Form8

ABSTRACT OF DISSERTATION

Title	Peripherally Administered Botulinum Toxin Type A Localizes Bilaterally in Trigeminal Ganglia of Animal Model （片側末梢投与された A 型ボツリヌス毒素は動物モデルにおいて両側三叉神経節に局在する）
Author's Name	Arief Waskitho, Yumiko Yamamoto, Swarnalakshmi Raman, Fumiya Kano, Huijiao Yan, Resmi Raju, Shaista Afroz, Tsuyoshi Morita, Daisuke Ikutame, Kazuo Okura , Masamitsu Oshima, Akihito Yamamoto, Otto Baba, Yoshizo Matsuka

[Background]

Peripheral nerve injury leads to sensory ganglion hyperexcitation, which increases neurotransmitter release and neuropathic pain. Botulinum toxin type A (BoNT/A) regulates pain transmission by reducing neurotransmitter release, thereby attenuating neuropathic pain. Despite multiple studies on the use of BoNT/A for managing neuropathic pain in the orofacial region, its exact mechanism of transport remains unclear. In this study, we investigated the effects of peripheral administration of BoNT/A in the treatment of neuropathic pain and evaluated its transportation in the trigeminal nerve.

[Methodology]

Male Sprague Dawley rats (weighing 120-360g) were used in these experiments. Two different neuropathic pain animal models were performed, by intraperitoneal cisplatin injection (2mg/kg/day) for four consecutive days or infraorbital nerve constriction (IONC). Quantitative sensory testing was performed using electronic Von Frey device. The mouse bioassays were performed to evaluate the transmission of BoNT/A through blood circulation. The Alexa Fluor-488-labeled C-terminal half of the heavy chain of BoNT/A (BoNT/A-Hc) was peripherally injected into the whisker pad to evaluate its transmission in the trigeminal ganglia. Bilateral trigeminal ganglia were obtained four days later, followed by immunohistochemistry results observation and densitometric analysis.

[Results]

Intraperitoneal administration of cisplatin induced bilateral neuropathic pain in the orofacial region. Unilateral infraorbital nerve constriction (IONC) also reduced the

ipsilateral head withdrawal threshold to mechanical stimulation. Unilateral peripheral administration of BoNT/A to the rat whisker pad attenuated cisplatin-induced pain behavior bilaterally. Furthermore, contralateral peripheral administration of BoNT/A attenuated neuropathy-induced behavior caused by IONC. BoNT/A appearance was detected in the blood after its peripheral administration. BoNT/A-Hc was localized in the neurons of the bilateral trigeminal ganglia following its unilateral administration.

[Conclusion]

These findings suggest that axonal and hematogenous transport are involved in the therapeutic effects of peripherally administered BoNT/A in the orofacial region.