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REVIEW ARTICLE

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Neurogenic inflammation in osteoarthritis of the knee

Abstract The synovium in a knee joint has an extensive neural network in the somatic and autonomic nervous systems. In medial compartmental osteoarthritis of the knee, neuropeptides were most abundant, with an especially large number of substance P and calcitonin gene-related peptide-immunoreactive free nerve endings. Some of the substance P-positive nerve endings were surrounded by monocytes. Substance P and calcitonin gene-related peptide were found more frequently in the medial than in the lateral or suprapatellar areas. Substance P-positive free nerve endings showed more dendritic morphologic features in the medial region than those in the lateral and suprapatellar regions, and small nerves were accompanied by newly developed vessels in synovial villi. In the medial region, the synovitis was more remarkable than in the lateral region. Patients suffering from medial compartmental osteoarthritis of the knee complain of pain on the anteromedial portion of the knee joint when walking or standing. Therefore, these findings suggest that free nerve endings containing substance P may be implicated in the development and persistence of inflammatory synovitis and the pain pathway in osteoarthritis of the knee.

Key words Osteoarthritis of the knee · Neurogenic inflammation · Neuropeptide · Synovitis

Introduction

Osteoarthritis of the knee is a common joint disorder in elderly people, and leads to progressive destruction of the articular cartilage. Although the etiology of osteoarthritis of the knee is multifactorial, the progressive failure of articular cartilage induced by biomechanical factors is considered to be a main cause of osteoarthritis,[1] which is deemed a non-inflammatory condition.[2] Osteoarthritic synovitis may be merely a secondary reaction brought about by the debris of cartilaginous destruction, and some cases show severe inflammatory change in the synovium.[3] Conversely, some patients with mildly destructive changes seen on radiographs complain of spontaneous pain in their knees from joint swelling and local heat. The clinical severity of osteoarthritis does not always correspond to radiographic findings. The development and modulation of synovitis in osteoarthritis have not yet been explained.

Since Levine et al.[4] proposed that neurogenic factors contributed to the severity of arthritis in 1984, the role of neurological mechanisms in the pathophysiological features of joint diseases has been discussed in several papers.[5–8] Several neuropeptides have been identified in the peripheral and central nervous systems, and the physiological properties of some of these neuropeptides in the inflammatory process have been clarified.[9] These various issues prompted me to determine the distribution of neural elements and the location of neuropeptides in the synovium of the osteoarthritic knee. I used specific immunohistochemical staining in examining the role of neuropeptides in the modulation of syonovitis and the pain pathway.

Clinical pathology of osteoarthritic knees

Primary osteoarthritis of the knee was classified by Ahlbäck's criteria[10] according to the location of joint-space narrowing in the compartments of the knee joint. In Japan, the majority of osteoarthritic knees treated by surgical intervention are reported to have medial involvement (medial-type OA), and account for 93% of cases.[11] Therefore, a single compartment is involved in the majority of osteoarthritic knees. Excessive biomechanical stress is loaded onto some focal area on either compartment of the knee joint owing to varus or valgus deformity of the lower

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limb alignment, and consequently, such overload induces the osteosclerosis of subchondral bone, which is likely to give rise to the degeneration of articular cartilage with aging. In the disintegration of the weight-bearing portion, our examinations show abnormalities of the articular surface, including softening, fibrillation, ulcerative change, or exposed subchondral bone. As the disease advances, patients with medial compartmental osteoarthritis have a more varus limb alignment, with tightness of the medial soft tissues and elongation of the lateral collateral ligament, showing a lateral thrust (adduction movement) while beginning the stance phase in walking. Osteoarthritic knees have protruding osteophytes around the medial femoral and tibial condyles. Accordingly, a repeated compressive force is exerted on the medial soft tissue, including synovium, the joint capsule, and the medial collateral ligament of the knee with knee motion.

Synovitis in osteoarthritis is deemed to be a secondary reaction to cartilage fragments and debris. However, several investigators pointed out the presence of prominent inflammatory pathology in the synovial membrane of knees with osteoarthritis,[3,12] indicating that synovitis can be induced by multiple factors. The causes of synovitis are still unclear. During joint surgery, the surface of the synovial membrane often shows signs of inflammation, including synovial proliferation with villous formation and congestion, and the severity of the synovitis varies depending on whether the medial, the lateral, or the suprapatellar portion of the knee joint is affected. The characteristic pathological features of synovium in osteoarthritis of the knee are thought to be mild hyperplasty of synovial lining cells, interstitial edema, increased vascularization, and moderate cellular infiltration of subsynovial tissue.[12]

Patients with medial compartmental osteoarthritis of the knee usually complain of pain, the main location of which is the anterior part of the medial joint space. Pain appearing in osteoarthritic knees may be closely related to inflammatory synovitis occurring in the vicinity of degenerated articular cartilage.

Synovial innervation

Early literature about the innervation of the knee suggested that nerve fibers were widely distributed in the synovium, and were generally accompanied by a vascular tree.[13] Recent reports discuss the existence of a plexus of nonmedullated nerves in addition to the perivascular ones.[14,15] Recent advances in immunohistochemical staining and neurohistological analysis have shown numerous free nerve fibers and endings in the synovium.[8,16–18] However, in order to clarify the exact modality of nerve distribution in connection with the anatomy of the synovium, it seems to be crucial to use a staining method with a high specificity for neural elements, and to use thicker sections than usual. Among neurostains, the modified gold chloride method is said to show free nerve endings and several mechanoreceptors well.[19] In immunohistochemical staining, the avidin–biotin–peroxidase complex method is a precise technique.[20] Therefore, I carried out a study of the synovial innervation of the human knee using both these methods.

Modified gold chloride staining showed an extensive neural network in the synovial tissue. In the stained section, neural elements, collagen bundles, and the fatty tissue were identified. In the deep layer adjacent to the fatty tissue there was a large nerve fiber bundle connected to medium-sized nerve fiber bundles having a net-like appearance. In the subsynovial tissue, nerve fibers branched almost at right angles, and then proceeded laterally. Some of the nerve fibers in the subsynovial tissue were directed toward the intimal layer, and the others were located parallel to the surface, forming a network of nerve fibers just under the synovial cell lining. Terminals of peripheral nerve fibers also were found in the subsynovial tissue. An abundant nerve supply was found around the walls of blood vessels; these small nerve fibers wound around the wall in a spiral manner. I failed to find mechanoreceptors such as Ruffini end-organs or Pacinian corpuscles in the synovium.

The immunohistochemical study showed that the synovium was composed of the synovial cell lining, the subsynovial tissue, and a layer formed of dense bands of collagen fibers. There was a large neurovascular network between the sublining tissue and the layer of collagen fiber bundles. The axons, which were immunoreactive for antisera to neuropeptides, appeared as brown strands in longitudinal sections of a nerve fiber bundle, and as brown spots in transverse sections. Fine, immunoreactive nerve fibers resembled brown beaded strands, indicating the axoplasmic transport of neuropeptides.

The results indicated that there may be two different neural systems in the synovium of a human knee, one somatic and the other autonomic. In the somatic neural system, there seem to be nerve fiber bundles of a large diameter accompanied by a large blood vessel. These are connected by medium-sized nerves, and form a neural network between the subsynovial tissue and a layer of dense collagen fibers. In the subsynovial tissue, nerve fibers with a small diameter run in longitudinal and transverse directions immediately underneath the intimal layer. These nerve fibers also form a neural network. The distribution of autonomic nerves may be strongly associated with that of blood vessels, and they are found around large- and medium-sized blood vessels, forming a web of fine nerve fibers. Small autonomic nerve fibers located along small vessels extend toward the synovial lining. Therefore, I think that the synovium of the knee may be nociceptive, and insensitive to pressure or tension.

Location of neuropeptides in the synovium of the knee

Substance P and calcitonin gene-related peptide were considered to be markers of sensory nerve fibers, and neuropeptide Y was said to be found in most peripheral noradrenergic neurons.[8] Vasoactive intestinal peptide re-

portedly lowered blood pressure by inducing vasodilatation and moving circulating cells to the region of inflammation.[21] For these reasons, I chose these four types of neuropeptide for the study investigating the modality of the nerve supply to the synovium of the human knee, and the mechanism that transmits pain in inflammation of the osteoarthritic knee.[22]

In osteoarthritic synovium, substance P immunoreactive nerve fibers were widely distributed, and substance P was found in free nerve endings and fibers, nerve fiber bundles with or without accompanying blood vessels, and in the perivascular neural network. The incidence of substance P-positive free nerve fibers or endings was most predominant on the medial side. Substance P-positive free nerve endings in the medial synovium showed marked axonal branching, and some free nerve endings containing substance P were surrounded by several monocytes forming a cluster.

The distribution of the nerves containing calcitonin gene-related peptide showed almost the same tendency as those containing substance P. The main location of calcitonin gene-related peptide was in large or medium nerve fiber bundles. The incidence of calcitonin gene-related peptide immunoreactive free nerve fibers or endings or both was most prevalent in synovium from the medial compartment, followed by the lateral compartment, and the suprapatellar pouch.

The localization of neuropeptide Y and vasoactive intestinal peptide revealed a different pattern from those of substance P and calcitonin gene-related peptide. The immunoreactivity for neuropeptide Y showed the most characteristic modality of the distribution of neuropeptides among the four neuropeptides. The positive nerve fibers were located predominantly in the perivascular area, and the immunoreactivity could not be detected in free nerve fibers or endings. The incidence of neuropeptide Y-positive nerves was highest in synovium from the medial compartment. The large nerve fiber bundles containing strands of neuropeptide Y were accompanied by blood vessels located between the thick collagen bundle layer and the sublining tissue.

Vasoactive intestinal peptide antiserum showed a decreased intensity of staining, and the lowest incidence among the four neuropeptides. The nerves that were immunoreactive for vasoactive intestinal peptide were found in large nerve fiber bundles between a tight and a loose collagen fiber bundle layer in deep areas of the specimens and around the wall of the blood vessels. There seemed to be no difference in the incidence between the medial and the lateral parts of the joint. In the samples of the suprapatellar pouch, it was hard to find vasoactive intestinal peptide-positive nerve fibers.

Roles of neuropeptides in osteoarthritic synovitis

Substance P, in particular, is suggested as one of the most important neuropeptides in the modulation of the inflammatory process of arthritis. Animal studies showed that the intraarticular injection of substance P increased the severity of arthritis,[4] and infusion of substance P antagonist reduced the exaggerated inflammation.[23] Substance P is not only a transmitter of the pain signal, but it also stimulates macrophages, neutrophils, and endothelial cells to induce phagocytosis, chemotaxis, and extraplasmavasation.[24,25] This activity is reportedly augmented in the presence of calcitonin gene-related peptide.[26,27]

When comparing the synovium from three different compartments of knees affected by medial compartmental osteoarthritis, the most important observation was that neuropeptides were more abundant in the synovium from the medial compartment than in the other two compartments. Free nerve fibers and endings containing substance P and calcitonin gene-related peptide were found most frequently in the medial compartment. Free nerve fibers have been recognized as type-4 pain receptors using the classification of Freeman and Wyke.[28] The abundance of substance P and calcitonin gene-related peptide in free nerve fibers suggests that the medial synovium may be very sensitive to noxious mechanical stimuli,[29] corresponding to the location of spontaneous pain and tender pain which patients with medial compartmental osteoarthritis of the knee most frequently complained about.

Neuropeptide Y immunoreactive nerve fibers were found in significantly high numbers, and the autonomic nervous system seemed to be activated in the synovium of the medial side. Conversely, it was difficult to explain fully why vasoactive intestinal peptide was detected in such minute amounts; however, it may be attributable to depletion or original scarcity.

As patients with medial compartmental osteoarthritis have horizontally protruded large spurs around the medial femoral and tibial condyles, synovium is impinged between the osteophytes and the medial collateral ligament. Knees show a screw-home motion on standing, and moreover, a lateral thrust is detectable in marked varus knees while beginning the stance phase in walking. Under those conditions, repeated mechanical stimuli are applied to the medial soft tissue around the medial compartment of the knee. Peripheral mechanical stimuli are said to increase the production of substance P in the dorsal horn of the spinal cord, and substance P is transported to the peripheral nerves, and then released to the surrounding area from the nerve terminals.[30] Synovitis has been recognized in the animal knee treated by anterior cruciate ligament transaction in an experimental model of osteoarthritis.[31] Therefore, the mechanical stimuli and excessive instability of the joint are considered to be a primary cause of neuropeptide accumulation in the medial synovium.

Substance P immunoreactive free nerve endings were found to encompass monocytes. There may be a possibility that these cells receive input from the nervous system terminal more directly and actively. Therefore, free nerve endings may function to transmit information from the nervous system to cells. This strongly supports the view that the nervous system is immunologically implicated in the development and persistence of the inflammatory synovitis in osteoarthritis.

Conclusion

Substance P-positive free nerve endings showed more dendritic morphological features in the medial region than in the lateral and suprapatellar regions, and small nerves were accompanied by newly developed vessels in synovial villi. In the medial region, the synovitis was more remarkable than in the lateral region. These findings suggest that free nerve endings containing substance P may modulate inflammation and the pain pathway in osteoarthritis. In the process of inflammation and destruction in medial compartmental osteoarthritis of the knee, I think that mechanical stimuli applied on the medial synovium may greatly activate nerve terminals, and accumulated neuropeptides in peripheral nerves may stimulate inflammatory cells. The nervous system may be immunologically implicated in the development and persistence of the inflammatory synovitis in osteoarthritis of the knee.

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