Annals of the Rheumatic Diseases 1990; 49: 649–652

REVIEW ARTICLE

Neurogenic influences in arthritis

B L Kidd, P I Mapp, D R Blake, S J Gibson, J M Polak

Pain is a pivotal symptom faced by patients with rheumatic disease. Nevertheless, mechanisms of articular pain remain unclear and there is little correlation between pain, disability, and radiological change.[1] Although a protective function for the pain sensory system has long been assumed, Wall and others have suggested that the system may also function to modify local responses to tissue trauma.[2 3]

In this review we describe the anatomy and physiology of articular nerves and speculate on how neurogenic mechanisms may play an important part in joint homeostasis in both health and disease.

Joint pain

The source of pain in arthritis remains controversial. Exactly 100 years ago Sappey noted that a piece of synovium attached to the stump of a disarticulated limb was insensitive to traction.[4] He concluded that joint sensation resided not in synovium but rather in articular ligaments and capsule. Others supported this view, but Davies reported that though synovium was insensitive to pressure, it was acutely sensitive to a needle prick, which induced a diffuse sensation of pain on the stimulated side of the joint.[5]

In a detailed study of articular sensitivity and innervation Kellgren and Samuel inserted needles into the knee joints of five normal volunteeers.[4] They found that ligaments and fibrous capsules were intensely sensitive and contained spots which, when stimulated with a needle, gave rise to sensations of pressure, pain, or both. In one, quite exceptional, volunteer the left knee joint was opened with a 1½" vertical incision and the synovium was alternately pricked and scratched with needles, crushed and pulled with artery forceps, or injected with saline. In contrast with the articular ligaments and capsule the synovium was found to be largely insensitive, though there were a few scattered spots along the upper border of the patella and at the sides of the joint which gave rise to slight pain when crushed with artery forceps and on several occasions pain could be produced by a needle prick in these regions. The quality and distribution of pain arising from synovium were similar to those arising from ligaments and capsule.

Our own less heroic observations on volunteers support the view that although synovium is largely insensitive, it nevertheless contains areas which give rise to acute discomfort when stimulated by joint aspiration or synovial biopsy. We have also noted that in patients with rheumatoid arthritis the synovium seems to become more sensitive in early disease and perhaps less so in longstanding disease.

Joint innervation

Classical histological studies of tissue innervation have clearly shown an extensive nerve supply to the normal joint.[6] For nearly a century agreement has existed on a network of myelinated and unmyelinated nerve fibres in the articular capsule with free, complex, or encapsulated nerve endings.[6 7] A similar innervation has been found in tendons, ligaments, deep fascia, and periosteum.[7] More controversially, the synovium was considered by many to be only sparsely innervated, predominantly with unmyelinated perivascular fibres, while free fibres were only rarely seen, if at all.[8]

Recent developments in immunohistochemical techniques have provided fresh insights into joint innervation. Antisera against specific neuronal markers combined with sensitive staining methods have allowed vastly improved resolution and characterisation of individual nerve fibres. Our group has reexamined synovial innervation with these techniques, using antisera to protein gene product 9·5, a major protein component of neuronal cytoplasm, as a marker for overall innervation (fig 1). We have shown vastly increased numbers of small diameter nerve fibres compared with previous studies using standard histological methods.[9] Small diameter nerve fibres immunoreactive for protein gene product 9·5 were found in all sections of normal joint tissue and were scattered throughout the fibrous capsule, ligaments, tendons, and synovium. Fibres were found in both a perivascular and a free fibre distribution.

Nearly all the small diameter nerves that we and others have noted in healthy synovium were immunoreactive for neuropeptides.[9 10] These included nerves containing immunoreactive substance P and calcitonin gene related peptide, which are considered markers of sensory fibres, as well as nerves containing immunoreactive neuropeptide Y and its C flanking peptide, found in most peripheral noradrenergic neurones. Many of the substance P and calcitonin gene related peptide immunoreactive nerves were found in perivascular areas, though numerous free fibres were also present, with

The Inflammation Research Group, ARC Building, London Hospital Medical College, London E1 2AD
B L Kidd
P I Mapp
D R Blake

Histochemistry Unit, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0NN
S J Gibson
J M Polak

Correspondence to:
Dr Kidd.

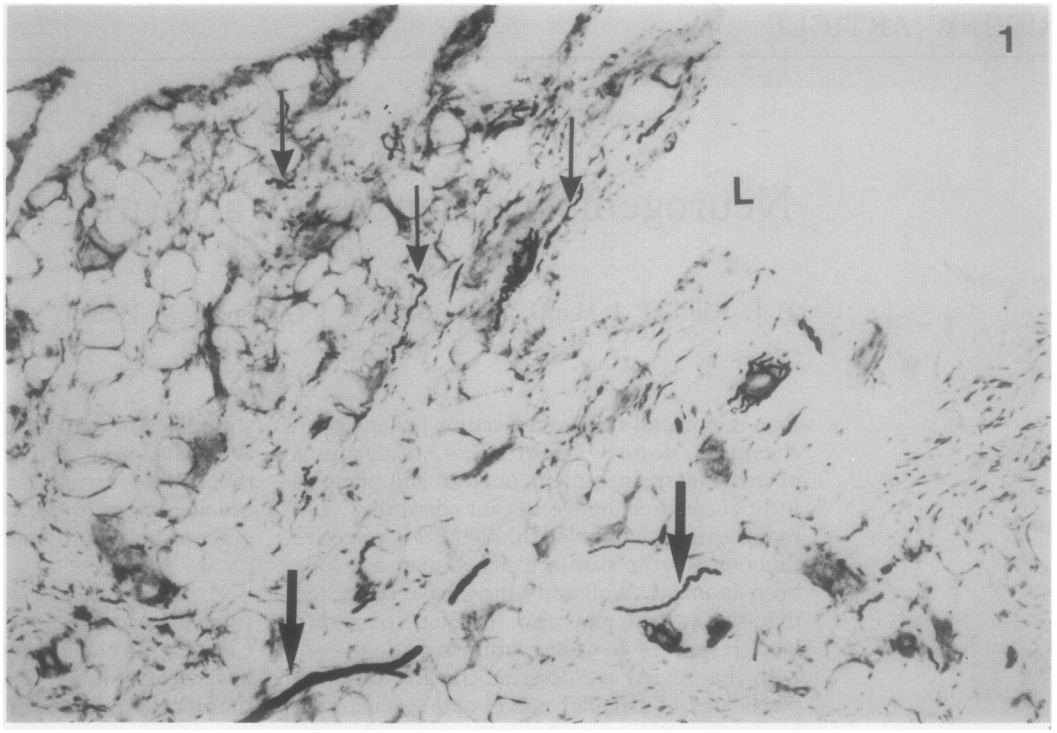

Figure 1: Normal human synovium showing the protein gene product 9·5 immunoreactivity. The intimal layer, dividing synovium from joint space, is marked (L). Large nerve fibre bundles are seen deep in the tissue (large arrows) while finer fibres are shown closer to the intimal layer (small arrows).

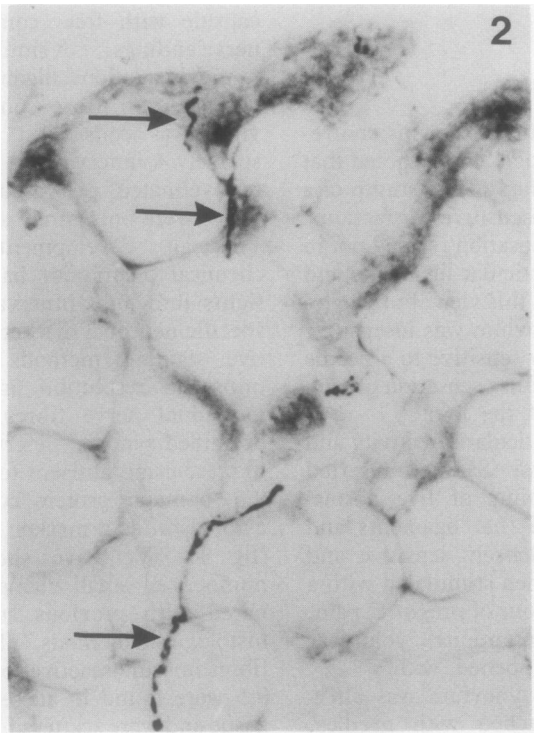

Figure 2: Free substance P immunoreactive fibres in normal synovium (arrows).

some extending through the intima almost as far as the synovial surface (fig 2). Other free fibres were shown to be immunoreactive for the peptides galanin and vasoactive intestinal peptide. Nerves containing neuropeptide Y and its C flanking peptide were exclusively associated with vascular structures (fig 3).

Sensory pathways

All synovial joints are supplied by articular nerves which convey sensory and autonomic information. A classification for receptors of the sensory fibres in these nerves has been proposed by Wyke.[8] In this classification type I and II receptors are corpuscular structures located within the fibrous capsule and related to small and medium sized myelinated nerve fibres. They serve as either static or dynamic low threshold mechanoreceptors. Type III receptors are applied to the surface of joint ligaments and function as high threshold dynamic mechanoreceptors. Type IV receptors are free endings of small myelinated (A delta) or unmyelinated fibres (C fibres) scattered in a diffuse network through the joint. Although the relative numbers of these receptors remain unknown, it is clear

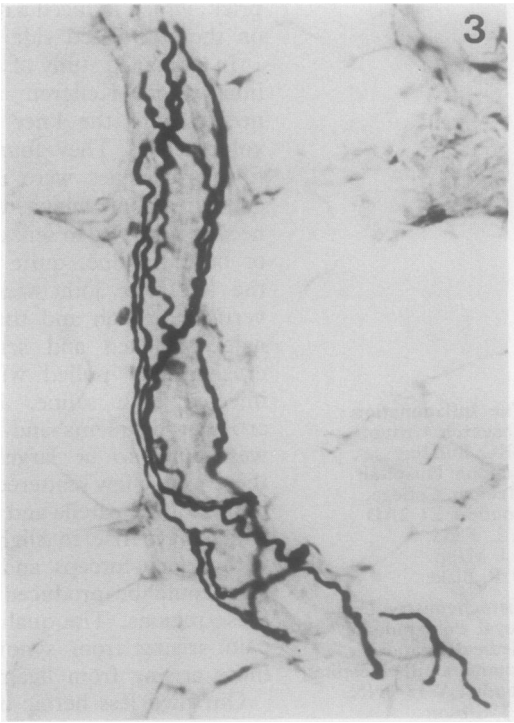

Figure 3: Neuropeptide Y and its C flanking peptide immunoreactive nerve fibres surrounding a deep blood vessel in the normal synovium.

that over 80% of the fibres in articular nerves are unmyelinated, comprising sympathetic and C fibres in nearly equal numbers.[11] It follows that the type IV receptors of C fibre nerves are the numerically dominant receptor group within the joint.

Schaible and colleagues have shown that in normal joints few of the fibres supplying type IV receptors are stimulated by non-noxious stimuli and thus these receptors have been regarded as pain receptors or nociceptors.[12] Studies in the cat knee have shown that some of the receptors have a higher resting activity than others, though the significance of this remains uncertain. Importantly, however, induction of experimental arthritis results in most of these receptors becoming responsive to previously innocuous stimuli, such as movement within the normal range.[12] A similar effect is noted after the intra-articular injection of those prostaglandins known to be released by inflammatory cells,[13] and a contribution of the sympathetic nervous system to sensitisation also seems likely.[14] Available evidence therefore suggests that a substantial proportion of joint receptors are type IV receptors concerned mainly with abnormal events and that sensitisation of these receptors is at least partly responsible for the sensation of pain which occurs after a noxious stimulus or during arthritis.

Central mechanisms also play an important part in arthritic pain. Activation of peripheral nociceptive pathways leads to widespread and prolonged changes in the sensitivity of the central nervous system to further sensory stimuli.[15] The duration of the change is dependent on the innervated tissue, and stimuli from muscle or joints evoke longer responses than those from skin.[15] This enhanced sensitivity has important implications for those projection neurones that relay nociceptive information from articular nerves to the brain. Many if not all of these neurones have inputs from other tissues, including muscles and skin. Although these inputs usually remain suppressed, enhanced central nervous system sensitivity leads to impulse transmission from these sites and may serve to explain the hyperalgesia of periarticular skin and muscle that often accompanies arthritis.

Neurogenic effects on acute arthritis

There is increasing evidence that the traditional sensory role ascribed to the small diameter articular fibres, which we and others have identified in human joints, is only partially correct. An 'axon reflex' has been proposed whereby activation of nociceptors results not only in impulse transmission to the spinal cord but also reversed transmission through the extensive network of peripheral fibres known to terminate near blood vessels and other structures.[16] Release of active compounds from the terminals of these fibres then stimulates an acute reaction—neurogenic inflammation. Within the joint antidromic (reversed) stimulation of articular C fibres has been shown to cause vasodilatation and plasma extravasation.[17] A similar result can be obtained with intra-articular injection of capsaicin,[18] a compound known specifically to stimulate C fibres, and the acute vascular response to intra-articular injections of inflammatory compounds such as carrageenan can be significantly inhibited by prior joint denervation.[18]

Interestingly, the sympathetic nervous system also appears to play a part in acute synovitis. Intra-articular infusion of 6-hydroxydopamine, a compound which stimulates sympathetic postganglionic nerves to release the contents of their peripheral terminals, produces a prolonged increase in synovial plasma extravasation.[19] The effect can be inhibited by pretreatment with indomethacin, suggesting partial mediation by prostaglandins.

Many of the peptides that we identified in small unmyelinated synovial nerves have been implicated in the aetiology of neurogenic inflammation. A substantial body of evidence is accumulating to suggest that these peptides act not only as neurotransmitters or trophic factors, or both, at central nerve terminals but that they are also transported and released peripherally, where they may have local actions on peripheral tissue.[16] Early work suggested that the tachykinin substance P may be involved in the axon reflex found in skin.[20] Subsequently, substance P has been shown to increase prostaglandin release and increase protein synthesis by cultured human synoviocytes, and to have diverse in vitro effects on cultured human neutrophils, mast cells, macrophages, B and T cells.[21]

Direct evidence of a role for neuropeptides in acute arthritis is accumulating. Intra-articular injections of substance P into experimental animals produce plasma extravasation and vasodilatation.[18] This effect is probably mediated, at least partially, by the release from endothelial cells of an endothelial cell derived relaxing factor—nitric oxide.[22] Specific substance P antagonists block neuropeptide induced plasma extravasation and significantly inhibit the early inflammatory responses to intra-articular carrageenan.[18] Finally, infusion of capsaicin into rat knees at doses sufficient to evoke a vascular response produces a parallel rise in substance P concentration in the perfusate.[23]

Neurogenic effects on chronic arthritis

A number of clinical observations point to a fundamental neurogenic mechanism operative in chronic synovitis. The clearest example is provided by the synovitis that often accompanies reflex sympathetic dystrophy. Sympathetic overactivity has also been implicated in the aetiology of frozen shoulder.[24] More controversial are the observations relating to hemiplegia and rheumatoid arthritis. Thompson and Bywaters reported four cases in which rheumatoid arthritis developed following hemiplegia.[25] In this series all the joints in the completely hemiplegic limbs were spared clinically, but in two ambulant cases five joints were affected in the used but partially hemiplegic limbs. Two patients developed rheumatoid nodules, and these were present on the non-hemiplegic side. Glick reported 12 cases of rheumatoid arthritis occurring in patients previously paralysed by poliomyelitis, in which there was almost total

sparing of the joints of the paralysed limbs.[26] Although it is tempting to consider these last observations as evidence of a neural component in rheumatoid arthritis, other causal factors have been proposed. Movement of the inflamed joint may induce a series of potentially damaging events through transitory rises in intra-articular pressure resulting in a hypoxic-reperfusion type injury.[27]

In isolated animal model systems a neurogenic mechanism becomes more apparent. The course of adjuvant arthritis in rats can clearly be modified by manipulation of neurological pathways. Rees and colleagues have reported significant unilateral increases in the severity of ankle joint destruction following sciatic nerve section,[28] though this contrasts with earlier studies which found clear evidence of amelioration after nerve section.[29] Substance P concentrations are reported to be greater in those joints which develop more severe adjuvant arthritis, and injection of substance P into minimally involved joints increases the severity of adjuvant disease in the injected joint.[30]

Immunohistochemical studies of normal and diseased human joints have reported that in specimens taken from rheumatoid joints there is a decrease in the total innervation and that the neuropeptide staining within synovial nerve fibres is weaker than that found in normal tissue or tissue taken from osteoarthritic joints.[9 10] These studies suggest either a rapid release of peptides or an inability of neural tissue to innervate proliferating rheumatoid synovium. It is of relevance that studies of peptide neuroanatomy in rat adjuvant disease show a striking increase in substance P and calcitonin gene related peptide immunostaining in early disease but a relatively sparse innervation in advanced or end stage disease.[31 32] The apparently profound neurogenic influences on normal immune regulation[21] perhaps justify the proposal that some aspects of the immune dysregulation seen in chronic rheumatoid disease are in part a consequence of neuropeptide depletion.

Conclusion

Longstanding clinical observations suggest important interactions between the nervous system and rheumatic disease. Experimental studies are now begining to confirm these observations and point to an interaction mediated by products of both C fibre and sympathetic nerves. Release of peptides from synovial nerve terminals seems to enhance or, alternatively, protect the synovium from continuing damage induced by a variety of harmful stimuli. In vivo and in vitro studies are unravelling the specific pathways by which these effects are produced, and may in turn stimulate the development of novel anti-inflammatory compounds. For example, the appreciation that substance P can induce the production of an endothelial cell derived relaxing factor—the radical species nitric oxide—potentially leads to anti-inflammatory compounds which block either substance P or nitric oxide. It is apparent that the further study of neurogenic mechanisms in arthritis has an exciting future.

1 Massardo L, Watt I, Cushnaghan J, Dieppe P. Osteoarthritis of the knee joint: an eight year prospective study. *Ann Rheum Dis* 1989; **48**: 893–7.
2 Wall P D. Introduction. In: Wall P D, Mezack R, eds. *Textbook of pain*. Edinburgh: Churchill Livingstone, 1984: 1–15.
3 Kidd B L, Mapp P, Gibson S J, *et al*. A neurogenic mechanism for symmetrical arthritis. *Lancet* 1989; **ii**: 1128–30.
4 Kellgren J H, Samuel E P. The sensitivity and innervation of the articular capsule. *J Bone Joint Surg [Br]* 1950; **32**: 84–92.
5 Davies D V. Anatomy and physiology of diarthrodial joints. *Ann Rheum Dis* 1945; **5**: 29–35.
6 Samuel E P. The autonomic and somatic innervation of the articular capsule. *Anat Rec* 1952; **113**: 84–93.
7 Ralston H J, Miller M R, Kasahara M. Nerve endings in human fasciae, tendons, ligaments, periosteum and joint synovial membrane. *Anat Rec* 1960; **136**: 137–47.
8 Freeman M A R, Wyke B. The innervation of the knee joint. An anatomical and histological study in the cat. *J Anat* 1967; **101**: 505–32.
9 Mapp P I, Kidd B L, Gibson S J, *et al*. Substance P, C9RP and neuropeptide Y-immunoreactive nerve fibres are present in normal synovium but depleted in patients with rheumatoid arthritis. *Neuroscience* (in press).
10 Grondblad M, Konntinen Y T, Korkala O, Liesi P, Hukkanen M, Polak J. Neuropeptides in the synovium of patients with rheumatoid arthritis and osteoarthritis. *J Rheumatol* 1988; **15**: 1807–10.
11 Langford L A, Schmidt R F. Afferent and efferent axons in the medial and posterior articular nerves of the cat. *Anat Rec* 1983; **206**: 71–8.
12 Grigg P, Schaible H, Schmidt R F. Mechanical sensitivity of group III and IV afferents from posterior articular nerve in normal and inflamed cat knee. *J Neurophysiol* 1986; **55**: 635–43.
13 Schaible H, Schmidt R F, Willis W D. Spinal mechanisms in arthritis pain: Enhancement of responses of tract neurons in the course of inflammation. In: Schmidt R F, Schaible H, Vahle-Hinz C, eds. *Fine afferent nerve fibres and pain*. Weinheim: VCH Publishers, 1987: 399–409.
14 Nakamura M, Ferreira S H. A peripheral sympathetic component in inflammatory hyperalgesia. *Eur J Pharmacol* 1978; **135**: 145–53.
15 Woolf C J, Wall P. Relative effectiveness of C primary fibres of different origins in evoking a prolonged facilitation of the flexor reflex in the rat. *Neuroscience* 1986; **6**: 1433–42.
16 Holzer P. Local effector functions of capsaicin-sensitive sensory nerve endings: involvement of tachykinins, calcitonin gene-related peptide and other neuropeptides. *Neuroscience* 1988; **24**: 739–68.
17 Ferrell W R, Russell N J W. Extravasation in the knee induced by antidromic stimulation of articular C fibre afferents of the anaesthetised cat. *J Physiol* 1986; **379**: 407–16.
18 Lam F Y, Ferrell W R. Inhibition of carrageenan induced inflammation in the rat knee joint by substance P antagonist. *Ann Rheum Dis* 1989; **48**: 928–32.
19 Coderre T J, Basbaum A I, Levine J D. Neural control of vascular permeability: interactions between primary afferents, mast cells, and sympathetic efferents. *J Neurophysiol* 1989; **62**: 48–58.
20 Pernow B. Substance P. *Pharmacol Rev* 1983; **35**: 85–141.
21 Lotz M, Carson D A, Vaughan J H. Substance P activation of rheumatoid synoviocytes: neural pathway in pathogenesis of arthritis. *Science* 1987; **235**: 893–5.
22 Whittle B J R, Lopez-Belmonte J, Rees D D. Modulation of the vasodepressor actions of acetylcholine, bradykinin, substance P and endothelin in the rat by a specific inhibitor of nitric oxide formation. *Br J Pharmacol* 1989; **98**: 646–52.
23 Yaksh T L. Substance P release from knee joints afferent terminals: modulation by opioids. *Brain Res* 1988; **458**: 319–24.
24 Mani R, Cooper C, Kidd B L, Cole J D, Cawley M I D. Use of laser Doppler flowmetry and transcutaneous oxygen tension electrodes to assess local autonomic dysfunction in patients with frozen shoulder. *J R Soc Med* 1989; **82**: 536–8.
25 Thompson M, Bywaters E G. Unilateral rheumatoid arthritis following hemiplegia. *Ann Rheum Dis* 1962; **21**: 370–7.
26 Glick E N. Asymmetrical rheumatoid arthritis after poliomyelitis. *Br Med J* 1967; **iii**: 26–9.
27 Blake D, Merry P, Unsworth J, Gray L, Lunec J. The inflamed human joint is an example of hypoxic-reperfusion injury. *Lancet* 1989; **i**: 292–5.
28 Rees R G, Dixey J J, Lightman S L, Brewerton D A. The influence of unilateral sciatic nerve section on the course of adjuvant arthritis in rats [Abstract]. *Arthritis Rheum* 1989; **32**: S54.
29 Courtright L J, Kuzell W C. Sparing effects on neurological deficit and trauma on the course of adjuvant arthritis in rat. *Ann Rheum Dis* 1965; **24**: 360–7.
30 Levine D J, Clark R, Devor M, Helms C, Moskowitz M A, Basbaum A I. Intraneuronal substance P contributes to the severity of experimental arthritis. *Science* 1984; **226**: 547–9.
31 Weihe E, Nohr D, Millan M J, *et al*. Peptide neuroanatomy of adjuvant-induced arthritic inflammation in rat. *Agents Actions* 1988; **25**: 255–9.
32 Rees R G, Konttinen Y T, Hukkanen M, *et al*. The synovial innervation of normal and arthritic rats. *Br J Rheumatol* 1989; **18** (suppl 2): 41.