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ABSTRACT OF DISSERTATION

Title	Analgesic Effect of Tranilast in an Animal Model of Neuropathic Pain and Its Role in the Regulation of Tetrahydrobiopterin Synthesis (神経障害性疼痛モデル動物におけるトラニラストの鎮痛効果とテトラヒドロビオプテリン合成制御の役割)
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【Background】

Chronic orofacial pain is considered challenging for effective management due to its complex underlying mechanisms. Trigeminal neuralgia is one of the chronic orofacial pain, characterized by the episodic, unilateral, lancinating type of pain which can often be triggered by routine activities. Carbamazepine is the drug of choice but possesses several side effects. Nerve decompression surgery can be effective in treating the pain, although it is invasive. Therefore, effective treatment of chronic orofacial pain is desired. Tetrahydrobiopterin (BH4) is an essential cofactor involved in the production of several neurotransmitters. Previous research reports suggested upregulation of BH4 in chronic pain. This study aimed to evaluate the analgesic effect of tranilast in relieving neuropathic pain and analyze the changes in the gene regulation involved in BH4 synthesis using trigeminal ganglion.

【Methodology】

Four weeks old male Sprague-Dawley rats were used. Trigeminal neuropathic pain was induced by infraorbital nerve constriction (IONC). Intraperitoneal injection of tranilast (50-200 mg/kg) was compared with carbamazepine (30 mg/kg) or saline. von Frey's behavior test was done for measuring the mechanical sensitivity of the whisker pad area. The rotarod performance test was done for evaluation of motor coordination. Trigeminal ganglia were excised and tested for genes that regulate the BH4 pathway

using RT2 Profiler PCR Array.

【Results】

von Frey test showed significant changes in the ipsilateral side of the nerve injury model ($p < 0.05$). Tranilast (75, 100 & 200 mg/kg) and carbamazepine responded well with significant changes in pain tolerance ($p < 0.05$). The rotarod performance test showed no significant changes in the tranilast group whereas, a reduced retention time on the rod for carbamazepine treated group, which signifies reduced motor coordination. Downregulation of the sepiapterin reductase (Spr) and aldoketo reductase (Akr) genes after tranilast injection was observed compared to the pain model.

【Conclusion】

These findings suggest that tranilast effectively treats neuropathic pain. Tetrahydrobiopterin (BH4) mechanism would be a new avenue for neuropathic pain intervention.