学 位 論 文 の 要 旨

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学 位 論 文 名　Electroconvulsive Treatment Ameliorates Lipopolysaccharide-induced Depressive Like Behaviour in Rats.

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論 文 内 容 の 要 旨

INTRODUCTION

Major depression (MD) is the most prevalent mood disorder worldwide. This mental disorder has increased social burden with a significant proportion of mortality. MD affects about 280 million people worldwide. The influences of MD can be persistent or recurrent and can dramatically affect a person's ability to function and live a rewarding life.

Electroconvulsive treatment (ECT) is a highly effective treatment in psychiatry and shows efficacy in patients who were resistant to pharmacotherapy. ECT elicits substantial improvement in approximately 80% of patients. Both the generalized seizure and the dose of electricity used are believed to be critical for the therapeutic effect of ECT. However, the exact mechanism of therapeutic action of ECT remains unknown.

Recent retrospective cohort studies have shown that ECT is highly effective in ameliorating depressive symptoms with fewer unwanted effects. To establish further efficacy of ECT in rodent depression models, we investigated the effect of ECT on depressive-like behaviour induced by lipopolysaccharide (LPS) in rats. LPS is a well-establish proinflammatory stimulant to induce depressive-like behaviour in rodents.

MATERIALS AND METHODS

Twenty adult male Sprague-Dawley (SD) rats were randomly divided into four groups (n=5), namely, control, LPS, ECT, and LPS+ECT. The SD rats received intraperitoneal injection of LPS

(*Escherichia coli* serotype 055: B5; 1 mg/kg body weight) or sterile saline, followed by ECT or sham treatment for 7 consecutive days. To avoid hitting such organs as the liver, bladder, and cecum of rats, i.p. injection was administrated into the lower right quadrant of the abdomen.

All experiments were carried out during the light period. ECT was administered 2 hours after the i.p. injection of LPS. Body weight was monitored and recorded every day before i.p. injection. In every ECT, an electric shock was given under such anesthesia. ECT was administered transcranially via bilateral ear clip electrodes by using an E.C. Stimulator MK-810 (Muromachi Kikai, Tokyo, Japan). The stimulus was a sine wave pulse, 100 V, 60 Hz, 50 mA for 1.5 s. Each stimulation resulted in a typical tonic-clonic seizure lasting for less than 10 s. The rats in the control groups received sham treatment, including isoflurane anesthesia and placement of the ear clip electrodes without delivery of the electroconvulsive shock.

Each SD rat received the behaviour tasks one by one. The Y-maze test and habituation of forced swimming test were performed on day 14 after the last ECT and the forced swimming test (FST) was performed on the next day. The behavioural tests were monitored and recorded by a digital camera. After completing the behaviour tests, the animals were killed by the overdose of Carbon dioxide (CO2) in the specific container.

All experiments with animals in this study were approved by the Animal Care and Use Committee of Shimane University (Authorization No: IZ31-37). All data were presented as the mean ± standard error of the mean (S.E.M.). We used a one-way analysis of variance followed by post hoc Tukey's honestly significant difference test to evaluate differences among groups. The statistical analyses were performed with SPSS software (IBM SPSS Statistics for Windows Version 23, SPSS Japan Inc., Tokyo, Japan). The p-value was considered as significant when less than 0.05.

RESULTS AND DISCUSSION

The average body weight of LPS group (236.20 ± 5.04 g) was significantly decreased compared to the control group (263.43 ± 6.89 g). However, ECT did not significantly increase the rat body weight in the LPS group (236.20 ± 5.04 g). These findings suggest that ECT does not restore the appetite loss caused by LPS injection.

The FST showed that the immobility time in the LPS group (169.73 ± 15.46 s) was significantly longer than that in the control group (63.16 ± 4.48 s). However, ECT administration to LPS-injected rats significantly shortened the prolonged immobility. Climbing time and Swimming time in the LPS group was significantly shorter than that in the control group and ECT group. The Y-maze test showed a significant decrease in % spontaneous alternation behaviour (SAB) in the LPS group compared to the control group. ECT administration to LPS- injected rats significantly restored such a decrease in % SAB. To our knowledge, this is the first study showing the therapeutic effects of ECT on LPS-induced depressive-like behaviour in rats.

The first finding is consistent with the previous studies of depressive rodent models using FST, in which ECT significantly shortened immobility time in MAP6 KO mice and in rats under chronic restraint stress. Accordingly, ECT may exert therapeutic effects even in different pathogeneses associated with MD. Immobility time in the FST can be regarded as behavioural despair, which is supposed to reflect depressed moods. The FST on rodents has been extensively used as a simple animal model for investigating the neurobiology of MD because of its procedural simplicity and its high reproducibility.

In this study, we employed an inflammation-induced depression model to determine ECT efficacy. Yirmiya et al. (1996) first demonstrated that the systemic administration of LPS caused depressive-like behavior in rats. A number of animal studies have demonstrated that systemic inflammation induced by peripheral administration of LPS increases the expression of pro-inflammatory cytokines in both the periphery and brain and causes abnormal behaviour similar to MD.

Increasing evidence suggests that infection and persistent low-grade inflammation in peripheral tissues play roles in the MD pathogenesis. Periodontitis is the most common inflammatory disease in adults. Accordingly, treating periodontitis may be therapeutic for MD.

It is clinically known that many people begin to notice an improvement in their symptoms after about six treatments with electroconvulsive therapy. Our result showed that ECT performed for consecutive 7 days improved depressive-like behaviour. Therefore, our experimental condition of ECT seems relevant to a clinical setting.

CONCLUSION

Our results suggest that repeated ECT ameliorated LPS-induced depressive-like behaviour in SD rats. Further studies are warranted to elucidate the molecular mechanism of such therapeutic effects of ECT.