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ORIGINAL ARTICLE

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Indomethacin blocks the nucleus pulposus-induced effects on nerve root function

An experimental study in dogs with assessment of nerve conduction and blood flow following experimental disc herniation

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Abstract Inflammatory mechanisms have been suggested to be involved in the basic pathophysiologic events leading to nerve root injury after local application of nucleus pulposus. To assess if these nucleus pulposus-induced effects could be blocked by anti-inflammatory treatment, 41 dogs were exposed to either incision of the L6-7 disc to induce experimental disc herniation with (n=12) or without (n=14) indomethacin treatment per os (5 mg/kg per day), and no incision with (n=5) or without (n=10) indomethacin. Intraneural blood flow and nerve conduction velocity were assessed after 7 days to evaluate the degree of nerve injury. Disc incision induced a reduction in nerve root and dorsal ganglion blood flow as well as nerve function, similarly to previous studies. However, simultaneous treatment with indomethacin efficiently blocked the negative effects on both blood flow and nerve conduction but had no effects per se. The present study thus indicates that inflammatory mechanisms may be of relevance in the pathophysiology of nucleus pulposus-induced nerve root injury and thereby also for sciatica.

Keywords Sciatica · Disc herniation · Nerve roots · Inflammation · Inflammatory mediators

Introduction

The recently discovered effects of nucleus pulposus on nerve roots after epidural application are still not fully understood [10]. It is known that the nucleus pulposus induces an increase in the permeability of intraneural capillaries with subsequent formation of an intraneural edema [2, 16]. It is also known that intraneural blood flow is reduced [15], probably due to edema formation, and that the resulting ischemia induces histologic and neurophysiologic changes [5, 10, 13]. However, the mechanisms responsible for these changes are less well known. Since nucleus pulposus, apart from inducing increased vascular permeability, also attracts white blood cells [8, 12, 20] and since the effects on nerve function and structure may efficiently be blocked by intravenous methylprednisolone [11], it has been assumed that inflammatory mechanisms are involved. To assess this hypothesis further, the present study was designed to ascertain whether indomethacin, an anti-inflammatory drug, can block nucleus pulposus-induced effects on nerve function and intraneural blood flow in a dog model that has been used previously to study such parameters [5, 14, 15].

Materials and methods

Animals

A total of 41 dogs weighing 7–12 kg each were anesthetized with intramuscular injection of 25 mg/kg body weight of ketamine, (Parke-Davis, Morris Plains, N.J., USA) and 5 mg/kg body weight of thiopental (Ravonal, Tanabe Yaku, Osaka, Japan). After endotracheal intubation, anesthesia was maintained by inhalation of 3 l/min of nitrous oxide, 3 l/min of oxygen, and 1% halothane (ISC, Bristol, U.K.). The dogs were prone and medial hemilaminectomy of the sixth and seventh lumbar vertebrae was performed under sterile conditions. In control animals, the nerve root was retracted for 10 sec and then replaced. In the others, the seventh lumbar nerve root was gently retracted and the dorsolateral portion of the annulus fibrosus incised. An 18-gauge needle was inserted through the incision into the nucleus pulposus and approximately 0.01 ml of saline was gently injected into the center of the disc. This procedure always resulted in a visible leakage of nucleus pulposus into the spinal canal. After the specific procedure, the wounds were carefully sutured and the dogs brought back to the animal house. Inspections were made daily regarding general condition, neurologic dysfunction, and wound healing.

Starting the day after surgery, 17 dogs (disc incision n=12, control n=5) received 5 mg/kg/day of indomethacin (Sigma, Tokyo, Japan) per os for 6 days. The other 24 dogs (disc incision n=14, control n=10) received no medication. Seven days after the initial procedure, the dogs were reanesthetized accordingly. The content of the spinal canal was exposed by laminectomy from the fifth lumbar to the first sacral vertebra. The left seventh lumbar nerve root was defined.

Assessment of blood flow

Under controlled temperature and moisture, blood flow was analyzed by hydrogen washout (DHM-3001, M.T. Giken, Tokyo, Japan). With this technique, hydrogen is generated in the target tissue for 25 s with a polarovoltage of 600 mV and direct current of 20 μA [7, 19]. One electrode was inserted into the nerve root at the take-off from the central dura sac and one into the dorsal root ganglion. The blood flow measurements were performed in vivo. After the nerve conduction velocity measurements that followed blood flow analysis, the dogs were killed and the diffusion value of hydrogen in the nerve tissue was measured 1 h after death. The intraneural blood flow rate was obtained by subtracting the postmortem diffusion value from the in vivo value.

Neurophysiologic assessment

The nerve root was stimulated approximately 5 mm cranially and about 5 mm caudally from the L6-7 disc using a SEN-7203 electronic stimulator (Nihon Kohden, Tokyo, Japan). An EMG recording was obtained from the ipsilateral gastrocnemius muscle and amplified by a SEN-6102 preamplifier (Nihon Kohden). The muscle action potentials (MAP) were visualized on a Macintosh computer (Macintosh, Cupertino, Calif., USA) using Superscope II software and a MacAdios II A/D converter (GW Instruments, Sommerville, Mass., USA). The stimulation voltage was kept at twice the level required to induce maximal muscle action potential and thus in the range of 2–4 V. Stimulation duration was 1 ms. To ensure that impulses were recorded only from stimulated nerve roots, the nerve roots were gently elevated from the surrounding tissues during stimulation. The nerve conduction velocity (NCV) between the two stimulation sites, i.e., over the exposure area, was calculated by dividing the distance between the two stimulation sites by the time difference between the two stimulations as recorded by computer.

The differences between the various series were evaluated statistically for both blood flow and nerve conduction velocity using analysis of variance (ANOVA) and Fischer's PLSD at 5%. The experimental protocol was approved by the local animal ethics research committee.

Results

All animals seemed to tolerate surgery and medication well, and no apparent effects on general condition, neurologic function, or wound healing were noted.

Assessment of blood flow

The results of the assessment of nerve root blood flow are presented in Fig. 1. Nerve root blood flow in the group with incised discs and no treatment (Inc+Ind–) was statistically lower than in the control group (Inc–Ind–). However, the series with incised discs plus indomethacin treatment (Inc+Ind+) showed no statistically significant reduction in blood flow over controls. The difference between the Inc+Ind+ and Inc+Ind– series was also statistically significant. The nonincised but treated group (Inc-Ind+) showed blood flow similar to that of the control group.

The data for dorsal root ganglion blood flow were similar, showing a reduction after disc incision in the Inc+Ind– series, with a statistically significant difference to the Inc+Ind+ series (Fig. 1).

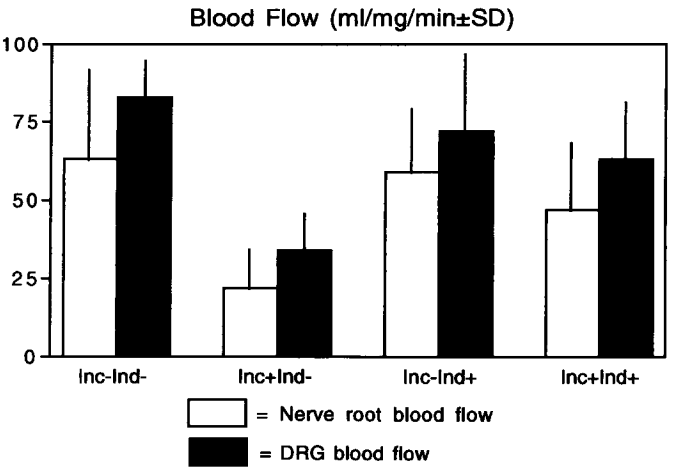

Fig. 1 Data from the blood flow measurements. Inc+Ind– dogs showed statistically significant reductions in nerve root blood flow (P<0.0007) and dorsal root ganglion (DRG) blood flow (P<0.0001). Inc+Ind+ data were statistically different for both nerve root (P<0.0121) and DRG blood flow (P<0.0034) vs Inc+Ind–. Treatment with indomethacin without disk incision (Inc–Ind+) induced no changes vs controls

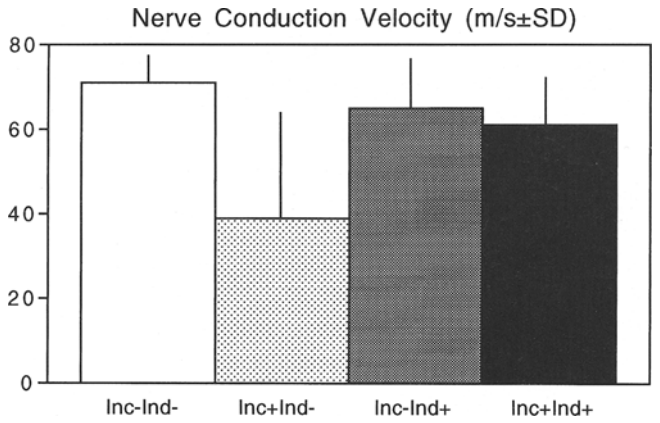

Fig. 2 Data from the nerve conduction velocity measurements. There was a statistically signification reduction in the Inc+Ind– group vs controls (Inc–Ind–) ($P<0.0001$). Nerve conduction velocity in the Inc-Ind+ group was similar to controls. The reduction in the Inc+Ind+ group was statistically significantly different vs Inc+Ind– ($P<0.0012$)

Neurophysiologic assessment

The Inc+Ind– series showed a statistically significant reduction in conduction velocity from that of the control group (Inc–Ind–) (Fig. 2). The Inc+Ind+ series displayed a statistically significantly difference from the Inc+Ind– series.

Discussion

The study presents data which indicate that previously observed nucleus pulposus-induced effects on blood flow and nerve conduction velocity on adjacent nerve roots are efficiently blocked with indomethacin.

It has been speculated whether the nucleus pulposus-induced effects on the nerve tissue are based on inflammatory events. Assessment of herniated disc material also demonstrates the presence of inflammatory cells and substances related to inflammatory reactions [3, 4, 18]. Likewise, subcutaneous placement of nucleus pulposus is known to attract inflammatory cells and results in an accumulation of inflammatory mediators [12, 20]. However, despite experimental observations that high-dose intravenous methylprednisolone blocks the nucleus pulposus-induced effects (presumably by its anti-inflammatory action) and that anti-inflammatory medication for sciatic pain may sometimes be useful clinically, it is not understood whether these inflammatory reactions merely reflect a normal resorption phenomenon or if they have any pathophysiologic implications.

The model in the present study has been previously used to study the effects of epidural nucleus pulposus, where it was seen that the disc incision procedure may induce histologic and functional changes such as reductions in intraneural blood flow and nerve root conduction velocity [5, 14, 15]. In the present investigation, these changes were reproduced when discs were incised without the simultaneous treatment with indomethacin. However, with indomethacin, both effects were efficiently blocked, although not fully. These results strongly indicate that the injurious effects induced by nucleus pulposus are related to inflammatory events that may also play an important role in the basic mechanisms behind sciatica.

One interesting observation in this study is that the indomethacin treatment blocked the effects not only on conduction velocity but also on blood flow. It has been argued that the sequence of pathophysiologic events is initiated by substances related to the cell membranes of the nucleus pulposus cells that, after reaching the endoneural capillaries through an epidural transport route, induce intraneural edema [1, 2, 6, 16]. Such edema may increase the intraneural tissue fluid pressure, thereby reducing intraneural blood flow [9, 17]. It was recently confirmed that nucleus pulposus application induces such a reduction in the nutritional blood supply, and it has been suggested that the resulting neuroischemia is the main responsible factor for inducing both the functional and structural nerve root changes observed previously [15]. Since the present study also showed that blood flow reduction was efficiently blocked by the indomethacin treatment, its results strongly support the suggested pathophysiologic sequence.

Despite the clear indication that indomethacin blocks the injurious effects of nucleus pulposus and that inflammatory mechanisms are of pathophysiological importance, one must remember that the experimental setting presents an ideal situation, with treatment already beginning on the day after the disc herniation. The dose was also of a concentration that could not be used clinically. As previously discussed, it is known that nerve roots are already affected by nucleus pulposus minutes after application, starting with the formation of an intraneural edema and a reduction in blood flow within 24 h [2, 15]. One may assume that once these reactions have been initiated, the neuroischemic injury of the nerve tissue may be difficult to reverse after the first hours or days. In the clinical situation, patients usually do not receive treatment this early and not at this dosage. One can therefore understand that, for the humans, the effects of anti-inflammatory treatment may not provide such dramatic relief of sciatic symptoms as the effects on blood flow and nerve conduction demonstrated here.

In conclusion, the data from the present study indicate that inflammatory mechanisms are involved in the structural and functional effects on the nerve roots induced by the nucleus pulposus after incision of the intervertebral disc. Continued research in this field should be directed toward understanding which inflammatory mediators are present, what initiates the reaction, and what differentiates it from normal resorption in the spinal canal.

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