A review of contralateral responses to a unilateral inflammatory lesion

N. Shenker, R. Haigh, E. Roberts¹, P. Mapp¹, N. Harris and D. Blake

Symmetry is a remarkably constant clinical feature of chronic inflammatory disease. Rheumatoid arthritis is almost by definition symmetrical [1]. Osteoarthritis, psoriasis and some of its associated arthritides are also symmetrical [2–4]. Pulmonary fibrosis, glomerulonephritis and sympathetic ophthalmia are also symmetrical inflammatory conditions. Whilst the pathophysiology behind this symmetry is unexplained, we and others have speculated that it is likely to be mediated via neurological mechanisms crossing through the spinal cord [5, 6]. The two sides of the spinal column have largely been thought to function independently of each other. There are three lines of evidence to suggest that this is not true.

Careful anatomical studies of the spinal cord show transmedian fibres decussating posteriorly at all levels of the spinal cord to synapse in the laminae on the contralateral dorsal horn. These neuronal connections have been seen in many different species, including several primates (Fig. 1). Szentagothai [7], using Golgi analysis on young cats and dogs, showed that neurons with their cell bodies in the substantia gelatinosa send contralateral axons that appear to synapse in the contralateral substantia gelatinosa. Perl and Light [8] corroborated these findings after they had applied horseradish peroxidase to rat, cat and monkey dorsal rootlets. They found projections into the contralateral substantia gelatinosa as well as the ventral portion of the nucleus proprius. Culberson et al. [9], using cresyl violet acetate (Fink-Heimer method), identified crossed afferent projections throughout the spinal cord, originating and terminating in laminae III–IV, in four mammalian species. These anatomical studies provide evidence that the opportunity exists for crosstalk between the left and the right sides of the spinal column.

Functional studies of decerebrate rats demonstrate that such cross-communication can produce contralateral responses. Electrical stimulation of contralateral peripheral nerves is known to inhibit flexor reflex pathways in the spinal cord [10] as well as the long latency of C-fibre-evoked activity in dorsal horn cells [11, 12]. Contralateral dorsal horn cells are inhibited in response to noxious stimuli applied to the limb or tails of rats [13, 14]. Further electrophysiological studies confirm the presence of neurons in the dorsal horn that have bilateral receptive fields. Of relevance to this article is that the number of these neurons with bilateral receptive fields increases in the presence of unilateral inflammation [15, 16]. Grubb et al. [17] also showed that some of the fields on the contralateral side can become excitatory rather than inhibitory.

At what level are these contralateral responses mediated? Woolf [16] documented the persistent reduction in flexor reflex thresholds contralaterally after noxious thermal stimuli had been applied to decerebrate rats with an intact brainstem. Fitzgerald [18], using a decerebrate, spinalized rat model, showed that a contralateral effect on dorsal horn fibres need not involve such higher pathways. Although direct contralateral spinal pathways exist in experimental conditions, there are likely to be significant supraspinal influences in vivo. This is suggested by several studies detailing an attenuation of central sensitization and secondary hyperalgesia following spinalization or inactivation of the rostral ventral medulla in a review of rat models of acute pain [19].

In addition to these functional responses, there is also a wealth of evidence to show that contralateral structural and biochemical changes can occur both centrally and in the periphery in response to a unilateral insult. Koltzenburg et al. [20] have reviewed the literature detailing contralateral effects from a unilateral neurological lesion. They identified papers illustrating such phenomena either serendipitously or through experimental design. Although there were methodological explanations for some of the findings, these were inadequate in explaining all of the results. For example, sprouting of the contralateral nerve terminal at the neuromuscular junction of frogs was seen to occur in response to unilateral nerve section, but not to tenotomy (leaving the nerve intact) in controlled, reproducible experiments. Interestingly, this sprouting was observed at a later time (12 vs 5 days) the more distal the cut had been to the spinal cord. This suggests that the contralateral sprouting phenomenon is dependent upon...
slow signals. The wide variety of responses to a wide variety of lesions in different laboratories with good experimental designs led the authors to conclude that a novel transmedian pathway using 'slow' signalling should be proposed to explain these findings.

The confirmation of neurological pathways capable of influencing inflammation at distant sites would be of major significance. Firstly, this would add further evidence to support the role of the nervous system in inflammation. Clinical observations show that the nervous system may have a role in inflammation. Denervation of joints leads to regression of established rheumatoid arthritis and protection from the development of RA. This has been seen in both upper and lower motor nerve lesions [21, 22]. Psoriasis also improves following skin denervation [2]. Purpura fulminans was strikingly prevented in the arm of a young boy with brachial plexopathy [23].

Certain neuropeptides are proinflammatory and important in the pathophysiology of inflammatory arthritis, and this has been reviewed [24]. In brief, neuropeptides, such as substance P (SP) and calcitonin gene-related peptide (CGRP), have been shown to have proinflammatory effects. They influence vasodilation, extravasation, leucocyte mobilization and leucocyte-driven microbial destruction systems [25, 26]. SP also promotes leucocyte recruitment into the synovium [27]. Joints primed with neuropeptides mount larger inflammatory responses to proinflammatory substances such as histamine [28] and bradykinin [29]. A neurological component to explain the clinical phenotype of symmetry in inflammatory conditions would therefore confirm the experimental work that suggests that neuropeptides have an important role in propagating chronic inflammation.

Secondly, contralateral phenomena would have implications in conditions other than chronic inflammation. Many painful conditions are widespread. Complex regional pain syndrome (CRPS) can be symmetrical and the involvement of distant regions is under-recognized. Documented bilateral presenting symptoms occurred in about 5–15% of patients with CRPS [30, 31]. However, detailed investigations, such as with technetium pertechnetate bone scanning, demonstrate that symmetrical involvement might occur more commonly than clinical symptoms suggest [31]. Further important clinical observations suggesting that contralateral effects may be important in painful conditions have come from induced cord lesions. For example, Bowsher [32] describes contralateral mirror-pain resulting from a therapeutic anterolateral cordotomy.

Thirdly, the development of contralateral responses would be a useful outcome measure in the design of an experimental model upon which to test novel anti-inflammatory agents and analgesics. Fourthly, illustrating that the contralateral homonymous area is affected by unilateral insults would have profound effects on the design of experimental models that use the contralateral body part as a control. Indeed, many of the papers appraised in this article only detected a contralateral response when they compared the contralateral area with that of a control group that was not exposed to the original unilateral insult. Results of studies in which the contralateral area was used as a control may therefore have underestimated the inflammatory response of an insult or a therapeutic manoeuvre, as the contralateral responses would have reduced the difference between the control and experimental groups.

The concept of contralateral responses is controversial but nevertheless, for the reasons outlined above, very important. The aim of this review, therefore, is to identify published papers that identify mirror-image contralateral responses to painful and inflammatory stimuli. The experimental design of these papers was appraised in order to clarify the type of contralateral response and to exclude alternative explanations. The existence of contralateral responses could then be assessed, and possible mechanisms and pathways could be postulated on the basis of the available evidence.

**Methods**

A Medline search (Ovid) was performed in October 2001 to find relevant papers published after 1966. The terms 'symmetry', 'inflammation', 'contralateral' and 'mirror-image' were used in combinations. Abstracts were then scanned. Papers were included if a contralateral effect was observed in response to a unilateral inflammatory stimulus. Original papers were obtained and appraised. References were scanned to identify further papers until no more relevant papers were identified. Papers were excluded if the inflammatory insult caused systemic features. For example, high doses (e.g. 250 μg) of Freund’s complete adjuvant (CFA) are known to induce a systemic arthritis in rats, whereas 50 μg induces only a monoarthritis [33]. Papers that showed the contralateral effects occurring in the CNS at levels higher than the spinal cord segment of the lesion were also excluded [34]. Duplicate results published in different forms were excluded. Each paper was appraised on the following criteria: a priori hypothesis; appropriate unilateral lesion; controls that were not exposed to the unilateral lesion; alternative explanation offered by investigators. Papers that were excluded are listed with explanations in Appendix 1.
Results

The Medline search yielded 710 titles. From these abstracts, 30 papers were identified as satisfying the inclusion criteria and the original papers were obtained. The references of these papers were scanned and a further nine articles were identified. Of these 41 papers, the appraisal process excluded 23. These are listed with the reason for their exclusion in Appendix 1. A number of papers identified an anti-inflammatory contralateral response following a unilateral anti-inflammatory stimulus. These papers were excluded from this analysis because all of the animals had pre-existing polyarthritis.

Therefore 18 papers were identified and found to fulfil the criteria applied in the appraisal process. In all of the papers, the a priori hypothesis had been that an appropriate unilateral inflammatory lesion might cause contralateral effects, and controls that had not been exposed to this lesion were used. These papers are presented in Table 1.

Table 1. The contralateral effects of localized unilateral inflammation

<table>
<thead>
<tr>
<th>Contralateral effect</th>
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<tr>
<td><strong>Lesions inducing arthritis</strong></td>
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<tr>
<td>CFA (1 µg) in knee</td>
<td>Decrease in anabolism of cartilage for 6–72 h</td>
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<tr>
<td>Freund’s adjuvant in knee (0.05 ml of 1 mg/ml)</td>
<td>Increase in SP, CGRP and NPY in knee for 2–24 h</td>
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<tr>
<td>Carrageenan 2% (0.05 ml) in knee</td>
<td>Increase in NK-A in knee at 2 and 24 h</td>
</tr>
<tr>
<td>Human recombinant IL-1 (0.05 ml of 1 mg/ml) in knee</td>
<td>Increase in CGRP and NPY for 2–24 h</td>
</tr>
<tr>
<td>SP (0.05 ml of 10−5 m) in knee</td>
<td>Increase in CGRP and NPY for 2–24 h</td>
</tr>
<tr>
<td>SP in knee (0.2, 1, 2, 10, 20 µg in 50 µl)</td>
<td>Increase in NK-A at 2–6 h and SP at 2 h</td>
</tr>
<tr>
<td>500 µl of mBSA in knee of rats pre-immunized with 1 ml CFA/2 mg MTb</td>
<td>Increase in SP for 2–24 h, CGRP for 6–24 h and NPY for 2–6 h</td>
</tr>
<tr>
<td>500 µg (50 µl) mBSA in knee of presensitized rats</td>
<td>No increase in NK-A</td>
</tr>
<tr>
<td>100 µl of 1% latex spheres in knee</td>
<td>Decrease in anabolism of cartilage for 6–72 h</td>
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<tr>
<td><strong>Lesions inducing hindpaw oedema</strong></td>
<td></td>
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<tr>
<td>CFA (100 µl)</td>
<td>Histopathological and biochemical evidence of joint</td>
</tr>
<tr>
<td>Carrageenan (0.1 ml of 2%)</td>
<td>destruction up to 80 days</td>
</tr>
<tr>
<td>Carrageenan (100 µl of 2%)</td>
<td>Increased proteoglycan loss and mechanical</td>
</tr>
<tr>
<td>Formaldehyde 50 µl (0.1%, 5%, 10%)</td>
<td>hyperalgesia up to 9 days</td>
</tr>
<tr>
<td>Bee venom 100 µl (0.2 mg)</td>
<td>Bradykinin-induced plasma extravasation enhanced</td>
</tr>
<tr>
<td>Repeated saline injection (150 µl on 3 consecutive days)</td>
<td>between 1 and 21 days; macrophage infiltration</td>
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<tr>
<td>Urate, pyrophosphate and oxalate crystals (3 mg in 150 µl)</td>
<td>noted between 3 and 10 days</td>
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<tr>
<td>CGRP 100 µl (300 pmol)</td>
<td></td>
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<tr>
<td>NGF injections (3 days of 4 µg/day) in hindpaw or ear or forepaw</td>
<td></td>
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<tr>
<td>IL-1β (10 ng)</td>
<td></td>
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<tr>
<td>Thermal stimuli (55°C for 15 s)</td>
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<tr>
<td>Thermal stimuli (55°C for 15–20 s)</td>
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<tr>
<td>Thermal stimuli to decerebrate rat (75°C for 60 s)</td>
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All studies were performed in rats unless otherwise indicated.
CFA, complete Freund’s adjuvant; NPY, neuropeptide Y; NK-A, neurokinin A; IL-1, interleukin 1; mBSA, methylated bovine serum albumin; MTb, Mycobacterium tuberculosis; TNF, tumour necrosis factor; NGF, nerve growth factor.

Discussion

Contralateral responses were seen in many different laboratories, and they were consistently identified independently of the type of stimulus (e.g. CFA, thermal injury and SP) and the various strains of rats used (Wistar, Lewis and Sprague–Dawley), both males and females. No alternative explanations were offered by the investigators to explain their findings. This suggests that these distant responses are not artefactual. Most of the experiments were performed in rats and the application of these results to other species needs further work. Are the contralateral responses simply a species effect? The review by Koltzenburg et al. [20] of the contralateral responses to unilateral neurological lesions suggests not. Contralateral responses were demonstrable not only in rats but also in guinea-pigs, frogs, mice, cats and ferrets.

There are several reasons to think that these contralateral responses are mediated through neural mechanisms rather than reflecting a systemic or circulatory effect. Lesioning nociceptive nerves supplying either
the contralateral or the ipsilateral limb prior to the inflammatory insult, using a variety of lesions, such as surgery [6, 35, 48, 50, 51], capsaicin [6, 29, 52] and local anaesthesia [6, 49, 50], abolished the contralateral responses. However, ligating the draining venous system of the inflamed area prior to the insult does not abolish the contralateral response [6]. The hypothesis that contralateral responses are neurologically mediated is not new. These identified papers add to the body of evidence to support this hypothesis and also point to a prominent role for the nervous system in inflammation.

It is therefore of some interest to examine the contralateral spinal cord during unilateral inflammatory lesions. The metabolism of 2-deoxyglucose has been used as a surrogate marker of neuronal activation in the rat. Increases in metabolism have been measured in the contralateral regions of the spinal cord following unilateral hindpaw inflammation caused by formalin [42, 53] and thermal injury [54].

The proteins of immediate-early genes and transcription factors are rapidly expressed in response to many stimuli. The gene products include Fos, Jun and Krox-24. The expression of these genes and their products has been seen contralaterally in the spinal cord. After CFA was placed into either the hindpaw [55] or the ankle [56], c-Fos was expressed in lamina VIII contralaterally. After thermal stimulation, immediate-early genes and their products were also seen in the deep laminae contralaterally [57, 58]. After electrical stimulation of unmyelinated sensory afferents [59, 60], products were expressed in laminae IV and VI. After carrageenan was used to cause hindpaw oedema, Fos-like immunoreactivity was seen in laminae V and VI [61]. All of these studies support the hypothesis that there is activation of contralateral neurons, which in turn could influence the contralateral periphery. Undoubtedly, as suggested by the attenuation of central sensitization and secondary hyperalgesia following spinalization, there are also likely to be supraspinal influences from the brainstem and higher centres upon these pathways [19].

Given the role of neuropeptides in inflammatory processes outlined above, of particular interest would be the expression of these neuropeptides and their receptors centrally. Neuropeptides can modulate inflammation, as discussed above, and by selectively blocking C-fibres with capsaicin [6, 29, 52] it is possible to block previously expressed contralateral responses. Again, there are many examples of contralateral changes in the nervous system in response to a unilateral inflammatory lesion. Increases in SP, CGRP and their receptors are seen in lesions produced by methylated bovine serum albumin, latex spheres or CFA. These increases have been seen in the spinal cord [62–65] as well as the contralateral dorsal root ganglion [29, 38, 62]. However, de Ceballos et al. [64] found SP levels to be decreased at 24 h in the contralateral spinal cord following a thermal injury.

It is tempting to speculate on properties that relate to these contralateral responses. First, the contralateral responses appear to require the inflammatory stimulus to be of a certain magnitude before appearing. There are several examples in the literature of this threshold effect. The studies of Bileviciute et al. [43] did not demonstrate contralateral hindpaw oedema with low doses of subcutaneous CGRP (75 and 150 pmol), but did with a higher concentration (300 pmol) [43]. Adjuvant arthritis in the rat induced with intradermal injections of small doses of CFA around the tibiotarsal joint causes contralateral arthritis if the dose is increased from 75 to 150 μg [31]. Noceptive behaviours towards the contralateral paw were not seen after 0.1% formaldehyde injections but were observed after injections of 5% solution, and were even more frequent after injection with a 10% solution [40]. Other papers did not examine the effects of varying the dose of the initial stimulus upon the contralateral responses.

Secondly, where studied, the contralateral responses appear to be topographically precise. Three separate studies that were designed to detect this were identified. Kidd et al. [27] placed latex spheres within one knee joint of a rat before examining the inflammatory response in the contralateral knee, ankle and hip joints using bradykinin-induced plasma extravasation and histological examination. They found that only the contralateral knee exhibited enhanced plasma extravasation and macrophage infiltration, and these responses were not seen in the contralateral hip or the contralateral ankle. Meyer et al. [35] examined the contralateral knee and both ankles for cartilage metabolism and histological damage. They too found that only the contralateral knee showed a decrease in cartilage anabolism and signs of histological damage, and these were not seen in either ankle. Amann et al. [44] used repeated injections of nerve growth factor and examined the mRNA of neuropeptides in the contralateral nerve [44]. They found increases only in the contralateral sciatic nerve if the hindpaw was injected, only in the contralateral trigeminal nerve if the ear was injected and only in the contralateral brachial plexus if the forepaw was injected. The topographical precision of the contralateral response strongly implies a neurogenic mechanism rather than a systemic effect.

Thirdly, the contralateral responses are broadly stimulus-specific. If a pro-inflammatory stimulus is induced unilaterally, the contralateral response is pro-inflammatory, as evidenced by the identified papers, all of which show contralateral proinflammatory responses. However, if the ipsilateral response is neurological, such as the response to sectioning of a peripheral nerve, then the contralateral response is also appropriately neurological: the corresponding neuromuscular junction exhibits nerve sprouting. Also, if the insult is anti-inflammatory, such as detailed in some of the papers in Appendix 1, the contralateral response is anti-inflammatory.

Fourthly, the contralateral responses are only a shadow of the original lesion, both in magnitude and temporally. In all of the identified papers, the contralateral changes were less than the ipsilateral changes. The withdrawal latencies were reduced to a greater extent on the side of the lesion than on the contralateral side; the
magnitude of the biochemical or histopathological abnormalities was greater on the side of the lesion; and the macroscopic changes, such as oedema, were also greater on the side of the lesion.

Contralateral responses unrelated to any ongoing disease process have recently been demonstrated in man [66]. They are therefore likely to have a physiological role. One hypothesized role is that contralateral mirror-imaging phenomena can up-regulate protective pro-inflammatory responses in the contralateral limb in preparation for an insult that has already occurred [27, 60]. Biologically, this could be protective. The inflammatory response could be focally up-regulated and, should a similar noxious insult appear on the contralateral side, then it could be dealt with more effectively. The advantage that this precise response has over a systemic response to inflammation is that it is economic with the energy expended and limits widespread self-damage caused by inappropriate inflammation. Similarly, pain withdrawal reflexes are primed so that the contralateral limb can be withdrawn more quickly. There is more chance of damage limitation from a dangerous environment if such responses exist, and it could be argued that survival is enhanced through the use of such pathways.

However, physiology often begets pathology. It should therefore be of no surprise if these pathways accounted for the symmetry of chronic inflammatory diseases. It is therefore further hypothesized that the physiological neural pathways that mediate contralateral mirror imaging of inflammatory stimuli may be amplified to generate pathology when no contralateral insult has been applied. This could be viewed as an example of an auto-neuro-inflammatory response that could contribute to the aetiology of chronic symmetrical inflammatory diseases, such as rheumatoid arthritis and psoriasis. This hypothesis is testable. By understanding the neuropharmacology of these pathways, new opportunities may be explored for preventing the spread, and perhaps the chronicity, of such inflammatory diseases.

**Conclusion**

Contralateral mirror-imaging of inflammatory and neural injuries exist and they have been demonstrated under controlled experimental conditions in animal models and in early reports in man. These pathways are mediated through neurological mechanisms. Their existence is important when planning experiments, as the contralateral limb is not appropriate for use as an internal control. They demonstrate the importance of the nervous system in inflammation, and they are likely to be important in the pathophysiology of chronic symmetrical inflammatory diseases, such as rheumatoid arthritis and psoriasis. Down-regulation of the activity of such neurological pathways may be the basis of new treatments for these chronic debilitating conditions.

**Acknowledgements**

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**Conflicts of interest**

The authors have declared no conflicts of interest.

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Appendix 1. Papers excluded after appraisal

<table>
<thead>
<tr>
<th>Paper Reference</th>
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<tr>
<td>Hypothesis not a priori (inadequately controlled/not unilateral lesion)</td>
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