

S15-MRI and Clinical Changes after MSC Injection in the Human Spinal Cord Injury

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Objective: Mesenchymal stem cells (MSCs) from bone marrow can be used as donor cells in cell transplantation therapies for patients with spinal cord injuries (SCI). We describe here the long-term clinical and MRI results of these patients who underwent direct MSC transplantation into their injured spinal cords.

Methods: Autologous MSCs were harvested from each patient's iliac bone and expanded by culturing for 4 weeks. We directly injected 8×10^6 MSCs into the spinal cords and 4×10^7 cells into the intradural space of 10 patients with ASIA A or B due to traumatic cervical SCI. After 4 and 8 weeks, additional 5×10^7 MSCs were injected into each patient by lumbar tapping. After more than 30 months, MRI evaluations of 7 patients were done annually.

Results: Three patients showed gradual improvements in ADL and MRIs also showed gradual changes, including the decrease of cavity size and new appearance of fiber-like low signal intensity streaks, suggesting axon regeneration. However, the other 4 patients who didn't show any changes in ADL showed no change in their MRI. There were no complications of MSC transplantation such as infection, neurological aggravation, ectopic calcification, neoplastic development or syrinx formation.

Conclusions: In the long term results of three patients, direct injection of autologous MSCs into the spinal cord induced gradual clinical improvement and continuous MRI changes. MRI change seems to be related with their ADL improvement.

memo

S16-Spatial Memory Facilitation by Electrical Stimulation of the Medial Septum in Rats

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Objective: Recently, deep brain stimulation has been used to treat various neurological disorders. Some studies support that DBS can be a strategy to treat Alzheimer's disease. The aim of this study was to evaluate the effect of electrical stimulation in the medial septum using rat model mimicking basal forebrain cholinergic deficits of Alzheimer's disease.

Methods: Four experimental groups were composed of normal, lesion, lesion + implantation and lesion + stimulation. 192 IgG-saporin(Selective cholinergic toxin, 8 ul of 0.63 ug/ul) were bilaterally injected into the lateral ventricle. Electrode was stereotactically implanted into the left medial septum (AP + 0.6, ML 0.16, DV -6). Stimulation parameters are 50 Hz, 120us pulse width and 1 volt. One week after implantation, Stimulation started for 2 weeks. Two weeks after surgery, water maze was performed for 1 week and rats were sacrificed immediately after behavioral test. Features were verified by immunohistochemistry and western blot.

Results: During the training trials, latencies of lesion and implantation groups significantly increased in day 4. In contrast, latency of stimulation group had no differences as compared to normal group. In the probe test, lesion group had decreases in time in target quadrant, time in platform zone and the number of platform crossing. Stimulation group performed probe test as well as normal (time in target quadrant: 108% of normal, time in platform: 98% of normal, the number of crossing: 94% of normal). Although they did not perform as normal group, implantation group showed tendency of recovery. IHC and Western blot are ongoing.

Conclusion: Spatial memory is associated with hippocampus and frontal cortex. We had expected activation of hippocampus by stimulation of the medial septum. We confirmed that stimulation of the medial septum facilitates acquisition and recall of spatial memory. Currently we are studying the effects of medial septal stimulation on the hippocampus and frontal cortex.

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S17-Hindlimbs Mapping of the Motor Cortex of the Rat by a Intracortical Microstimulation Method

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Objective: Electrical microstimulation methods have in recent years been used for detailed studies of the cortical motor representations of the limbs and facial muscles in white rats. But The motor representations of the hindlimbs have remained few studied. We were more detailed mapping on the hindlimbs.

Methods: Six female Sprague-Dawley rats weighing 250-350 g were used in this study. The rats were anesthetized with ketamine hydrochloride (150 mg/kg, i.m.) for surgery, and ketamine was added as needed. The rats were then placed in a stereotaxic apparatus, and a median axial incision was made in the scalp, exposing the dura mater after a unilateral rectangular craniotomy (8-mm long and 4.5-mm wide) with the bregma as the reference point. And we analyzed cortical vein differences of length from bregma. Using intracortical microstimulation (ICMS) we show that movements evoked in the hindlimbs (hip, knee, ankle) of the rat motor cortex.

Results: Evoked movements from hind limb segments could be clearly observed, including hip, knee, ankle. In 62.7% of the stimulated sites, simultaneous movements were observed in more than one body segment during the first stimulation. new sequence of electrical stimulation was performed using more graduated currents, inducing muscle contraction in a specific body segment obtained at lower current intensities. The map generated in this procedure reveals the cortical topography of the different body segments according to the stimulation coordinates.

Conclusions: This work provides hind-limb map of the motor cortex of the rat using intracortical microstimulation method. The fact that this stimulation technique is similar to the one used in humans may facilitate future studies that aim at understanding the mechanisms involved in antinociception or in other beneficial effects of MCS in different CNS disorders.

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S18-The Effect of Electrical Stimulation of the Medial Septum in 192 IgG-saporin Lesioned rat: Pilot Study Using MicroPET

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Objective: Although various treatments are tried for Alzheimer's disease patients, the effects of treatment are not satisfactory. Recently, clinical trial of deep brain stimulation for Alzheimer's disease was done and the study showed optimistic results. We evaluated the effect of electrical stimulation of the medial septum in dementia model rat and took microPET for change of brain metabolism

Methods: Same-aged two rats were used for this study; One was for control, the other one was simultaneous injected 192 IgG saporin and taken electrical stimulation of medial septum. All rat were taken micro PET at 2 weeks after stimulation and injected FDG to control and electrical stimulation rat during interstimulation period and stimulationperiod. After then, rats were sacrificed for immunohistochemistry and western blot.

Results: Previous PET studies of Alzheimer patients were revealed regional reduction of glucose metabolism at temporal lobe and posterior cingulate gyrus. In our study, electrical stimulation on 192 IgG saporin lesioned rat showed tendency to increase glucose metabolism at bilateral hippocampus and medial septal area, which were known to be associated with memory function. In contrast, glucose metabolism on cerebellum and frontal associated area were decreased, which was possibly resulted from 192 IgG saporin lesioning.

Conclusion: Because of small sample size, the findings of this pilot study can't decide the effectiveness of electrical stimulation of the medial septum. However, by this study, we can see the possibility for changing memory-associated brain function by electrical stimulation of the medial septal area. Further study is needed for reveal the effect on brain metabolism by electrical stimulation of the medial septum and for possible clinical application.

memo

S19-뇌종양제거술을 위한 원격수술 로봇시스템의 개발

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기존 뇌종양제거술은 현미경을 이용하여 수행하는 것이 전반적인 추세였으나, 최근에는 내시경을 이용한 기술이 활발해지고 있다. Kassam 등은 2010년 발표한 논문에서 뇌심부에 위치한 intraparenchymal tumor를 제거하기 위해 내시경을 이용한 tubular surgery를 소개하였다. 이 논문은 endoscopic tubular surgery가 최소 침습 수술이 가능하고, 시술 편의성 또한 높음을 증명함으로써 신경외과 분야에서 endoscopic surgery의 가능성을 보여주었다.

그러나 endoscope가 microscope 보다 시야가 넓지만 집도의에겐 충분하지 않다는 점, 3차원 시각화의 부재로 수술도구끼리 부딪히거나 tumor 너머 brain tissue 또는 vessel과 같은 정상조직을 침해할 수도 있다는 점들 때문에 수술 수행에 어려움을 겪을 수도 있다. 후자의 경우는 숙련도에 반비례하여 겪을 가능성도 크다. 이러한 한계는 내비게이션과 같은 감시 시스템과 스테레오 내시경과 같은 3차원 영상 장치를 이용하여 해결이 가능할 수 있으며, 충돌, 침해와 같은 문제는 robotized device의 제어를 통해 해결할 수 있을 것이다.

이러한 통찰을 토대로 저자들은 뇌종양제거술을 수행하기 위한 원격 수술로봇 시스템을 4년동안 개발하여왔다. 개발된 원격 수술로봇 시스템은 마스터 장치, 슬레이브 장치, 내비게이션 소프트웨어로 구성되며, tubular surgery에 최적화 되도록 구현되었다.

마스터 장치는 상용제품(Phantom Omni, Sensable Inc., USA)으로서 6자유도 출력과 3자유도 force feedback이 가능하다. 슬레이브 장치는 corridor의 크기에 맞춰 20 mm의 직경을 갖는 tube 형태로 디자인되었다. 2개의 end-effector가 장치되어 있고, 10 mm의 직경을 가진 스테레오 내시경이 장착되어 있다. End-effector 중 하나는 4자유도를 가진 suction이며, 다른 하나는 5자유도를 가진 gripper로 구현되었다.

시스템은 수술 전, 수술 중 두 단계로 지원한다. 내비게이션 소프트웨어는 preoperative volume image를 이용하여 수술 전에 환부의 볼륨, extracranial 영역에서 환부로 경로의 등을 데이터화 하여 저장한다. 또한 수술 중에는 Optical tracker를 이용한 레지스트레이션을 통해 영상좌표와 로봇좌표의 매칭을 지원하며, 매칭된 데이터를 토대로 환부의 위치와 end-effector들의 위치를 실시간 감시함으로써 위험한 충돌 및 정상 조직 침해를 사전에 막을 수 있다. 수술 중에 집도의는 3차원 화면을 보면서 시술하게 되며, 내비게이션의 감시로 인해 생성되는 신호는 소리, 경고색, 마스터 장치에서 느낄 수 있는 반력 등으로 위험도 확인이 가능하다.

본 시스템은 팬텀 실험까지 마무리 된 상태이며 결과는 만족스러웠다. 하지만, 실제 임상시에 corridor를 고정하는 방법과 고정 중에 CSF 유출로 인한 brain shift 문제, tendon 방식 메커니즘이 갖는 단점의 극복 등은 더 연구해야 할 과제이다.

*본 연구는 지식경제부 및 정보통신연구진흥원의 IT핵심기술개발사업의 일환으로 수행하였음.[2008-F-042-01, 원격 로봇 수술을 위한 영상 유도 시스템 기술 개발]

S20-Introduction of Sonomo[®] Focused Ultrasound (FUS) in Neurological field

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SonomoTM is a commercially-available FUS which is developed recently in Harvard and our institute. FUS can deliver acoustic energy to small and steerable regions of the brain (e.g HIFU for thermal ablative therapy of tumor). Heat is not desired for safety reasons. Microscopic vibration can alter the excitability in neurons. Instead of continuous application of HIFU, apply the low intensity FUS stimulation as a train of pulses with sufficient inter-pulse intervals.

We will present the results of animal experiments on seizure control and extracellular neuro transmitter changes.

We will try clinical applications for migraine, neuropathic pain (including; post-stroke pain) and intractable seizure.

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S21-The Effect of Human Brain-derived Neural Stem Cell and Human Dental Papilla-derived Stem Cell Transplantations in a Rat Model of Parkinson's Disease

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Objective: The transplantation of various stem cells has been reported to be able to replace impaired dopaminergic neurons. However, it has limitations, which are low survival of grafted neurons, a lack of synaptic connection with host neurons, and graft induced dyskinesia. Here, we have tested the efficacy of human brain-derived neural stem cell (HB-NSC) and human dental papilla-derived stem cell (HDP-SC) in the 6-hydroxydopamine (6-OHDA) lesion model of Parkinson's disease (PD). They are characterized by behavior test, microPET scan using multitracer (2-deoxy-2-[18F]-fluoro-D-glucose ([18F]-FDG) and [18F]-N-(3-fluoropropyl)-2-carbomethoxy-3-(4-iodophenyl) nortropane ([18F]-FP-CIT)), and histological evaluations.

Methods: Twenty three female Sprague-Dawley rats received a unilateral injection of 6-OHDA into the right medial forebrain bundle (MFB), followed 3 weeks later by injections of PBS only (control group, n=7) or HB-NSC (HB group, n=8) or HDP-SC (HDP group, n=8) into the ipsilateral striatum. Stepping tests were performed to evaluate the recovery of motor deficit in contralateral paw. Apomorphine-induced rotation tests were performed 1 week after 6-OHDA injection, and 4 and 8 weeks after each injection. Dopamine transporter (DAT) and glucose metabolism were detected by microPET using multitracer of [18F]-FP-CIT and [18F]-FDG. Histological changes after cell transplantations were evaluated by immunostaining and immunofluorescence.

Results: All rats in HDP group had died within 2 weeks after cell transplantation, and one rat in HB group died 8 weeks after cell transplantation. As a result of postmortem study, homogeneous malignant tumors were found in the injected striatum. Stepping tests revealed HB-NSC transplantation could not improve motor dysfunction because contralateral paw touch rate in HB and control group showed similar patterns in time dependant variation. In apomorphine-induced rotation tests, both HB and control group didn't show a significant change among different time points in contralateral rotations. MicroPET showed DAT impairment and glucose metabolism.

Conclusion: We explored the effect of HB-NSC and the early stage of HDP-SC in the PD rat models. In HB-NSC group, TH positive cells in the lesioned striatum were observed, but we couldn't find that they have the abilities to recover a complete motor dysfunction. In HDP-SC group, we failed to find the positive effects of PD model in rats.

S22-Progress of Neural Stimulation in Neuropathic Pain using Animals

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To establishing the treatment method for neuropathic pain, we are currently studying on neural stimulation methods such as deep brain stimulation (DBS) and motorcortex stimulation (MCS).

In DBS, we focused on ventral posterolateral nucleus (VPL). In our study from DBS, we demonstrated that the pain was effectively reduced in mechanical allodynia and cold allodynia.

In MCS, the pain was also effectively reduced.

Besides, we studied on imaging studying using micro-PET. We measured the activities of brain structures from micro-PET images.

In present, to develop the efficiency of neural stimulation on neuropathic pain, we are currently focused on developing novel and easier neural system and electrode. Moreover, we are also focused on the changes of neuronal activation using extracellular recording including removing stimulation artifact.

In next, we are planned to develop a new system including novel features such as wireless communication and wireless neural recording.

In our study, we expect that our system could be very helpful for researchers and clinicians to understand the mechanism of neuropathic pain.

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