Neurophysiological basis for neurogenic-mediated articular cartilage anabolism alteration

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Gouze-Decaris, Elvire, Lionel Philippe, Alain Minn, Philippe Haouzi, Pierre Gillet, Patrick Netter, and Bernard Terlain. Neurophysiological basis for neurogenic-mediated articular cartilage anabolism alteration. Am J Physiol Regulatory Integrative Comp Physiol 280: R115–R122, 2001.—This study was designed to investigate the pathways involved in neurogenic-mediated articular cartilage damage triggered by a nonsystemic distant subcutaneous or intra-articular inflammation. The cartilage damage was assessed 24 h after subcutaneous or intra-articular complete Freund’s adjuvant (CFA) injection measuring patellar proteoglycan (PG) synthesis (ex vivo [Na235SO4] incorporation) in 96 Wistar rats. Unilateral subcutaneous or intra-articular injection of CFA induced significant decrease (25–29%) in PG synthesis in both patellae. Chronic administration of capsaicin (50 mg·kg−1·day−1 during 4 days), which blunted the normal response of C fiber stimulation, prevented the bilateral significant decrease in cartilage synthesis. Similarly, intrathecal injection of MK-801 (10 nmol/day during 5 days), which blocked the glutamatergic synaptic transmission at the dorsal horn of signal originating in primary afferent C fibers, eliminated the CFA-induced PG synthesis decrease in both patellae. Chemical sympathectomy, induced by guanethidine (12.5 mg·kg−1·day−1 during 6 wk), also prevented PG synthesis alteration. Finally, compression of the spinal cord at the T3-T5 level had a similar protective effect on the reduction of [Na235SO4] incorporation. It is concluded that the signal that triggers articular cartilage synthesis damage induced by a distant local inflammation 1) is transmitted through the afferent C fibers, 2) makes glutamatergic synaptic connections with the preganglionic neurons of the sympathetic system, and 3) involves spinal and supraspinal pathways.

neurogenic inflammation; proteoglycan synthesis; neural pathways

RHEUMATOID ARTHRITIS (RA) is a chronic inflammatory joint disease that, interestingly, is typically distal, bilateral, and symmetric, features that might be connected with the density of innervation and with cross-spinal reflexes. The levels of neural interactions may be numerous and can contribute to peripheral sensitization, as well as to neurogenic inflammation, central processing, hyperexcitability, and neuroplasticity (see Refs. 22 and 32 for extensive reviews). The role of both peripheral (PNS) and central (CNS) nervous systems in the genesis and development of arthritis (see Refs. 4 and 32 for reviews) has long been proposed, notably based on clinical reports. For instance, patients with cerebrovascular accident, poliomyelitis, or peripheral nerve lesion (12, 24, 46) developed an atypical RA, the paralyzed joints being spared by the arthritic process, thus suggesting the involvement of a neural signal in the transmission of this disease.

However, possible implications of the nervous system during RA were described mainly on the basis of clinical symptoms such as inflammation (18), edema (5), and pain (6) and usually only late degenerative consequences on cartilage were depicted (18, 26). However, it was not elucidated if the degenerative consequences on cartilage were triggered by an inflammatory event or if they were also directly mediated by neurogenic processes. In a previous work (10), we developed an experimental approach to study early effects on distant articular cartilage of a nonsystemic local inflammatory event. Nonsystemic conditions were chosen grounded on the absence of both fever, measured by biotelemetry, and serum production of interleukin (IL)-6, a characteristic cytokine of systemic participation. Articular cartilage damage, an early and important characteristic of arthritic or osteoarthritic processes, was evaluated by assessing the synthesis of patellar proteoglycan (PG) by ex vivo [Na235SO4] incorporation. The amount of [35S]sulfate incorporated is considered a reliable measurement of the newly synthesized sulfated glycosaminoglycan amounts and is used as a major index of cartilage anabolism (11, 50). Indeed, arthritis is correlated by a marked inhibition of PG synthesis (48, 49). Moreover, PG synthesis is one of the most sensitive parameters to IL-1β effects, a proinflammation; proteoglycan synthesis; neural pathways

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flamatory cytokine considered to be the key mediator of early anabolism decrease and of latter degenerative cartilage process (3, 9). In our previous study, bilateral PG synthesis reductions, triggered by the local inflammation, were observed from hour 6 to hour 72 in both patellae. IL-1β mRNA were expressed in both synovial membranes, suggesting that PG synthesis alterations probably implicated this cytokine and can then be similar to degenerative-like effects (10). In the second part of this work, the implication of the nervous system in the transmission of the degenerative-like signal was examined using a surgical approach. Indeed, the PG synthesis reduction was abolished by blocking surgically the spinal transmission at the L4-L6 lumbar vertebrae level, showing the possible involvement of spinal and/or supraspinal components (10). Thereafter, in the present work, to confirm the neurogenic participation, we investigated the neural pathways that seem to be involved in articular cartilage alteration (10), namely the afferent and efferent pathways and the site of integration. We propose that the stimulation of primary afferent nociceptive (PAN) fibers can be implicated in the transmission of the signal from the site of inflammation to distant articular cartilage. Indeed, type IV/C PANs are stimulated by numerous inflammatory mediators such as bradykinin, serotonin, histamine, H⁺, and prostaglandin in the form of PGE₂ (13, 15, 19, 28, 34, 41). These polymodal fibers can also be stimulated by the mechanical consequences of local hyperemia (14).

Several pharmacological and surgical experiments were then sequentially performed to selectively modulate different levels of the neural transmission (see Refs. 22 and 32 for reviews). The implication of type IV/C fibers was studied using chronic administration of capsaicin, which selectively provoked the destruction of those nociceptive fibers (16). PANs are known to stimulate spinal and/or supraspinal components. Indeed, stimulation of PANs in arthritis leads to the corelease of glutamate and substance P (SP) from the central spinal terminals (38). Then we administered intrathecally an antagonist of the N-methyl-D-aspartate (NMDA) receptor to block synaptic glutamatergic connection (25, 52). Supraspinal components were studied after compression of the spinal cord at the T3-T5 vertebrae level to suppress any stimulation of supraspinal structures. We also used guanethidine, a peripheral sympatholytic, to suppress the stimulation of postganglionic sympathetic afferents (PGSEs) (26), which can be logically suspected to transduce the signal to the synovial membrane, modifying the microcirculation (blood flow and vascular permeability) (33) and releasing substances such as IL-1 (22), which can transduce the degenerative-like signal into articular cartilage. Finally, to study the role of the neural component, we compared the responses 1) in both knees to a contralateral injection into one hindpaw and 2) in the contralateral knee to an intra-articular injection through the infrapatellar ligament, in both cases in rats with or without modification of the neural transmission of any signal.

**MATERIALS AND METHODS**

The experimental protocols were approved by our local ethics committee. Guidelines for animal care and laboratory procedures were followed at all times.

**Animals.** Experiments were performed on 96 Wistar male rats weighing 175–200 g (Charles River, Saint-Aubin-lès-Elbeuf, France), housed in individual cages with free access to standard laboratory food and water. Rats were kept in a 12:12-h light-dark cycle (light-on period 6:00 AM–6:00 PM) at controlled room temperature (24 ± 1°C).

**Induction of inflammation.** Inflammation was promoted (hour 0) by a single unilateral injection of 1 μg CFA, either subcutaneously into one hindpaw in 100 μl, or intra-articularly in 50 μl through one infrapatellar ligament (10). CFA is an emulsion of heat-killed *Mycobacterium tuberculosis* H37 RA (Difco Laboratory, Detroit, MI) in sterile mineral oil (paraffin oil, NaCl 0.9%, Tween 80).

**Capsaicin treatment.** Capsaicin (8-methyl-N-vanillyl-6-nonenamide) (ICN, Biomedicals, Orsay, France), solubilized in 10% Tween 80, 10% ethanol in isotonic saline, was administered chronically in adult rats (2, 16, 31). After a deep anesthesia by intraperitoneal injection of 50 mg/kg ketamine hydrochloride and 1.25 mg/kg acepromazine, capsaicin was injected subcutaneously at the dose of 50 μg·kg⁻¹·day⁻¹ during 4 days. Rats were at rest for 7 days. During this period, effectiveness of destruction of C fibers induced by the chronic capsaicin administration was assessed using the eye wipe response to topical capsaicin (0.1% capsaicin in alcohol) before induction of experimental inflammation (8). The decrease in the number of eye wipes reflected the decrease in type IV/C fibers. Injection of CFA was performed 7 days after the end of the treatment with capsaicin, according to the eye wipe response numbered during 20 s (mean of 7.8 ± 1.5 eye wipes after capsaicin treatment vs. 24.6 ± 3.2 eye wipes without capsaicin treatment, P < 0.05; for ethical concerns, a minimum number of animals were used). The rats were killed 24 h after CFA injection (n = 6 per group). Comparisons were made with untreated controls and controls given injections of CFA but without injection of capsaicin (n = 6 in each of these groups). Two other control groups (n = 6 per group) were subjected to only capsaicin or the vehicle.

**Intrathecal NMDA receptor antagonist administration.** MK-801 (dizocilpine) (ICN Biomedicals, Orsay, France) was administered intrathecally at the dose of 10 nmol/day in 10 μl sterile artificial cerebrospinal fluid (CSF; in mM: 124 NaCl, 3.3 KCl, 1.24 KH₂PO₄, 1.3 MgSO₄, 2.5 CaCl₂, 26 NaHCO₃, 10 glucose). Intrathecal injections (30, 36, 52) were performed once daily for 5 days before injection of CFA. Injections in the region of the lumbar enlargement of the spinal cord were performed as described by Mestre et al. (35). Animals were held securely in one hand by the pelvic girdle, and the injection was performed by inserting a 26-gauge × 1/2-in. needle connected to a 100-μl Hamilton syringe into the tissues between the dorsal aspects of L4, L5, and L6, perpendicular to the vertebral column. When the needle entered the subarachnoidal space, a sudden lateral movement of the tail was observed. This reflex was used as an indicator of successful puncture. No other specific behavior or sign of distress or pain was observed at this time. A constant 10 μl volume was injected. Then the syringe was held in position for a few seconds and progressively removed to avoid any outflow of the drug. Control groups with only intrathecal artificial CSF or with intrathecal MK-801 pretreatment without injection of CFA were performed (n = 6 in the MK-801-treated group, the untreated control group, and the artificial CSF-treated group).
Spinal cord injury. Spinal cord injuries were performed at the thoracic vertebral level to prevent any stimulation of supraspinal structures. They were performed using the extradural balloon compression method as described by Khan and Griebel (21). Animals were anesthetized with intraperitoneal ketamine hydrochloride (50 mg/kg) and acepromazine (1.25 mg/kg). Spinal cord injury was produced 1 cm on the T3 vertebra using a model 12–060–2F Fogarty arterial embolectomy balloon catheter (Baxter, Irvine, CA) to produce cord compression. The maximum air capacity of the balloon is 0.2 ml. The distal tip of the catheter is soft and short; after being positioned accurately, the catheter is held in place manually. After a partial dorsal laminectomy, the deflated balloon catheter was inserted 1 cm above the site of the partial laminectomy, on the dorsal surface of the spinal cord. The balloon was inflated with a manual air compressor to a pressure of 2 bar, was held in place for 3 min, and then was deflated and removed from the spinal canal. The rats were housed individually, and their bladders were expressed manually once daily, beginning on the day of operation. They were all kept for 3 days after the surgery to recover from the postoperative shock. The rats were killed 24 h after CFA injection (n = 6 per group). Comparisons were made with untreated controls and controls given injections of CFA but whose spinal cords were not injured (n = 6 in each of these groups). Another control group (n = 6) was subjected only to spinal cord compression to evaluate any changes resulting from the lack of movement.

Sympathectomy. Rats, weighing <30 g at the beginning of the experiment, were sympathectomized by injecting guanethidine intraperitoneally (Ismeline, Laboratoires CIBA-GEIGY) at the dose of 12.5 mg·kg⁻¹·day⁻¹ for 6 wk before injection of CFA. In rats, guanethidine produces a depletion of catecholamines by inhibiting the postganglionic sympathetic neurons without injuring catecholaminergic neurons of the CNS (26). This depletion is irreversible after 6 wk of administration. A control group received guanethidine without CFA injection (n = 6 in the guanethidine-treated group and the untreated control group).

Cartilage anabolism. To investigate the damaging process occurring in cartilage, PG synthesis was assessed ex vivo by measuring the incorporation of [Na₂³⁵SO₄] in the patella (11, 39). Rats were anesthetized by intraperitoneal injection of ketamine hydrochloride (50 mg/kg) and acepromazine (1.25 mg/kg) and killed by cervical dislocation. Both patellae were carefully dissected out and were incubated for 3 h with [Na₂³⁵SO₄] in the patellar sodium chloride (0.6 μCi/ml; Amersham, Les Ulis, France). After decalcification, the central area of the patellae was sampled with a 2-mm diameter biopsy punch (Stiefel, Nanterre, France). The amount of [³⁵S]sulfate incorporated, considered a reliable measurement of the newly synthesized sulfated glycosaminoglycan amounts, was counted by liquid scintillation spectrometry. For cartilage anabolism studies, rats were killed 24 h after induction of the local inflammation.

Statistics. After a global comparison with ANOVA, the different groups were compared using Fisher’s t-test; a P value of <0.05 was considered significant. Statistical analysis was performed on experimental data only, not on percentages.

RESULTS

After a unilateral subcutaneous injection of CFA, significant 26–29% ipsilateral and contralateral decreases in PG synthesis were observed in both patellae 24 h after induction of inflammation (Fig. 1). A similar significant 25% decrease was observed in the contralateral patella 24 h after a unilateral intra-articular injection of CFA, whereas no significant variation was observed at the same time in the ipsilateral patella, which was the site of injection (Fig. 2). To analyze the nervous regulations implicated in this response, several pharmacological and surgical manipulations were performed to modulate the transmission of the nervous message and to investigate the nervous regulatory system. Therefore, we studied their effect on PG synthesis modifications induced by either subcutaneous or intra-articular injection of CFA.

Effects of chronic treatment with capsaicin. We first demonstrated that either chronic administration of capsaicin, which depletes unmyelinated afferent type IV/C PAN fibers (16), or its vehicle, had no significant effect alone on PG synthesis in articular cartilage. On the contrary, a chronic administration of capsaicin before a unilateral subcutaneous injection of CFA prevented the significant decrease in PG synthesis observed in both patellae (Fig. 1A). After a unilateral intra-articular injection of CFA (Fig. 2A), the treatment with capsaicin also eliminated the decrease in PG synthesis in the contralateral patella. In the ipsilateral patella, which was the injection site, the destruction of PANs by capsaicin induced a significant 20% increase in PG synthesis.

Effects of sympathectomy. The involvement of the stimulation of PGSEs in the transmission of the PG synthesis alteration mediated by an injection of CFA was studied using a chronic treatment with guanethidine, which depletes the peripheral sympathetic postganglionic neurons (26). This chemical alone had no effect on PG synthesis. After a unilateral subcutaneous injection of CFA, the chemical sympathectomy erased the bilateral decrease in patellar PG synthesis (Fig. 1B). Guanethidine also prevented the decrease in PG synthesis in the contralateral patella triggered by a unilateral intra-articular injection of CFA (Fig. 2B), whereas this treatment induced a 28% increase in PG synthesis in the ipsilateral side.

Effects of an intrathecal MK-801 pretreatment. To establish the role of NMDA receptors in the spinal mediation of the PG synthesis variations observed after CFA injection, we administered intrathecally MK-801, a noncompetitive NMDA receptor antagonist, to block the glutamatergic synaptic transmission. Neither the injection of MK-801 alone nor that of artificial CSF into the subarachnoidal space modified PG synthesis in both patellae, but MK-801 abolished both ipsilateral and contralateral decreases in PG synthesis in patellar cartilage induced by a unilateral subcutaneous injection of CFA (Fig. 1C). The intrathecal administration of MK-801 also eliminated the contralateral decrease in patellar PG synthesis mediated by a unilateral intra-articular injection of CFA (Fig. 2C). In the ipsilateral patella, the NMDA receptor antagonist had no effect on PG synthesis.

Evidence of a supraspinal component. The supraspinal component of the PG synthesis signal observed in patellae was demonstrated using the spinal cord com-
pression technique. This compression was performed at the T3-T5 vertebrae level to stop any stimulation of supraspinal structures. Alone, spinal compression had no effect on PG synthesis in patellar cartilage, thus changes observed in the joints during the experiment were not artifacts due to the lack of movement caused by the paraplegia. Thoracic spinal cord compression totally eliminated the bilateral decrease in PG synthesis observed after a unilateral subcutaneous injection of CFA in both patellae (Fig. 1D). In the contralateral patella, the decrease in PG synthesis induced by a unilateral intra-articular injection of CFA was also prevented after spinal cord compression (Fig. 2D). By contrast, in these experimental conditions, PG synthesis was increased in the ipsilateral patella, up to 26%.

**DISCUSSION**

The aim of this study was to investigate if during an inflammatory process degenerative effects on cartilage were triggered only by inflammation or were they also directly induced by a neural signal. In previous work (10), we showed that, after a unilateral subcutaneous injection of CFA (Table 1), a significant bilateral decrease in PG synthesis occurred from 6 until 72 h after the induction of inflammation, the maximal effect being observed 24 h later. The implication of a neural signal in early PG synthesis alterations in cartilage, occurring at a distance from local inflammation independent of any systemic effects, was strongly suspected on the basis of spinal cord compression experiments. In other words, the stimulation of the PNS may lead to
intrarticular 1 \( \mu \text{g} \) CFA injection

A  capsicain treatment

B  sympathectomy

C  intrathecal MK-801

D  supra-spinal component

Early degenerative-like effects, occurring on distal patellar cartilage. On the other hand, SP is the main neurotransmitter of neurogenic inflammation and is released after the stimulation of unmyelinated type IV/C PAN fibers (22, 23, 32). PG synthesis alterations were also prevented by the administration of an antagonist of the neurokinin (NK)-1 receptor of SP (10), supporting the idea that a neurogenic component

Table 1. Effects of pharmacological or surgical modifications of the nervous system on CFA-induced modifications of patellar PG synthesis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect on</th>
<th>Subcutaneous Injection of CFA</th>
<th>Intra-Articular Injection of CFA</th>
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<td></td>
<td></td>
<td>Ipsilateral</td>
<td>Contralateral</td>
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<td>CFA alone</td>
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<tr>
<td>CFA + capsaicin</td>
<td>Afferent C fibers (16)</td>
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<tr>
<td>CFA + guanethidine</td>
<td>Sympathetic efferent fibers (26)</td>
<td>↑</td>
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<tr>
<td>CFA + MK-801</td>
<td>Spinal NMDA receptors (36)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>CFA + spinal cord compression</td>
<td>Supraspinal component (42)</td>
<td>↑</td>
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↓, Significant decrease of proteoglycan (PG) synthesis versus untreated control; ↑, significant increase of PG synthesis versus untreated control; →, no variation of PG synthesis versus untreated control. CFA, complete Freund’s adjuvant.
seemed involved. Thereafter, the aim of the present work was to investigate and to identify the neural pathways involved in this articular cartilage alteration model. Thus we characterized the nervous fibers whose stimulation led to PG synthesis alterations after CFA injection. These pathways included stimulation of type IV/C PAN fibers, spinal and supraspinal involvements, and PGSEs. Therefore, we modulated the nervous transmission, alternating between chemical or surgical means (Table 1).

Capsaicin is an agent selectively neurotoxic to type IV/C fibers (16). When administered chronically, capsaicin induces a desensitization and/or degeneration of these polymodal nociceptive fibers. It has been established that PANs are implicated in neurogenic inflammation (22, 32). Indeed, stimulated polymodal type IV/C fibers release SP and calcitonin gene-related peptide (CGRP) (2), which synergistically exert proinflammatory paracrine effects in synovium (1, 15, 25). Capsaicin treatment has been reported to ameliorate experimental inflammatory arthritis (7, 8, 14) as well as RA (14, 31). These observations specifically implicate the PANs in the pathogenesis of RA, via SP and CGRP release. Therefore, in our early cartilage alteration model, we used chronic capsaicin to induce the degeneration of those fibers, and thereafter to confirm their implication. Following this treatment, the bilateral PG synthesis response was totally prevented. This result indicates, as expected (22, 32), that PANs participate in the transmission of the signal from the inflammatory site to distal articular cartilage.

It has also been established that the stimulation of PANs leads to the corelease of SP and glutamate from the central spinal terminals (27). Interactions of glutamate with NMDA receptors and of SP with NK-1 receptors lead to the formation of wind-up and hyperexcitability of nociceptive neurons and wide dynamic-range projection neurons (22, 25, 32). These phenomena (peripheral sensitization and central hyperexcitability) are probably implicated in the pathophysiology of RA (22, 32). In our previous work, spinal and/or supraspinal pathways were suspected to be involved in the nervous signal leading to early PG synthesis alterations. In this study, we thus confirmed the implication of a spinal level, by blocking specifically NMDA receptors in the spinal cord, and of supraspinal pathways. These latter were studied after spinal cord compression of the T3-T5 thoracic vertebra to block any involvement from supraspinal components.

PGSEs are also suspected to be implicated in our model. Indeed, those fibers activated by local stimulation or via a spinal reflex, release norepinephrine (NE) as well as prostaglandin E2, neuropeptide Y, and IL-1, especially in synovial fluid (see Refs. 22, 32 for reviews). Therefore, the active involvement of PGSEs is suggested in arthritis. Furthermore, chemical sympathectomy has been shown to ameliorate experimental arthritis (4, 26). Guanethidine is a peripheral sympatholytic. When chronically administered, guanethidine acts as a substitutive neurotransmitter taking the place of NE in storage vesicles, thus causing NE depletion (26). Therefore, in this study, we used guanethidine to explore the role of PGSEs in the mediation of an early PG synthesis cartilage damage, which is already known to be mediated by neurogenic pathways (10). The chemical sympathectomy totally eliminated the PG synthesis decrease in both patellae, demonstrating that PGSEs are involved in the transmission of the signal, probably modifying the microcirculation of the synovial membrane (33).

We demonstrated that, in the spinal cord, PANs, stimulated by a non systemic peripheral inflammation, make glutamatergic synaptic connections with the preganglionic neurons of the sympathetic system, because intrathecal MK-801 pretreatment prevented the bilateral PG synthesis decrease triggered by a non systemic inflammation. The transmission of the signal also needed supraspinal regulations, because the compression of the spinal cord at the level of thoracic vertebrae (T3-T5) reduced the subcutaneous CFA-mediated bilateral decrease in PG synthesis.

After a unilateral intra-articular injection of CFA, the contralateral response was induced by similar nervous pathways, i.e., through PANs, and then made synaptic connections with PGSEs, via spinal and supraspinal pathways. In the contralateral patella, the stimulation induced a decrease in PG synthesis occurring 24 h after CFA injection and any modification of the nervous transmission abolished the contralateral decrease in PG synthesis (Table 1). By contrast, in the ipsilateral patella, which is the injection site, the mechanisms involved in the control of PG synthesis were quite different and more complex, because modifications of the nervous transmission induced an important ipsilateral increase in PG synthesis (Table 1). The suppression of the afferent transmission by type IV/C fibers, of PGSE transmission, or of supraspinal component, induced an increase in PG synthesis in the ipsilateral patella. However, intrathecal pretreatment with an antagonist of NMDA receptors did not affect ipsilateral PG synthesis, indicating a more complex mechanism probably due to the presence of inflammatory site to distal articular cartilage.

This bivalence might be explained by the presence of several neuropeptides with opposite effect (44). It has been established that after peripheral nerve insult, glial cells are activated and secrete growth factors (43). The important PG synthesis increase observed in our study may result in the secretion of growth factors such as nerve growth factor, which can reverse the articular cartilage synthesis response (37, 45), or similar to transforming growth factor-β, which can either inhibit or enhance extracellular matrix development (51). On the other hand, the PG synthesis increase may result in the suppression of inhibitory mechanisms, suggest-
neurogenic involvement in cartilage damage

by the absence of effect of intra-articular CFA injection, 24 h later, results from both negative and positive regulations and that nervous system modification revealed only the positive component.

In conclusion, a peripheral local stress, in addition to classical systemic and immunological processes and the stimulation of the nervous system, can lead to degenerative-like effects on distal tissues, particularly on articular cartilage. This mechanism implicates different nervous pathways of regulation, particularly a supraspinal one, which induced a sympathetic response, probably through α-adrenoceptor stimulation (26, 47). We demonstrated as a new concept that, beyond painful stimulus, the stimulation of the nervous system, either central or peripheral, can induce an early degenerative-like signal, altering distal tissues such as articular cartilage.

Perspectives

This research is a part of work designed to elucidate the relations existing between the nervous system and articular cartilage. This phenomenon has long been suspected in osteoarticular diseases, and this work applies for the first time the concept of neurogenic inflammation driving damaging consequences on cartilage.

Indeed, we have shown that local peripheral injury, subcutaneous or intra-articular, which produces both inflammation and pain, may induce a distant degenerative process within articular cartilage (10). This signal implies the peripheral stimulation of type IV/C fibers, makes glutamatergic synaptic connections with the preganglionic neurons of the sympathetic system, and involves spinal and supraspinal pathways (present work). Such degenerative cartilage damage, mediated by the proinflammatory cytokine IL-1β within the synovium, can be prevented by the modulation of type 2 cyclooxygenase in the spinal cord (in preparation).

The aim of this whole research was to understand better the early mechanisms involved in the genesis of degenerative diseases, such as osteoarticular diseases. The specific objective will be to test if iterative neurogenic stresses can provoke distal osteoarthritic-like cartilage damage, increasing the first detectable injury of the cartilage, which is seen in our study. This concept that a local inflammation through repetitive neurogenic stimulation can trigger distal degenerative processes may be of great importance for several degenerative pathologies, other than osteoarticular ones.

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