cortex, the brain slice was fused with Mai Atlas to verify the accuracy of lesion. Red dots (n=7) were only used for data analysis.

6. Statistical analysis

Data are reported as means ± SEM. For comparison of changes within group, statistical analysis was performed using paired student T-test. For comparison of difference between groups, we used the Kruskal-Wallis one-way analysis of variance (ANOVA), followed by Tukey's post hoc comparison. The p-values of < 0.05 were considered significant. All statistical analyses were performed using SPSS (Version 20, SPSS Inc., Chicago, IL, USA).

Ⅲ. RESULTS

1. Changes of mechanical threshold in group A and B

One week after pain surgery, we measured mechanical allodynia in rats. Mechanical thresholds significantly decreased from 17.51 ± 1.01 to 1.3 ± 0.5 g (ipsilateral) in group B and from 16.96 ± 0.7 to 1.27 ± 0.28 g in group A. The mechanical threshold of group B on 2nd week was increased (2.96 ± 0.47 g) and this is also significantly higher ($p<0.001$) than that of group A (0.41 ± 0.09 g). On 3rd week after the surgery, the increased mechanical threshold of group B was maintained (2.51 ± 0.45 g) and this is also significantly higher than group A (0.46 ± 0.09 g) ($p<0.001$). The change of each group's mechanical thresholds are presented in Figure 4.

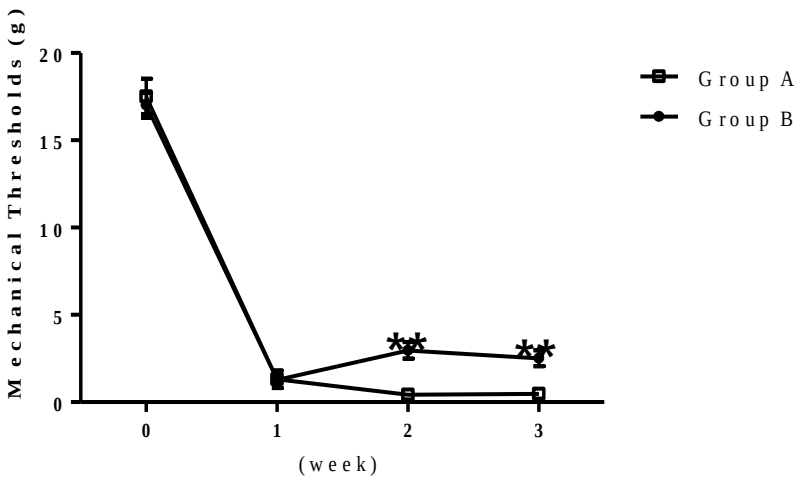

Figure 4. Mechanical thresholds change was noted 1-3 weeks after pain modeling. Compared to group A, group B showed higher mechanical threshold at 2nd and 3rd week ($p<0.001$).

2. Behavioral test comparison of group A and B after MCS

In 3rd week from the pain surgery, we measured pain threshold in group A and B with “MCS on” or “MCS off”. Two features were observed; the alteration of threshold with time and the altered extent of pain suppression in each group.

On behavioral test, the pain threshold for group A was 0.46 ± 0.09 g (pre-MCS), 3.85 ± 0.69 g (during MCS on), 2.94 ± 0.42 g (1 min after MCS off), 2.22 ± 0.32 g (10 min after MCS off), 1.70 ± 0.35 g (20 min after MCS off), 1.01 ± 0.33 g (30 min after MCS off), 0.85 ± 0.21 g (40 min after MCS off), 0.66 ± 0.19 g (50 min after MCS off), 0.52 ± 0.11 g (60 min after MCS off). In group B, the threshold was 2.51 ± 0.45 g (pre-MCS), 8.85 ± 2.08 g (during MCS on), 7.87 ± 2.24 g (1 min after MCS off), 7.72 ± 2.25 (10 min after MCS off), 4.93 ± 1.04 g (20 min after MCS off), 3.54 ± 0.73 g (30 min after MCS off), 3.07 ± 0.64 g (40 min after MCS off), 2.39 ± 0.40 g (50 min after MCS off), 2.36 ± 0.47 g (60 min after MCS off).

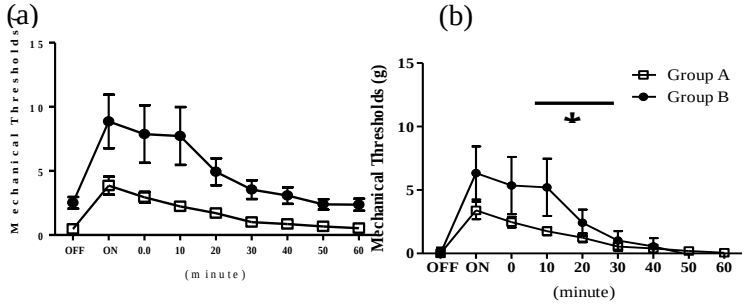

Figure 5. Changes of mechanical threshold after motor cortex stimulation in two groups. (a) data are presented as raw, (b) the base line was set as 0, and the other data was adjusted to compare each group.

To compare the difference of threshold change amount in groups, we made a graph that shows the amounts of increase of decrease from baseline threshold (Fig. 5). In group A, the variation values are 3.38 ± 0.63 (during MCS), 2.47 ± 0.36 (after MCS off), 1.75 ± 0.27 (10 min after MCS off), 1.23 ± 0.31 (20 min after MCS off), 0.54 ± 0.29 (30 min after MCS off), 0.38 ± 0.20 (40 min after MCS off), 0.19 ± 0.13 (50 min after MCS off) and 0.06 ± 0.05 (60 min after MCS off). The values of variation for group B are 6.33 ± 1.87 (during MCS), 5.35 ± 1.85 (after MCS off), 5.20 ± 1.84 (10 min after MCS off), 2.41 ± 0.84 (20 min after MCS off), 1.02 ± 0.40 (30 min after MCS off), 0.56 ± 0.41 (40 min after MCS off), -0.12 ± 0.13 (50 min after MCS off) and -0.15 ± 0.16 (60 min after MCS off).

Overall, the amount of behavioral change of group B was higher than that of group A for 30 minutes after MCS off, and especially, the differences were significant for 10 minutes after MCS off.

3. Latency

In measuring painful response latency on 3rd week (Fig. 6), the baseline mechanical latency was 9.44 ± 0.37 sec (ipsilateral) and 24.65 ± 1.02 sec (contralateral) in group A. The latency was increased after MCS on; 15.37 ±

0.89 ($p<0.001$) sec for ipsilateral and 27.64 ± 1.61 sec ($p<0.01$) for contralateral. In group B, the baseline latency was 16.12 ± 0.62 sec for ipsilateral and 25.13 ± 1.00 sec for contralateral. However MCS on increased only in ipsilateral side (20.16 ± 0.80 sec, $p < 0.001$) not in contralateral (26.02 ± 0.61 sec).

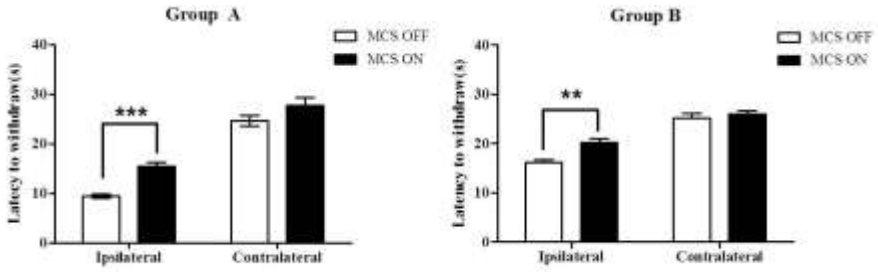

Figure 6. The change of response latency withdrawal of both paws between two groups. Latency to withdrawal of ipsilateral hindpaw was significantly increased in both groups. (***: $p<0.0001$; **: $p=0.0016$)

In comparing the difference among animal groups, the normal group had the highest latency (24.65 ± 1.02 sec). The latency was markedly decreased in group A (9.44 ± 0.37 sec) and it was increased to 15.37 ± 0.89 sec by MCS on. In group B, the baseline latency measured before electrical stimulation was 16.12 ± 0.32 sec, and it is higher than that of group A with MCS on. The latency of group B with MCS on was 20.16 ± 0.80 sec, and it is higher than both the latency without MCS and group A with MCS on. Besides, the difference between group A with MCS on and group B with MCS on is significantly differed ($p<0.001$) (Fig 7). Therefore MCS with additional lesioning of RAIC were effective for pain suppression than the effect from MCS only.

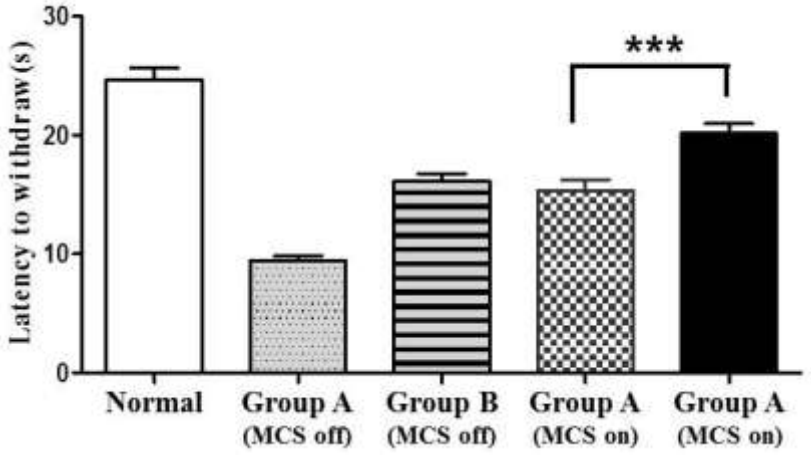

Figure 7. Overall change of latency to withdrawal from normal, group A, group B with or without MCS on. Latency to withdraw of group B with MCS on was significantly higher than that of group B with MCS on. (***: p=0.0008)

4. Electrophysiological changes in RAIC after MCS

Percentage change in spontaneous activity decreased with MCS on (VPL: 107.04 ± 11.42%; RAIC: 96.70 ± 5.99%) than without MCS (VPL: 176.03 ± 21.28 %; RAIC: 128.21 ± 7.70 %) in two sites which was statistically significant (VPL: p=0.0353; RAIC: p=0.0152) (Fig 8).

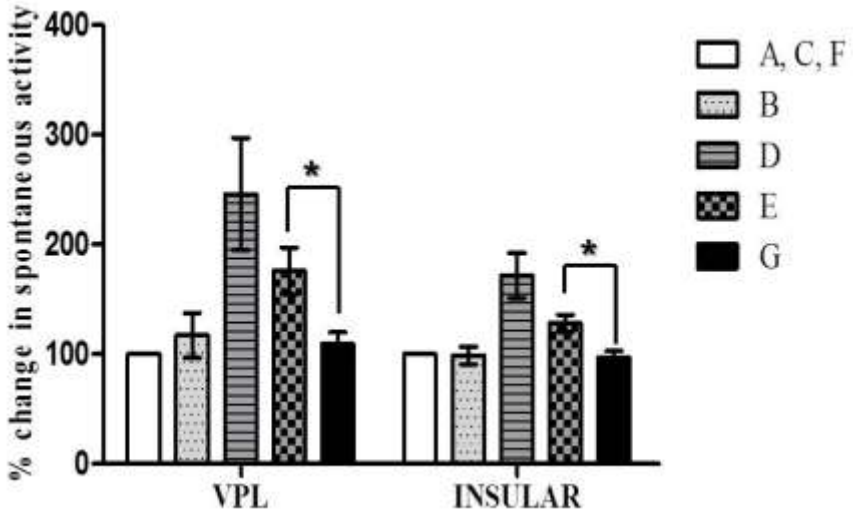

Figure 8. Percentage change in spontaneous activity recorded from VPL and RAIC. After MCS on, the percentage was significantly changed compared with MCS off after mechanical stimulation. As percent change of control response from VPL after MCS, changes were noted in RAIC after MCS. (*VPL: p=0.0353; *Insular: p=0.0152)

Ⅳ. DISCUSSION

In 1990, Hirayama et al. reported that MCS had long-lasting inhibitory effect on high frequency burst hyperactivity of thalamic neurons following spino-thalamic tractomy in cats [17]. Since Tsubokawa et al.,[18] first reported that thalamic pain syndrome was effectively treated by chronic motor cortex stimulation in 1991, epidural MCS has been used for the treatment of various types of neuropathic pain with 45-75% of satisfactory results [10,19-25], including central pain after ischemic or hemorrhagic stroke, trigeminal neuropathic pain, spinal cord injury, plexus avulsion pain, phantom limb pain, and etc. [20]. Thus MCS procedure was accepted as a promising therapy for patients with severe drug refractory neuropathic pain. But the mechanism of MCS for pain modulation is still not elucidated though clinical use in practice.

The one of antinociception hypothesis by MCS is pain modulation on descending inhibitory systems [1,26-28]. The corticospinal tract from motor cortex descends through internal capsule and, after decussating in caudal medulla, to reach spinal cord neurons in anterior and posterior horn [29]. Because of lack of direct projection from M1 to superficial layers or marginal zone of dorsal horn, MCS may indirectly inhibit nociceptive inputs in spinal cord [30]. Also motor cortex has diverse efferent projections to wide cortical and subcortical area. Among these structures, thalamic nuclei receive strong projections from the motor cortex, and which is important site for sensory modulation [31]. And this was the reason that we choose VPL to compare electrophysiological changes from RAIC after MCS. The periaqueductal gray (PAG) system, coupled with rostral ventromedial medulla (RVM) contains descending antinociceptive effect by activating opioid system, and these two locations are also connected to

descending tracts [32]. Another antinociception mechanism by MCS could be modulated by ascending inhibitory system. The thalamus, activated by MCS, could inhibit nociceptive processing, but the specific nuclei affected by MCS and the source of altered inhibition are still in debate [33]. Masri et al. reported that enhanced inhibitory inputs from nucleus of zona incerta (ZI) to the posterior thalamus (Po) were associated with the antinociceptive effects of MCS in their laboratory animal study [34].

Melzack and Casey suggested that the pain experience reflected interacting sensory, affective and cognitive dimensions which could influence each other [35]. Such in point of pain matrix, not only activities of sensory system to noxious inputs but also activity of affective or cognitive system could be involved in pain. There were some efforts to determine the mechanism underlying the MCS with imaging studies. Using positron-emission tomography (PET), MCS was associated with increased blood flow in orbitofrontal, subgenual anterior cingulate cortex, midcingulate cortex, insula cortices, thalamus, and brainstem [36-38]. Another PET study showed that anterior midcingulate cortex and PAG was significantly correlated with the degree of clinical outcome of MCS showing that these structures decreased in opioid binding because of increased secretion [39].

From previous imaging studies, one could consider that MCS could influence on insular cortex. But there were no other experimental study advance in point of insular cortex. The insular cortex is known as the convergence of neuroanatomy and the multidimensional nature of pain. By direct connection from thalamo-insula, information of pain could be received as a site for sensory and affective integration. Historically, pain related to insular cortex was only noted by asymbolia and pseudothalamic pain syndrome [40,41]. Another evidence was from electrical stimulation of the posterior insula which produced pain with thermal sensations in distinct sites on the contralateral body [42]. In animal studies, rostral agranular insular

cortex showed somatic afferences and relation to nociceptive input [43-45]. Also Coffeen et al. showed diminish of neuropathic pain-related behaviors after lesioning in RAIC, which was used in our study. But the MCS effect on RAIC was not demonstrated yet. So we divided neuropathic pain model in two groups either with RAIC lesioning (group B) or without lesioning (group A), and compared during pain response with behavioral test and electrical physiologically. On mechanical stimulation, thresholds were significantly lower in group A which was expected as previous study. But when adding MCS on both group, group B showed significant increase of threshold than group A. And these findings were also noted on latency to withdrawal tests. So one could regard that RAIC is not influenced or merely influenced by MCS. But in our electrophysiological study, the percentage change in spontaneous activity are both increased in VPL and RAIC after mechanical stimulation with 300g vonFrey filament. And after MCS, the percent changes in spontaneous activity were noted in both regions which mean RAIC is also influenced by MCS. The centromedian/parafasciculus (CM/Pf) nuclei, which receive dense projection from motor cortex, were inhibited by MCS, and these nuclei have interconnection with limbic circuit. So our electrophysiological study could be from direct response to MCS or from indirect through CM/pf nuclei [46], which need to be clarified. Future work for blocking this connection would be needed to make clear the effect of MCS on RAIC.

Ⅴ. CONCLUSIONS

The results in this work suggest that RAIC is influenced by MCS, and lesioning RAIC could produce more pain reduction. Together with previous data, our finding may contribute to a better understanding of the MCS effect and the role of RAIC in pain modulation.

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ABSTRACT (IN KOREAN)

운동피질의 자극에 의한 신경병증성 통증 조절 작용에 있어서 섬엽의 역할

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정 현 호

임상적으로 운동피질 자극술은 다양한 통증질환에 대하여 적용되어 왔다. 다양한 뇌 구조물이 운동피질 자극에 의해 통증 조절에 작용한다는 것을 보여줬지만, 여전히 이 기전에 대하여서는 명확히 밝혀지지 않았다. 그러한 구조물중 섬엽의 신경조절 작용을 보고자, 입쪽 무과립성 뇌 섬엽에 병변을 만들어 연구하였다. 그룹 A(n=7)는 신경병증성 통증 모델에 운동피질 자극을 하게 하였고, 그룹 B(n=8)은 신경병증성 통증 모델에 우측 입쪽 무과립성 뇌 섬엽에 병변술을 만들고 운동피질 자극을 하였다. 이후 각각의 그룹에서 자극 전후에 통증의 한계점, 잠재기를 측정을 하였고, 전기생리적 검사를 위해 시상의 후외측복측핵과 입쪽 무과립성 뇌 섬엽에서 운동피질 자극 전후의 신호 변화를 관찰하였다.

통증의 한계점이나 잠재기는 그룹 A 에서는 운동피질을 자극하였을 때에만 의미 있게 변화가 관찰되었으며, 그룹 B 에서는 운동피질의 자극 전후 모두 변화가 관찰되었다. 이러한 변화는 운동피질을 자극한 그룹 B 에서의 잠재기 변화가 가장 크게 나타났다. 전기생리적 검사에서도 후외측복측핵에서의 변화와 같이 입쪽 무과립성 뇌

섬엽에서도 운동 피질자극 전후에 변화차이가 있는 것으로 관찰되었다.

따라서 섬엽이 그 자체로도 통증 조절의 역할을 하고 있으며, 특히 입쪽 무과립성 뇌 섬엽이 운동 피질자극에 의해 통증 조절을 더 향상시킴을 알 수 있었다.

핵심되는 말 : 운동피질자극, 신경병증성 통증, 섬엽