Nerve Growth Factor Affects Characteristics Of Sensory Innervation And Synovia Of The Hip In Rat.

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Introduction: Pathogenesis of hip pain is unclear regarding sensory innervation and pain transmitting substance in the hip joint. Nerve growth factor (NGF) is a promising analgesic target in patients with osteoarthritis (OA).

To determine the direct effects of intra-articular injection of NGF into normal rat hips and the time course of pain-related mediator appearance, focusing particularly on both inflammatory and neuropathic pain-related states using local tissues and sensory innervation of the peripheral nervous system including the dorsal root ganglion (DRG).

The purpose of this study was to clarify characteristics of histology and sensory innervation in rat NGF model.

Methods: We used 36 eight-week-old male Sprague-Dawley rats weighing 250 g to 300 g. Using a 26-gauge needle, 30μl of 1% Fluoro-Gold solution (FG); (Sham-operated group; n=12), 30μl of 1% FG with 50μg/ml NGF; (NGF50 group; n=12), and 30μl of 1% FG with 100μg/ml NGF; (NGF100 group; n=12) were injected into the left hip joints. Histological examination of hematoxylin and eosin stain was performed on the synovia in the left hip joint. The number of FG-labelled neurons and those with FG-labelling and calcitonin gene-related peptide-immunoreactivity (CGRP-IR) were counted.

Results: The NGF50 and NGF100 groups showed evidence of synovitis compared with the Sham-operated group. At 7 days, the proportions of CGRP-IR FG-labeled to total FG-labeled neurons were 12%, 18%, and 36% in the Sham-operated, NGF50, and NGF100 groups, respectively. At 14 days, the proportions were 13%, 22% and 35% in the Sham-operated, NGF50, and NGF100 groups, respectively. At 7 and 14 days, the NGF50 and NGF100 groups showed a significantly higher proportion of CGRP-IR FG-labeled neurons than the Sham-operated group.

Discussion: We demonstrate that intra-articular injection of NGF into the rat hip produced mild inflammation without osteoarthritic change. To our knowledge, this is the first report describing an NGF-induced rat model of hip pain. Ashrafs et al. reported intra-articular injection of NGF into the rat knee. OA was induced in rat knees by meniscal transection or intra-articular monosodium iodoacetate injection, and then NGF added to evoke pain-related behavior. However, there are no reports to our knowledge of intra-articular injection of NGF into rat hips. We found that NGF induced invasion of inflammatory cells in synovial tissue and angiogenesis in rat hips as it does in knees. By contrast, we did not observe any joint space narrowing or cartilage degeneration. Furthermore, invasion of inflammatory cells in synovial tissue and angiogenesis were sustained for at least until 14 days after NGF application. NGF is a neurotrophin that regulates neuronal development, survival, and maintenance. NGF plays a key role in many persistent pain states, notably those associated with inflammation. We believe that direct application of NGF into the hip evokes an inflammatory condition in rat and that NGF can be used to
model hip pain in rats. In the current study, CGRP was upregulated in DRG neurons by intra-articular injection of NGF. CGRP is a marker of sensory neurons typically involved in nociception. Pain from the hip is most likely transmitted by CGRP-IR DRG neurons. Orita et al. reported that the concentration of NGF was significantly elevated after 7 days in synovium in a rat model of knee MIA. NGF is retrogradely transported to DRG and mediates CGRP production. Thus, intra-articular injection of NGF influenced nociceptive transmission at the DRG via production of CGRP. The mechanism of pain transmission in hip disorders is not completely understood. Nakajima et al. reported that CGRP-IR neurons play an important role in the perception of pain in the hip joint in rats. They also documented that FG-labeled neurons were distributed throughout the ipsilateral DRGs from T13 to L5, primarily at L1, L2, L3, and L4 in the hip joint. The current study showed almost similar distributions and the distribution was not changed despite NGF administration. These results explain the clinical observation that pain is referred to the thigh and lower leg in patients with disorders of the hip. In patients with OA of the hip, sensory innervation and inflammatory cytokines in hypertrophic synovia are associated with nociception. Shirai et al. stated that hip pain occurs following the invasion of the labrum with blood vessels and nerve fibers from inflamed synovial tissue following labral degeneration in the hip joint affected by OA. Shigemura et al. reported that 6% of patients with OA of the hip showed neuropathic pain. These findings may provide leads to the development of novel analgesic therapies for hip joint pain including the use of treatments targeting NGF. Recently, a randomized clinical trial of an NGF inhibitor in OA of the hip and knee was reported to reduce joint pain.

**Significance:** Intra-articular administration of NGF into the hip joint produces a novel rat model for hip pain. The NGF elicits synovitis and expression of CGRP in sensory nerves. Our findings suggest that NGF is involved in hip joint pain transmission.

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