Contribution of sympathetic nervous system on lumbar radicular pain
-Electrophysiological study using patch clamp recordings-

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INTRODUCTION:
Neuropathic pain following peripheral nerve injury is considered as two types of pain state: sympathetically maintained pain (SMP) and sympathetically independent pain (SIP). SMP is a condition in humans for which pain can be attenuated by sympathectomy or sympathetic nerve block. In neuropathic pain with animal models, it has been reported that sympathetic nerve fibers sprouted to DRG in which sympathetic postganglionic axons wrapped into DRG neurons. Likely, the sympathetic nervous system is considered to be involved in causing lumbar radicular pain. However, the pathophysiological mechanisms have not been fully explored. Norepinephrine (NE) is the neurotransmitter, which postganglionic neurons in the sympathetic nervous system release, and may be crucial for the generation or maintain of SMP. The purpose of the present study is to clarify the effects of NE in modulating the excitability of DRG neurons with root constriction model.

MATERIALS & METHODS:
All experiment protocols were approved by the Sapporo Medical University Animal Care and Use Committee. We used a total of 20 adult male Sprague-Dawley rats weighing 150-200g at the beginning of the study. In lumbar root constriction group (n=10), the left L5 spinal root was exposed and tightly ligated with 8-0 nylon suture. While in sham group (n=10), the left L5 spinal root was exposed only without the ligation. At postoperative days 10-14, the ipsilateral L5 DRG neurons were quickly excised and enzymatically digested with collagenase.

To evaluate the excitability of DRG neurons, we used two kind of protocol. One protocol (short stimulation) was that depolarizing currents of 0.2-4.0nA (0.5ms duration) were injected in increments 0.2nA until an action potential was evoked. We examined the threshold current, resting membrane potential (RMP), amplitude, afterhyperpolarization, threshold voltage, APD50, and dv/dt max. The other protocol (long stimulation) was depolarizing currents of 0.01-0.39nA (1ms duration) in increments 0.02nA, which was evoked by repetitive discharge. We confirmed the discharge pattern, and examined the maximum values of number of the spike in each current (max spike).

NE stock solution was dissolved in distilled water with an equivalent amount of ascorbic acid. Final concentration of NE was 10µM. Five minutes after NE application, electrophysiological recording was performed.

Data were expressed as the mean ± SEM and analyzed statistically using Student’s t-test or paired t-test. P<0.05 was the accepted level for statistical significance.

RESULTS:
In the root constriction group, the mean RMP was more depolarized and the mean threshold current was lower compared with the sham group. The max spike of the root constriction group was greater than that of the sham group (Fig. 1).

In the root constriction group, NE application induced an increase in the dv/dt max. The max spike during NE was 15.9±2.1, which was significantly greater than the mean of 10.7±1.8 before NE (Fig. 2). In contrast, there were no significant changes in the sham group (Fig. 3).

DISCUSSION:
The present study showed that the max spike was further increased by applying NE, suggesting that NE enhanced the excitability of DRG neurons with root constriction model. The rise of the dv/dt max indicates an increase in inward current, which may mainly be involved in sodium ions.

The presence of adrenoreceptors in DRG and spinal dorsal horn neurons has been demonstrated, suggesting a role of NE at presynaptic and postsynaptic sites in the modulation. Therefore, the NE releasing to DRG may have different modulation of pain sensation depending on the types of the adrenoreceptor. Although speculating that the sympathetic nervous system play an important role in generating lumbar radicular pain, further studies for the subtype of adrenoreceptor or the current property for the NE-induced hyperexcitability of DRG neurons should be needed for comprehensive understanding.

REFERENCES: