

Pain, neurogenic inflammation and symmetry in medical practice

**N Shenker,^a R Haigh,^a E Roberts,^b P Mapp,^b
N Harris^a and D Blake^a**

^a*Royal National Hospital for Rheumatic Diseases, Bath and*

^b*University of Bath, UK*

Symmetry is a cardinal feature of certain painful and inflammatory diseases, including rheumatoid arthritis and psoriasis. This symmetry does not occur by chance, but it is as yet unexplained. It has been hypothesized by this group and others that mechanisms of neurogenic inflammation could explain both this symmetrical distribution and the chronicity of these diseases. A recent review has demonstrated contralateral responses in the nervous system to unilateral neurological insults. These responses were topographically precise and stimulus specific in nature. This article details similar responses that have been observed to inflammatory stimuli in animal models. The role of pro-inflammatory neuropeptides, such as substance P, in these pathways is discussed. The hypothesis could be tested in both animals and humans.

Introduction

A symmetrical pattern of involvement in some diseases, such as rheumatoid arthritis, is clinically so important that it is a feature of their diagnostic criteria.¹ Is this a statistical aberration secondary to the large number of joints involved, or are there underlying mechanisms to explain the symmetry? Insight comes from another inflammatory condition, psoriasis. Skin psoriasis and some of the arthritides associated with it affect the topographically precise contralateral side much more frequently than a mathematical model would predict if there was a random pattern of disease distribution.^{2,3} There are many other painful and inflammatory conditions that exhibit symmetry.

Complex regional pain syndrome (CRPS) has also been described as symmetrical in a substantial number of patients. Documented bilateral presenting symptoms have been noted to occur in about 5% of patients with CRPS.⁴ However, detailed investigations, such as with technetium pertechnetate bone scanning, demonstrate that a symmetrical involvement may occur more commonly than clinical symptoms suggest.⁵

Osteoarthritis is a painful condition in which biomechanical factors are undoubtedly important. However, as in inflammatory arthritis, neurological lesions are protective against developing osteoarthritis⁶ and a symmetrical distribution to the joints affected by osteoarthritis is also a feature.⁷

Sympathetic ophthalmia is a rare bilateral granulomatous panuveitis that occurs days, months or years after a penetrating eye injury. The histopathology is characterized by diffuse choroidal thickening and lymphocytic infiltration,

Address for correspondence: Prof. David Blake, Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath BA1 1RL, UK. E-mail: secretary.blake@mhhd-tr.swest.nhs.uk

interrupted at multiple sites by collections of epithelioid cells and a few multinucleated giant cells, both containing pigment. The only way to prevent sympathetic ophthalmia is enucleation of the traumatized eye, and some reports suggest that this procedure, even after development of the disease, ameliorates its course.⁸ There must be factors in the traumatized eye that influence the prognosis of the 'sympathizing' eye. These are most likely to be hidden antigens, exposed at the time of trauma to trigger an autoimmune reaction, but other hypotheses could be put forward to explain the chronic destructive lymphocytic involvement, not dissimilar in appearance to another symmetrical disease, rheumatoid arthritis.

The improvement of imaging techniques, specifically the use of magnetic resonance imaging (MRI), has yielded much more information. Minor neurological abnormalities, as detected by brain MRI scans enhanced by gadolinium diethylenetriaminepentaacetic acid and diffusion studies, were seen to predate contralateral plaque development in patients with active multiple sclerosis.⁹ In testicular malignancy, the nonaffected testes of 21 patients were seen to have changes detected by gadolinium-enhanced MRI scans, which persisted for up to 45 months after orchidectomy.¹⁰

All of this clinical evidence suggests that symmetrical patterns are not simply the product of a disease process that affects distant areas of the body in a nonrandom manner. There is order to the distribution of disease. This order is, however, unexplained.

A hypothesis has been proposed by this group and others that the symmetry of disease is neurologically mediated by the mechanisms of neurogenic inflammation. This pathophysiology contributes to the severity and chronicity of these diseases.^{11,12}

Experimental evidence for the symmetrical spread of pain and inflammation

The nervous system is anatomically symmetrical, both peripherally and centrally. The two sides of the spinal column have generally been thought to

function independently from each other. This is clearly not true. Koltzenburg *et al.*¹³ have reviewed the literature detailing the various neuronal insults that result in contralateral identical responses.

The body has contralateral responses to neurological lesions, so does it have contralateral responses to inflammatory lesions? Numerous experimental observations in the rat hindpaw and monoarthritic lesions have provided evidence that such responses do occur (Tables 1 and 2).

These contralateral responses to ipsilateral inflammation are not artefactual. They have been described in different animal models, using different insults, and have produced a variety of responses observed in different laboratories. In some experiments, contralateral effects were documented even though they had not been postulated. For instance, some investigators used contralateral joints or hindpaws as controls and were surprised to find changes.¹⁶

A nociceptive explanation for contralateral effects

There are three possible mechanisms to explain these contralateral responses: neurological, circulatory, or a combination of both routes. There is strong evidence to implicate the nervous system and reasons to suggest that the circulatory system is unlikely to be solely responsible; but some evidence suggests that the nervous system focuses circulation-dependent inflammatory responses.

Neuropeptide-containing unmyelinated fibres are important in mediating contralateral responses. The response is abolished or attenuated if peripheral nerves are sectioned.^{15,28} If C fibres are targeted selectively by using capsaicin or intrathecal substance P antagonists, then the response is also abolished.^{15,19,34} Spinal cord compression also attenuates the contralateral response.¹⁵ It is therefore unlikely that supraspinal control is essential for contralateral responses to occur, although these pathways are likely to influence these responses.

The presence of such contralateral pathways is suggested both anatomically and electrophysiologically. Neurones, presumably nociceptive, that decussate in the spinal cord have been described in repeated histological studies.³⁵⁻³⁷ These occur

Table 1 Effect of monoarthritis on the contralateral joint

Inflammatory insult	Species	Contralateral effect	Ref.
Freund's adjuvant (0.5 ml of 1 mg/ml) in knee	Rat	Increase in SP 2–24 h Increase in CGRP at 2–24 h Increase in NPY 2–24 h Increase in NK-A at 2 h and at 24 h	Bileviciute <i>et al.</i> , 1993 ¹⁴
Carrageenan 2% (0.05 ml) in knee	Rat	Increase in SP at 2 h and at 24 h Increase in CGRP at 2–24 h Increase in NPY at 2–24 h Increase in NK-A at 24 h	Bileviciute <i>et al.</i> , 1993 ¹⁴
SP (0.05 ml of 1 µM) in knee	Rat	Increase in SP 2–24 h Increase in CGRP at 6–24 h Increase in NPY at 2–6 h No increase in NK-A	Bileviciute <i>et al.</i> , 1993 ¹⁴
Human recombinant IL-1 (0.05 ml of 1 mg/ml) in knee	Rat	Increase in SP at 2 h Increase in CGRP at 2–24 h Increase in NPY at 2–24 h Increase in NK-A at 2–6 h	Bileviciute <i>et al.</i> , 1993 ¹⁴
CFA (1 µg)	Rat	Decrease in anabolism of cartilage	Decaris <i>et al.</i> , 1999 ¹⁵
SP in knee (0.2, 1, 2, 10, 20 µg in 50 µl saline)	Rat	Decrease in anabolism of cartilage	Decaris <i>et al.</i> , 1999 ¹⁵
Retrovirus encoding IL-4 in ankle	Rat with AIA	Increase in IL-4 in the absence of transgene	Boyle <i>et al.</i> , 1999 ¹⁶
AIA in knee (500 µl of mBSA in rats immunized with 1 ml CFA 2 mg <i>Mycobacterium tuberculosis</i>)	Rat	Histopathological and biochemical evidence of joint destruction	Meyer <i>et al.</i> , 2000 ¹⁷
m-BSA in CFA and <i>Bordetella pertussis</i> in knee	Rat	Increased proteoglycan loss	Segond von Banchet <i>et al.</i> , 2000 ¹⁸
100 µl of 1% latex spheres (11.9 µm diameter) in knee	Rat	Bradykinin-induced plasma extravasation enhanced Macrophage infiltration	Kidd <i>et al.</i> , 1995 ¹⁹
CFA (0.2 ml) in knee	Rat	Reduces phenylephrine (α1-adrenoceptor agonist) vasoconstrictor response up to 21 days	Badavi <i>et al.</i> , 2000 ²⁰
50 µg mBSA in knee of sensitized rats	Rat	Histological evidence of cartilage damage and pannus formation at 14–20 days	Andersson <i>et al.</i> , 1998 ²¹

SP, substance P; CGRP, calcitonin gene-related peptide; NPY neuropeptide A; NK-A neurokinin A; IL, interleukin; CFA, complete Freund's adjuvant; AIA, adjuvant-induced arthritis; m-BSA, methylated bovine-specific antigen

at all spinal levels across all species examined, including primates.³⁷ Electrophysiological studies show sensory neurones with contralateral receptive fields.^{38–40} Receptive fields from some nociceptive fibres are seen to expand in the presence of inflammation from unilateral to bilateral in a topographically precise fashion.^{38,39}

A circulatory explanation for contralateral effects

An alternative hypothesis is that the contralateral effect is mediated via the circulation as part of a systemic response. It is difficult however to envisage how a circulatory factor could be so topographically specific as to trigger a response in the contralateral knee, but not the hip or the ankle.^{17,19} Equally persuasive against a circulatory basis for these responses are experiments in

Table 2 Effect of rat hindpaw inflammation on the contralateral hindpaw

Inducing agent	Contralateral effect	Ref.
IL-1beta (10 ng)	Bradykinin 1 receptor-mediated mechanical hyperalgesia elicited	Ganju <i>et al.</i> , 2001 ²²
CFA (100 µl)	TNF-alpha levels elevated	Woolf <i>et al.</i> , 1997 ²³
Carrageenan (0.1 ml of 2%)	CGRP levels increase in perfusate	Yu <i>et al.</i> , 1996 ²⁴
CGRP 100 µl (300 pmol)	Oedema induced at 5–24 h	Bileviciute <i>et al.</i> , 1998 ²⁵
Crystal-induced	Swelling observed	Denko and Petricevic, 1978 ²⁶
<i>Mycobacterium butyricum</i> 100 µl of 6 mg/ml in CFA	Hindpaw oedema in polyarthritic rats	Ianaro <i>et al.</i> , 2000 ²⁷
Repeated saline injection	Oedema and hyperalgesia	Levine <i>et al.</i> , 1985 ²⁸
Carrageenan 100 µl of 2%	Thermal and mechanical withdrawal latencies reduced	Yu <i>et al.</i> , 1996 ²⁴
Carrageenan 100 µl of 2%	Hyperalgesia induced	Kissin <i>et al.</i> , 1998 ²⁹
Bee venom 100 µl (0.2 mg)	Reduction in heat withdrawal latency	Chen <i>et al.</i> , 1999 ³⁰
Thermal	Heat hyperalgesia Response attenuated by spinal anaesthesia and systemic guanethidine	Coderre and Melzack, 1985, ³¹ 1987 ³²
Formaldehyde 50 µl (0.1%, 5% and 10% solution)	Licking responses occur at 25–45 min	Aloisi <i>et al.</i> , 1993 ³³

IL, interleukin; CFA, complete Freund's adjuvant; TNF, tumour necrosis factor; CGRP, calcitonin gene-related peptide

which the draining veins of an inflamed limb are ligated and the contralateral response is unaffected.²⁸

There are however studies that demonstrate leucocytes unexpectedly trafficking to the contralateral joint after inducement of a monoarthritis.^{41,42} Methotrexate appears in the contralateral knee within one hour after it is injected intra-articularly.⁴³ It is unknown whether this is an anatomically specific or a more generalized synovial response. Further evidence supporting the role of the nervous system in directing inflammatory responses comes from studies demonstrating the lateralization of T-cell responses in patients who have suffered a stroke.⁴⁴ It is therefore possible that a systemic inflammatory response could be targeted focally by a nervous system that upregulates local inflammatory responses.

Neuropeptides and inflammation: neurogenic inflammation

The role of neuropeptides in chronic disease has long been hypothesized.^{11,12} The role of neurogenic inflammation in psoriasis has been clearly shown in a photograph demonstrating resolution of part of a plaque after surgical severance of intercostal nerves.⁴⁵ Clinically, paralysed joints caused either by stroke or poliomyelitis, are spared in patients with rheumatoid arthritis and neurological compromise.⁴⁶⁻⁴⁹ Experimentally, by selectively lesioning C fibres with capsaicin, inflammation in animal models of arthritis is attenuated.⁵⁰

Neuropeptides, such as substance P and calcitonin gene-related peptide (CGRP) have pro-inflammatory effects. They influence vasodilation, extravasation, leucocyte mobilization and leucocyte-driven microbial destruction systems.^{51,52} The net effect of these properties is to 'upregulate' the inflammatory response and they are the peptides that cause the skin flare wheal in axon reflexes. It has been demonstrated that nerve fibres (C and A delta fibres) containing these neuropeptides are found in synovial joints and in an especially high concentration perivascularly. Some fibres also extend deeper into joint

synovium.⁵³ The dense innervation of joints with these fibres provides anatomical evidence that neuropeptides are well positioned to influence inflammatory responses there and could explain the presence of the histological findings in patients with CRPS.⁵

Systemic levels of CGRP are increased in patients with CRPS,⁵⁴ in whom the level of substance P in cerebrospinal fluid has been shown to be about three times that of a matched control population.⁵⁵ Neuropeptide levels are increased in synovial fluid taken from patients with rheumatic diseases.⁵⁶ Neuropeptides have also been shown to recruit leucocytes into the synovium.⁵⁷ Joints primed with neuropeptides mount larger inflammatory responses to pro-inflammatory substances such as histamine⁵⁸ or bradykinin.¹⁹ In animal models, joints injected with neuropeptides develop more severe experimental arthritis.⁵⁹

Patients with chronic pain syndromes or rheumatoid arthritis show differences in nociceptive pathways when compared with normal control patients. The area of secondary hyperalgesia (defined as increased pain that is distant from tissue injury) after topical capsaicin is larger in patients with rheumatoid arthritis than in normal controls.⁶⁰ Broadly speaking, this could be interpreted as an upregulation of inflammatory responses. At a higher level, cortical and subcortical changes have been observed⁶¹ in patients with chronic pain, which are different to those in people with rheumatoid arthritis and normal controls.

Testing the hypothesis

Anatomical and electrophysiological studies could be used further to elucidate transmedian pathways in spinal segments in both animals and humans. Animal models could also be developed further to understand the influence of neurogenic inflammation on the symmetry of arthritis. These could include rats treated with capsaicin neonatally to reduce significantly the number of neuropeptide-containing C fibres.

In humans, hyperalgesia and early inflammation can be safely and reliably induced by using capsaicin, histamine, or thermal burns, and can be measured by standard psychophysical

techniques.⁶² Skin blood flow, a marker of inflammatory response, can be assessed by thermographic and laser Doppler imaging. Cellular inflammatory response can be assessed histologically and by using immunocytochemical methods. Stable and reliable models of contralateral responses need to be developed. Candidate models include contralateral vasodilatation in response to topical or intradermal capsaicin. Contralateral responses to inflammatory stimuli could therefore be assessed in patients with inflammatory diseases and in normal controls. Physiological studies could then be performed further to understand the mechanisms of contralateral responses, and pharmacological compounds aimed at blocking them could be tested. Once perfected, these techniques could become a novel therapeutic strategy for use in inflammatory conditions.

Conclusion

Symmetry occurs frequently in medical practice. A nociceptive pathway has been proposed to explain this. Patients with chronic painful or inflammatory conditions demonstrate different peripheral neurological responses compared with normal controls. Neurogenic inflammation may therefore explain the symmetry seen in these conditions. Compounds that stabilize these nociceptive pathways to prevent neurogenic inflammation could alter significantly the prognosis of these diseases and thereby offer new therapies.

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