A MECHANISM OF THE PAIN RELATED BEHAVIOR INDUCED BY A DEGENERATIVE NUCLEUS PULPOSUS ASSOCIATED WITH A PH CHANGE IN RATS

*+Hashizume, H; *Kawakami, M; *Matsumoto, T; *Yoshida, M
*Department of Orthopaedic Surgery, Wakayama Medical University, Wakayama, Japan
hashizum@wakayama-med.ac.jp

Introduction
Low back and radicular pain induced by lumbar disc herniation are a major clinical problem with huge monetary. The study of low back pain has been hindered, until recently, by the absence of an adequate animal model. Recently we have reported applying nucleus pulposus tissue, obtained from tail intervertebral discs that had been subjected to chronic mechanical compression, to the lumbar nerve roots produces greater and of longer duration hyperalgesia, which is thought to be a pain related behavior, compared with normal nucleus pulposus. In this model, the underlying mechanisms producing pain related behavior are still unclear although the nucleus pulposus in the compressed tail vertebrae with an Ilizarov-type apparatus showed a certain histological degeneration. Previous reports have described that a reduction of pH of the lumbar disc may be associated with low back pain or radiouopathy in humans, and a change in pH may result in hyperalgesia produced by ligation of the sciatic nerve with chronic gut sutures. Moreover, it has been shown that inflammatory bioactive substances, related to arachidonic acid such as phospholipase A2 (PLA2) and proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) expressed by the NP around the nerve root are related to hyperalgesia. The purpose of this study were: 1) to evaluate if the expressions of PLA2, IL-1β, TNF-α and the pH change in the nucleus pulposus have a relation to pain-related behavior which was induced by application of the degenerative nucleus pulposus on the nerve root.

Materials and Methods
The experimental protocol was reviewed and approved by the Institutional Animal Care and Use Committee at our institution. A total of 30 male Sprague-Dawley rats weighing about 250 g was used. All surgical procedures were performed under total anesthesia by an intraperitoneal injection of sodium pentobarbital (50 mg/kg). An Ilizarov-type apparatus was applied to immobilize and chronically apply compression on two intervertebral discs between the third and fifth caudal vertebra in the rat. Rats were subjected to three different period of the tail compression – 4 weeks (n=6), 8 weeks (n=9) and 12 weeks (n=8). Immediate after removing the apparatus, the tail was amputated at the tail compression – 4 weeks (n=6), 8 weeks (n=9) and 12 weeks (n=8). Then the nucleus pulposus was relocated to the left L4 and L5 nerve roots, which were exposed by partial laminectomy. In a control group (n=6), after pH in the nucleus pulposus obtained from normal intervertebral discs of the tailwas measured, the nucleus pulposus was relocated to the left L4 and L5 nerve roots in the same rats. Motor function and sensitivity to noxious mechanical stimuli was measured in all rats preoperatively, and up to three weeks postoperatively. For the histological examination, nucleus pulposus of the 8 weeks compressed discs between the treated vertebrae were measured with a micro pH electrode. The pH of the nucleus pulposus contributes to the severity and the duration of the pain related behavior induced by the nucleus pulposus.

Discussion
Mechanical hyperalgesia observed in rats treated with the compressed nucleus pulposus tissue was greater and of longer duration than in the rats treated with normal discs. In this experimental model, in which mechanical compression was chronically applied to the tail intervertebral discs, production of inflammatory substances such as PLA2, IL-1β, and TNF-α did not increase in the nucleus pulposus cells. On the other hand, the pH in the nucleus pulposus was significantly low in the 4 and 8 weeks compressed group, compared to the non-compressed group. There is a possibility that the pH may contribute to the severity and the duration of the mechanical hypersensitivity induced by the nucleus pulposus. It is well known that pH in the nucleus pulposus is lower than other part of the disc because of the lactic acid production under anaerobic condition in the nucleus pulposus. Recently Urban and associates suggested that the viability of nucleus pulposus cells sensibly response to the changes of pH and/or oxygen concentration. The neutralization of the acidic condition in and around the nerve root may become an option for the treatment of radicular pain in the lumbar disc herniation in the future.

Conclusion
A chronic mechanical compression to the intervertebral disc induces a pH decrease in the nucleus pulposus in rats. It is possible that the lower pH of the nucleus pulposus contributes to the severity and the duration of the pain related behavior induced by the nucleus pulposus.

References

Figure
Changes of sensitivities to mechanical noxious stimuli. The percentage difference in withdrawal threshold from noxious stimuli between the ipsilateral and contralateral hindpaws was calculated using the appropriate formula: [(ipsilateral threshold – contralateral threshold) / contralateral threshold] × 100. Negative percentages in Y-axis reflect hyperalgesia.