The effect of THIP on the thermal and mechanical thresholds of chronic sciatic nerve cuff injury mice.

Saya Hakata\(^a\), Ayako Takahashi\(^b\), Akira Iura\(^a\), Seiichi Osako\(^a\), Hironobu Uematsu\(^a\), Yuji Fujino\(^a\)
\(^a\)Department of Anesthesiology and Intensive Care medicine, Osaka University Graduate School of Medicine

Introduction
Decreased Gamma-aminobutyric acid (GABA)-ergic phasic inhibitory transmission in the spinal cord is thought to be responsible for the development of neuropathic pain. However, the role of GABAergic tonic current in neuropathic pain is unknown. We and others previously reported that a subset of substantia gelatinosa (SG) neurons of the dorsal horn possess GABAergic tonic current mediated by GABA\(_{\text{A}}\) receptor (GABA\(_{\text{A}}\)R)s containing the a5, d subunits. Recently, GABA\(_{\text{A}}\)R d subunit preferring agonists 4,5,6,7-tetrahydroisoxazolo [5,4-c]pylidine-3-ol (THIP) has been reported effective to reduce acute thermal pain in normal mice. We have assessed the effect of GABA\(_{\text{A}}\)R d subunit mRNA by rt-PCR revealed the expression of d subunits were reduced.

Methods
Male ddY mice (4 weeks age) were anesthetized with 3% sevoflurane, a 2-mm long split section of polyethylene tubing (PE-20) was placed around the nerve to induce chronic constriction injury (CCI). To measure pain threshold, we evaluated the mechanical paw withdrawal thresholds and the latency of thermal stimulation by von Frey and Hargreaves tests. Two weeks after surgery, we made intrathecal administration of 6GABA\(_{\text{A}}\)R preferring agonists THIP(0.74 g i.t.) (N=15) or normal saline (NS)(N=15) by double blinds methods, and analyzed the effect on the thresholds of mechanical and thermal stimulation.

Results
CCI mice showed both mechanical and thermal allodynia. Thermal hypersensitivity disappeared by 3 weeks post-surgery, on the other hand, mechanical hypersensitivity continued more than three weeks as in a previous study. Intrathecal administration of THIP induced significantly improved both thermal (4.6±0.8 to 6.6±1.1 s) and mechanical (2.6±0.9 g to 5.6±1.6 g) thresholds (p<0.05, non-paired t-test). On the other hand, NS did not effect on both thermal (4.2±0.9 s to 4.3±1.2 s) and mechanical (3.1±0.5 g to 3.7±1.0 g) thresholds.

Conclusion
THIP showed effective on both thermal and mechanical hypersensitivity. This might be suggested that d GABA\(_{\text{A}}\)R mediated tonic current in the spinal cord contribute to the mechanism of neuropathic pain.

Discussion
THIP showed effective on both thermal and mechanical hypersensitivity. In the previous study, THIP showed therapeutic effects on acute pain of mice.\(^4\) Our study might be suggested that dGABA\(_{\text{A}}\)R mediated tonic current in the spinal cord contribute to the mechanism of neuropathic pain.

Our result suggests that GABA\(_{\text{A}}\)R d subunit-mediated tonic currents may likewise be a therapeutic target for neuropathic pain.

References
1) R.P.Bonin et al. PAIN. 2011

2016 Saya Hakata email: fanafana38@yahoo.co.jp