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European Journal of Pharmacology 429 (2001) 101–113

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Review

Neuroimmune alterations in the complex regional pain syndrome

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Accepted 27 July 2001

Abstract

This review focuses on some clinical aspects of the complex regional pain syndrome, such as oedema, local temperature changes and chronic pain, as a result of supposed neurogenic inflammation. Involvement of the immune system could imply the subsequent release of neuropeptides, pro-inflammatory cytokines and eicosanoids, which in turn leads to a complex cross-talk of primary and secondary generated mediators of inflammation. The development and application of drugs that act through selective receptor antagonism or enzymatic synthesis inhibition to prevent further stimulation of this cascade that could inevitably lead to chronicity of this disease are extensively discussed.

Keywords: Complex regional pain syndrome; Neurogenic inflammation; Pain; Oedema; Temperature; Neuropeptide; Cytokine; Eicosanoid

1. Introduction

Complex regional pain syndrome type 1 (CRPS1) is a complication occurring in an extremity after even minor surgery or operation on a limb. It is a major cause of disability. The reported incidence of complex regional pain syndrome 1 is 1–2% after various fractures and in prospective studies of Colles fracture, 7–35%. In 10–26% of the cases, no precipitating factor can be found. Complex regional pain syndrome type 1 has been given various names, depending on the precipitating factor, the country concerned, or the speciality treating the patient: Reflex sympathetic dystrophy (RSD); Sudeck's atrophy; algodystrophy. There has been confusion about the meaning of these terms (Veldman et al., 1993). In 1993, a special conference workshop was held in Orlando under the auspices of the International Association of Study of Pain (IASP) during which a new taxonomic system was developed. The members of the conference decided to choose the term Complex Regional Pain Syndrome. The term describes a variety of painful conditions following injury which appear regionally with a distal predominance of abnormal findings, whose magnitude and duration exceed the expected clinical course of the inciting event, often resulting in significant impairment of motor function, and showing variable progression with time.

A difference is made between complex regional pain syndrome type 1 and complex regional pain syndrome type 2 (CRPS2). Complex regional pain syndrome type 1 develops after an initiating noxious event. Complex regional pain syndrome type 2 develops after a nerve injury. In complex regional pain syndrome type 1, spontaneous pain or allodynia/hyperalgesia occurs, is not limited to the territory of a single peripheral nerve, and is disproportionate to the inciting event. There is, or has been, evidence of oedema, skin bloodflow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event. The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction (Stanton Hicks et al., 1995). Bruehl showed in 1999 that these IASP criteria for complex regional pain syndrome type 1 have an inadequate specificity and are likely to lead to overdiagnosis. He proposed modified research diagnostic criteria for complex regional pain syndrome type 1, see Table 1 (Bruehl et al., 1999). The pathophysiology of complex regional pain syndrome type 1 is not yet clear. Several studies suggest a peripheral afferent mechanism, others a peripheral efferent mechanism, or central mechanisms including psychological mechanisms or combinations of more than one mechanism have been suggested. Classically, the disease is characterised in the acute stage by symptoms of regional inflammation. In the chronic stage a more neuropathy-like disor-

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0014-2999/01/$ - see front matter
PII: S0014-2999(01)01310-3

Table 1
Modified diagnostic criteria for complex regional pain syndrome type 1

☑ Continuing pain which is disproportionate to any inciting event		☑ Report of at least one symptom in each of the following categories	☑ Must display at least one sign in two or more of the following categories
	Sensory:	hyperesthesia	evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch)
	Vasomotor:	temperature asymmetry and/or skin colour changes and/or skin colour asymmetry	evidence of temperature asymmetry and/or skin colour changes and/or asymmetry
	Sudomotor/oedema:	oedema and/or sweating changes and/or sweating asymmetry	evidence of oedema and/or sweating changes and/or sweating asymmetry
	Motor/trophic:	decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)	evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

der develops. A possible explanation for this alteration during the disease is the development of sensitisation or plasticity during the regional inflammation, which results in a neuropathic disorder. Sometimes, the signs of regional inflammation are exacerbated in the chronic stage. This could explain why combinations of peripheral afferent, efferent and central mechanism in complex regional pain syndrome type 1 are seen (Fig. 1).

2. Pathophysiology

2.1. Peripheral, afferent

2.1.1. Chronic constriction injury, an experimental model for complex regional pain syndrome type 1

In the rat, chronic constriction injury is produced by loose ligation of the sciatic nerve. Signs and symptoms are similar to those observed in reflex sympathetic dystrophy. Skin blood flow is increased after 4 days and returns to pre-ligation values after selective conduction blockade of the ligated sciatic nerve with capsaicin. There is an increase in polymorphonuclear leukocyte accumulation in the ligated hind paw. These findings indicate that antidromically acting c-nociceptor nerve fibres increase skin blood flow. In addition, these antidromic mechanisms may induce an inflammatory response, mediated from the peripheral endings of antidromically acting c-nociceptor nerve fibres. This inflammatory response could account for various signs and symptoms seen in the chronic constriction injury model and may mirror pathophysiological mechanisms of reflex sympathetic dystrophy (Daemen et al., 1998a,b).

2.1.2. The role of free radicals in the pathophysiology of complex regional pain syndrome type 1

The effect of free radicals was also investigated in an animal model. Infusion of the free radical donor, *tert*-butylhydroperoxide, induced acute signs and symptoms of early complex regional pain syndrome type 1, with alterations in pain sensation as found in the classical neuropathic animal model of complex regional pain syndrome type 1, and in complex regional pain syndrome type 1 patients. Infusion of *tert*-butylhydroperoxide induced an increased skin temperature, increased paw volume, redness of the plantar skin, impaired function and increased pain sensation (Van der Laan et al., 1998a).

2.1.3. Inflammatory mechanisms in complex regional pain syndrome type 1

A large prospective study with 829 patients paid particular attention to early signs and symptoms. In the initial

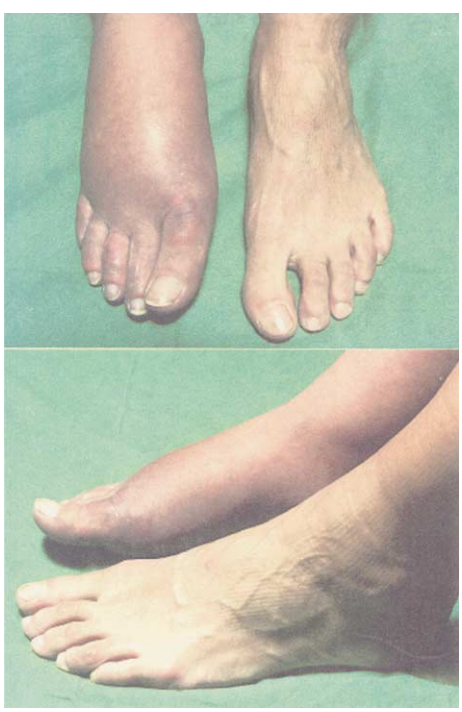

Fig. 1. This photograph represents complex regional pain syndrome type 1 in the right foot of a 35-year-old woman, 6 years after she had surgery of her hammer toe and some bone was removed from the heel. Now she is severely disabled and needs a pair of crutches to walk. All signs of complex regional pain syndrome type 1 are present: continuous pain, hyperesthesia, hyperalgesia, allodynia, cold/warm temperature, redness, oedema, trophic changes (hair, nail, skin) and motor dysfunction.

phase, reflex sympathetic dystrophy was characterised by signs of regional inflammation, which increases after muscular exercise. These findings support the concept of an exaggerated regional inflammatory response to injury or operation in reflex sympathetic dystrophy (Veldman et al., 1993). A scintigraphic study demonstrated vascular leakage of macromolecules in the acute phase of complex regional pain syndrome type 1. This suggests that an important characteristic of inflammation plays a role in the development of complex regional pain syndrome type 1 (Oyen et al., 1993). In another clinical study, the lower leg skeletal muscles of 11 patients affected by reflex sympathetic dystrophy were investigated at rest using ^{31}P nuclear resonance spectroscopy. Impairment of high-energy phosphate metabolism was found. This may be caused by cellular hypoxia or diminished oxygen utilisation, which would agree with previous findings that oxygen extraction is reduced in extremities affected by reflex sympathetic dystrophy. This is a phenomenon which is classically detectable in areas of inflammation (Heerschap et al., 1993).

2.1.4. Neuropathic mechanisms in complex regional pain syndrome type 1

The histopathology of skeletal muscles and peripheral nerves from patients with chronic complex regional pain syndrome type 1 of the lower extremity was investigated. In chronic complex regional pain syndrome type 1, efferent nerve fibres were histologically unaffected; of afferent fibres, only C-fibres showed histopathologic abnormalities. Skeletal muscle showed a variety of histopathological abnormalities, some of which were similar to the histologic abnormalities seen in muscles of patients with diabetes (Van der Laan et al., 1998b). Van der Laan et al. (1998c) also checked for changes in afferent A-beta fibre-mediated reflexes in lower extremities affected by acute complex regional pain syndrome type 1. They found no evidence of abnormal A-beta fibre-mediated reflexes or defective regulation of such reflexes. This finding has implications for both the theory regarding complex regional pain syndrome type 1 pathophysiology and for complex regional pain syndrome type 1 models, which are based on abnormal functioning of A-beta fibres (Van der Laan et al., 2000).

2.1.5. Neuroimmune considerations in complex regional pain syndrome type 1

Antigen associations were tested for lymphocytes from subjects with complex regional pain syndrome type 1, to study correlations of human lymphocytes antigen associations and treatment outcomes. This was the first study to suggest a possible genetic diathesis in complex regional pain syndrome type 1 patients with poor treatment outcome. Gene(s) conferring susceptibility to complex regional pain syndrome type 1 may be present within or near the MHC region of the short arm of chromosome 6 (Mailis and Wade, 1994).

2.2. Peripheral, efferent

2.2.1. Sympathetic mechanism in complex regional pain syndrome type 1

A reduction in sympathetic activity might accompany allodynia and influence vasomotor disturbances in patients with causalgic pain as expressed by blood levels of neuropeptide Y, a vasoactive transmitter which co-exists with noradrenaline in sympathetic nerve terminals (Drummond et al., 1994). Sudomotorfunction in patients suffering from sympathetic reflex dystrophy (median duration of disease 8 weeks (range 2–468 weeks) showed a differential disturbance of vasomotor and sudomotor mechanisms in affected skin. Whereas vasoconstrictor activity is apparently diminished, sudomotor output is either unaltered or may even be enhanced (Birklein et al., 1997b). Birklein et al. also investigated the sympathetic vasoconstrictor reflex in patients with complex regional pain syndrome type 1. Different manoeuvres were employed to induce vasoconstriction while the cutaneous blood flow of the affected and the contralateral limb was recorded. Sympathetic reflex vasoconstriction triggered by mental arithmetic, which represents a cortical-generated, moderate vasoconstrictor stimulus, was significantly reduced in the affected limb when compared to the control limb. Inspiratory gasp and cold pressor test (both spinal and supraspinal), representing stronger vasoconstrictor stimuli, revealed no significant side-to-side difference of sympathetic vasoconstriction and no significant difference from the controls. These findings demonstrated an impairment of sympathetic vasoconstrictor activity after central vasoconstrictor stimulation in complex regional pain syndrome type 1 (Birklein et al., 1998b). Vasomotor and sudomotor controls were substantially altered in complex regional pain syndrome type 1. In the acute stage, vasomotor control is decreased in the affected limb, whereas sudomotor function is enhanced. This may be the result of disturbances of thermoregulation, but different secondary peripheral mechanisms, concerning vasomotor and sudomotor function, contribute to clinical presentation of complex regional pain syndrome type 1 and affect autonomic function at all stages of complex regional pain syndrome type 1 (Birklein et al., 1998a). A complete functional loss of cutaneous sympathetic vasoconstrictor activity was observed in a patient in an early stage of complex regional pain syndrome type 1 (Wasner et al., 1999). The autonomic failure in patients with complex regional pain syndrome type 1 could be the result of central disturbances in thermoregulation, but secondary, peripheral mechanisms also contribute to these findings (Birklein et al., 1999). Autonomic signs are seen in 98% of the patients with complex regional pain syndrome type 1

but often change with the duration of complex regional pain syndrome type 1 (Birklein et al., 2000).

2.2.2. A possible role for adrenergic supersensitivity in complex regional pain syndrome type 1

Involvement of the adrenergic system was emphasised by results of measurements of adrenaline, noradrenaline and its intracellular metabolite, 3,4-dihydroxyphenylethyleneglycol (DHPG), in plasma from painful and from unaffected limbs. Plasma DHPG was lower on the painful side. The plasma concentration of noradrenaline was also lower on the painful side in patients with widespread allodynia, and in those with hyperhydrosis in the affected hand or foot. These findings suggest that sweating and changes in peripheral blood flow result from supersensitivity to sympathetic neurotransmitters (Drummond et al., 1991; Harden et al., 1994). The number of α_1-adrenoceptors was increased in the hyperalgesic skin of patients with complex regional pain syndrome type 1 (Drummond et al., 1996a). Sympathetic dysfunction in an experimental model of neuropathic pain, sciatic nerve ligation in rats, consists of denervation-induced supersensitivity to catecholamines rather than of an afferently induced increase in efferent sympathetic nerve impulses (Kurvers et al., 1998).

2.2.3. Motor considerations in complex regional pain syndrome type 1

Galer hypothesised that a neurologic neglect-like syndrome may explain the motor dysfunction seen in a subgroup of complex regional pain syndrome type 1 patients. This hypothesis is based on a selected series of 11 patients who underwent specific neglect testing. The aetiology of neglect in complex regional pain syndrome type 1 is not clear. Changes within central nervous system (CNS) structures may occur following persistent abnormal activation of the peripheral and autonomic nervous systems, which may then result in a neglect-like syndrome (Galer et al., 1995).

2.2.4. Disuse in complex regional pain syndrome type 1

Disuse of a limb can result in a clinical picture which is comparable with that of complex regional pain syndrome type 1. Especially signs of oedema and throphic changes are observed. It can be difficult to distinguish between disuse and complex regional pain syndrome type 1 (Butler, 2000).

2.2.5. Sympathetically maintained pain in complex regional pain syndrome type 1

Sympathetically maintained pain is pain that is maintained by sympathetic efferent innervation or by circulating catecholamines. It is accepted that pain that is relieved by a specific sympatholytic procedure, either nerve block or pharmacological intervention, is sympathetically maintained pain. Sympathetically maintained pain is a neuropathic pain that could be a component of complex regional pain syndrome type 1, although it still remains unknown how direct and indirect effects in the manifestation of pain are achieved (Stanton-Hicks, 2000).

2.3. Central mechanisms

2.3.1. Central sensitization in complex regional pain syndrome type 1

Gracely et al. performed sensory assessments before and during diagnostic tourniquet-cuff and local anaesthetic blocks in 4 patients diagnosed with complex regional pain syndrome type 1. Their observations led to proposal of a model of neuropathic pain in which ongoing nociceptive afferent input from a peripheral focus dynamically maintains the altered central processing that accounts for allodynia, spontaneous pain, and other sensory and motor abnormalities. Blocking the peripheral input causes the central processing to revert to normal, abolishing the symptoms for the duration of the block (Gracely et al., 1992). A spinal component of microcirculatory abnormalities at stage 1 of the complex regional pain syndrome type 1 could also be involved that most likely acts through neural (antidromic vasodilator) mechanisms and that could be initiated by traumatic excitation of a peripheral nerve on the clinically affected side (Kurvers et al., 1996). Cutaneous histamine application in patients with complex regional pain syndrome type 1 evokes a significant deterioration of afferent c-fibres in complex regional pain syndrome type 1, but gives evidence of sensitization of nociceptive function (Birklein et al., 1997a). Hyperalgesia to heat and mechanical stimuli in the acute phase of complex regional pain syndrome type 1 was also investigated. Hyperalgesia was not affected, whereas mechanical hyperalgesia to phasic impact stimuli was observed. Wind-up related pain was significantly enhanced in the affected limb. Application of 500 mg acetylsalicylic acid (i.v.) had no effect indicating a non-inflammatory pathogenesis in complex regional pain syndrome type 1 of central origin. (Sieweke et al., 1999).

2.3.2. Evidence of medullary dysfunction in complex regional pain syndrome type 1

Clinical examination and quantitative assessment of neurologic function in complex regional pain syndrome type 1 revealed abnormalities of spinothalamic, trigeminothalamic, and corticospinal function in half the population investigated. One-third of the remaining patients with complex regional pain syndrome type 1 had neuroimaging evidence of spinal cord or brain pathology. Most complex regional pain syndrome type 1 patients in this study had measurable abnormalities of the sensory and motor systems or neuroimaging evidence of spinal cord or brain dysfunction (Thimineur et al., 1998).

2.3.3. Prefrontal abnormalities in patients with chronic sympathetically mediated complex regional pain syndrome type 1

Functional magnetic resonance imaging has been used successfully to identify cortical regions that may be uniquely involved in pain consciousness in patients with chronic sympathetically mediated complex regional pain syndrome type 1 (Apkarian, 1999). From a case study of complex regional pain syndrome type 1 in which symptoms were resolved after the patient suffered a traumatic cerebral contusion in the left temporal lobe, which caused no neurological deficit, it could be concluded that symptoms of complex regional pain syndrome type 1 patients may largely be sustained by a complex network involving the brain (Shibata et al., 1999).

2.3.4. Do psychological factors play a role in onset or maintenance of complex regional pain syndrome type 1?

Bruehl et al. reviewed the literature for evidence that psychological factors predispose certain individuals to development of complex regional pain syndrome type 1. The data reviewed are consistent with a theoretical model in which depression, anxiety, or life stressors may influence the development of complex regional pain syndrome type 1 through their effects on α-adrenergic activity. Conclusions regarding the etiological significance of these factors are not possible due to the dearth of high-quality studies (Bruehl and Carlson, 1992). Psychological differences observed between complex regional pain syndrome type 1 and non-complex regional pain syndrome type 1 chronic pain patients provide partial support for the clinical assumptions that complex regional pain syndrome type 1 patients are more psychologically dysfunctional than other chronic pain patients (Bruehl et al., 1996). Stressful life events are more common in the complex regional pain syndrome type 1 patients (Geertzen et al., 1998).

3. Mediators in oedema, pain and temperature

3.1. Introduction

In general, inflammation is associated with increasing temperature, oedema, redness, pain and loss of function. The most prominent phenomena seen during initiation of the neurogenic inflammation underlying complex regional pain syndrome type 1 are fluctuating local temperatures, extravasation provoking oedema and pain. Concerning mediators of inflammation involved in these processes, the direct or indirect effects of individual neuropeptides, cytokines and eicosanoids should be considered (Table 2).

Table 2
Mediators of inflammation which could be involved in complex regional pain syndrome type 1

	Mediators
Neuropeptides	bradykinin
	calcitonin gene-related peptide
	neuropeptide Y
	vasoactive intestinal peptide
	substance P
Cytokines	interleukins 1β, 6 and 8
	tumour necrosis factor alpha
Eicosanoids	prostaglandins $F_2\alpha$ and E_2
	leukotriene B_4
	15-hydroxy eicosatetraenoic acid

In *oedema* involvement of the neuropeptide, substance P, in acute pancreatitis in rats and mice has been demonstrated (Grady et al., 2000), and its intra-arterial infusion in the human forearm provoked vasodilatation, flushing and plasma extravasation (Newby et al., 1997). Plasma extravasation and release of substance P and calcitonin gene-related peptide (CGRP) were also found after intradermal microdialysis and infusion of histamine (Schmelz et al., 1997; Weidner et al., 2000). In the nasal cavity, bradykinin stimulated nerve endings to release substance P, affecting plasma leakage simultaneously (Baumgarten et al., 1997). Substance P-induced oedema in rat skin was potentiated by CGRP (Newbold and Brain, 1993). Evidence also exists for the involvement of pro-inflammatory cytokines in oedema formation. Patients with idiopathic oedema have elevated levels of soluble interleukin-2 receptor, tumour necrosis factor α (TNFα), interferon γ and interleukin-2 (Hoffmann et al., 1998). Interleukin-2 indeed increases vascular permeability in melanoma patients (Ballmer-Weber et al., 1995), whereas interleukin-6 induces oedema in rats (Jongen-Lavrencic et al., 1996). Finally, it is well known that eicosanoids, and particularly prostaglandins E_2 and D_2, increase vascular permeability in the skin microcirculation and cause oedema (Flower et al., 1976; Kingston and Greaves, 1985). The synergistic effect of CGRP on oedema formation was also observed for prostaglandin E_2 and other eicosanoids, such as leukotriene B_4 (Brain and Williams, 1985).

Pain is strongly associated with kinins such as bradykinin. There is evidence that kinins are rapidly generated after tissue injury and that they modulate most of the events observed during inflammatory processes, including vasodilatation, increase of vascular permeability, plasma extravasation, pain and hyperalgesia (Levine et al., 1984a; Legat et al., 1994; Calixto et al., 2000). Furthermore, kinins seem to be directly implicated in neurogenic inflammation through activation of fine afferent C-fibres and consequent production of the neuropeptides substance P and CGRP (Geppetti, 1993). Bradykinin, acting via B_2 receptors, stimulates arachidonic acid release with subsequent formation of prostaglandin E_2 which in turn potentiates the pain response. The production of pro-inflammatory cytokines interleukin-1β, interleukin-6 and interleukin-8 is mediated through the same bradykinin B_2 receptor (Calixto et al., 2000). It is well known that in normal tissue B_1 receptors are downregulated, but upregu-

lated by these pro-inflammatory cytokines in pathological conditions. Specific blockade of B_2 receptors is still unwarranted because of the undesirable cardiovascular side-effects (Marceau and Bachvarov, 1998). In general, pro-inflammatory cytokines are believed to signal the central nervous system, thereby creating powerful pain, after situations involving infection, inflammation, or trauma of the skin or peripheral nerves (Watkins and Maier, 2000). It has been shown that in brains interleukin-1β causes hyperalgesia via prostaglandin E_2 through prostaglandin EP3 receptors, whereas analgesia is induced through EP1 receptors (Hori et al., 2000). Inhibition of prostaglandin activity through specific inhibition of the cyclooxygenase-2 pathway offers improved advantages (Urban, 2000).

Regarding *temperature* regulation, it is not always clear whether specific inflammatory mediators directly or indirectly affect this system. The subsequent formation of mediators during several stages of the disease and the interplay of cells involved in the inflammatory process contribute to the complex mechanism in which the microcirculation is affected. Either cold or warm extremities could be related with an overexpressed local formation of vasoconstricting or vasodilating mediators, resulting in a diminished or increased blood flow in the skin. Thermography can indicate and measure heat resulting from localised inflammation. In rheumatoid arthritis, juvenile arthritis, osteoarthrosis, gout and ankylosing spondylitis, abnormal heat distribution has been recorded over affected joints. Experimental evidence has shown that temperature changes reflect the inflammatory state of the joint, and that this may be used to measure the effect of therapy. In Raynaud's disease, it has been shown that intravenous infusion of CGRP has prolonged effects on hand skin blood flow and rewarming of the hand (Shawket et al., 1991). Comparable, but less pronounced, effects were observed after infusion of vasodilating prostaglandins, prostaglandin E_1 and prostaglandin I_2 (Shawket et al., 1991; Katoh et al., 1992). This was confirmed in patients with diabetic neuropathy in whom prostacyclin increased skin temperature by more than 2 °C, as measured by thermography (Shindo et al., 1991).

3.2. Inflammatory mediators in complex regional pain syndrome type 1

Only limited data are available for inflammatory mediators in complex regional pain syndrome type 1 measured in the hand, wrist, foot or ankle exhibiting signs of post traumatic dystrophy. There is, however, enough direct and indirect evidence to state that neurogenic inflammation underlies both early and chronic symptoms observed in complex regional pain syndrome type 1.

3.2.1. Neuropeptides

Neuropeptides are mainly associated with, and investigated as, mediators responsible for the initiation of the process, thereby expressing oedema, heat, pain and loss of function. When transported peripherally, substance P and CGRP have important roles in oedema formation and inflammation, and when transported centrally, these neuropeptides can cause excitation, possibly by increasing the excitability of NMDA receptors (Calder et al., 1998). Bradykinin, neuropeptide Y, CGRP and vasoactive intestinal peptide (VIP) were considerably increased in blood drawn from complex regional pain syndrome type 1 patients compared to those in healthy controls, whereas neither substance P nor neurokinin A and B were changed (Blair et al., 1998a,b). It was found, however, that neuropeptide Y levels in blood were significantly lower in the painful sides than in the non-affected extremities (Drummond et al., 1994; Abdulla and Smith, 1999). CGRP, substance P and neoropeptide Y were unchanged in samples of hyperalgesic skin from dorsal hand or foot (Drummond et al., 1996b). This was confirmed by immunohistochemically stained skin biopsies from patients with reflex sympathetic dystrophy, in which the binding to specific antisera of vasoactive intestinal peptide, CGRP and substance P did not indicate any inflammation of the skin (Calder et al., 1998). Infusion of exogenous substance P in the painful extremity potentiated complex regional pain syndrome type 1 activity (Weber et al., 2001), whereas depletion of substance P from primary afferent neurons by the topical application of capsaicin (a component of red pepper) effectively diminished symptoms observed in complex regional pain syndrome type 1 and comparable diseases (Cheshire and Snyder, 1990; Rumsfield and West, 1991).

3.2.2. Cytokines

The cytokine, TNFα, produced by activated macrophages, can induce ectopic activity in primary afferent nociceptors and thus is a potential cause of pain and hyperalgesia in complex regional pain syndrome type 1 (Sorkin et al., 1997; Sommer et al., 1998). Administration of the anti-inflammatory cytokine, interleukin-10, downregulates the inflammatory response of the nerve to injury induced by TNFα (Wagner et al., 1998). Furthermore, the pro-inflammatory cytokine, interleukin-6, is elevated in the spinal cord in response to peripheral nerve injury (Arruda et al., 1998). Despite all these indications, blood plasma levels of cytokines interleukin-1β, interleukin-6, interleukin-8, interleukin-10 and TNFα remained unchanged in complex regional pain syndrome type 1 patients compared to those in healthy controls (Van de Beek et al., 2001). This could be due to the fact that all 24 patients had a mean disease duration of 10 years. Furthermore, it is still questionable whether systemic cytokine levels with or without in vitro stimulation by lipopolysaccharide reflect local inflammation. As there is evidence that substance P induces the release of interleukin-1α and TNFα in human skin (Branchet-Gumila et al., 1999), research should be more focussed on local formation of cytokines.

3.2.3. Eicosanoids

Eicosanoids could also be involved in complex regional pain syndrome type 1, although no reports could be found confirming increased concentrations of eicosanoids in painful regions of complex regional pain syndrome type 1-classified extremities. Intrathecal administration of prostaglandin $F_2\alpha$ could evoke allodynia (Minami et al., 1992). Prostacyclin (prostaglandin I_2) and prostaglandin E_2 are probably the most important for their effects on sensory neurones. Although prostaglandins do not usually evoke pain when intradermally injected into human skin (Crunkhorn and Willis, 1971), more specifically prostaglandin E_1 and prostaglandin I_2 have been reported to increase the activity of nociceptors directly, while prostaglandin E_2 stimulates the release of substance P from sensory neurons (Dray, 1995). Leukotriene B_4 produces hyperalgesia that is dependent on polymorphonuclear leukocytes when injected intracutaneously in the same dose-range as bradykinin (Levine et al., 1984b). Furthermore, leukotriene B_4 decreases the mechanical and thermal thresholds of C-fibre nociceptors (Martin et al., 1988). Not only chemotactic products of the 5-lipoxygenase pathway of arachidonic acid metabolism exert hyperalgesic properties, a wide range of 15-lipoxygenase products could also contribute to inflammatory hyperalgesia (Levine et al., 1986). As 15-lipoxygenase products are mainly generated by endothelial cells, but also by macrophages, the interplay between damaged nerve endings and the microvascular system, triggered by migrated monocytes and macrophages, could contribute to the hyperalgesia seen in complex regional pain syndrome type 1. It is known that cysteinyl leukotrienes, leukotriene C_4, leukotriene D_4 and leukotriene E_4, which could be generated by mast cells, may increase the release of tachykinins substance P and neurokinin A from sensory nerves. Indirect evidence indicates that tachykinins contribute to their physiologic effects by stimulating the synthesis of cyclooxygenase products (Montuschi et al., 2000). The repeated circle of the cascade that represents the subsequent release of mediators of inflammation is thereby closed.

4. New perspectives for pharmacological intervention

The anti-inflammatory properties of glucocorticoids are attributed in part to their interference with prostaglandin synthesis. Phospholipase A_2 and cyclooxygenases, the key enzymes of prostaglandin biosynthesis, are targets of glucocorticoid action. In comparison with non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids could be considered as 'dirty drugs', due to the fact that they non-selectively inhibit cytokine synthesis and expression of other inflammation-related enzymes, but also exhibit a number of severe unwanted metabolic actions (Goppelt-Struebe, 1997; Aksoy et al., 1999; Garrelds et al., 1999). So far, there is no convincing evidence that glucocorticoids affect neurogenic inflammation through inhibition of neuropeptide release from afferent C-fibres or through upregulation of peptidases which degrade pro-inflammatory peptides (Tafler et al., 1993; Proud et al., 1994; Van der Velden et al., 1999). In complex regional pain syndrome type 1, systemic application of high-dose corticosteroids is only successful when it is started at the onset and continued for several months (Christensen et al., 1982; Poplawski et al., 1983). The limited long-term anti-inflammatory actions of glucocorticoids in chronic complex regional pain syndrome type 1 patients, however, has been attributed to corticosteroid resistance, as mainly observed and proven in asthma (Sher et al., 1994; Matsuse et al., 1999) and ulcerative colitis (Munkholm et al., 1994; Madretsma et al., 1995). Depending on the dose and route of application, duration of the treatment, severity of the inflammation and the parameters under investigation, approximately one-third of the patients do not respond or respond insufficiently to corticosteroids. These patients could be treated with other, recently available immunosuppressive drugs such as azathioprine, cyclosporine and methotrexate (Egan et al., 2000; Sandborn, 2000; Sands, 2000).

More specifically, considering different steps in the cascade of inflammatory mediators, each of which triggers forthcoming events during the whole process, pharmacological intervention could be focussed on either symptomatic treatment or prevention of the development of a chronic disease with inflammatory phenomena. Following the above-mentioned initial event, sub-acute and continuous inflammation, roughly three main groups of pharmaceuticals could be further developed for adequate application in complex regional pain syndrome type 1.

4.1. Substances which affect neuropeptides

During initiation of the inflammatory process the main clinical events which are observed in complex regional pain syndrome type 1 are oedema and pain. Since substance P can provoke oedema, vasodilatation and extravasation of lymphocytes and mast cells through the microvascular wall, after which pro-inflammatory mediators, interleukin-1α and TNFα, are released (Branchet-Gumila et al., 1999) and neuropeptides also stimulate the release of interleukin-6, interleukin-8 and TNFα in epithelial cells (Veronesi et al., 1999), the use of selective tachykinin NK_1 receptor antagonists could be beneficial. Observations in rats showed that the neurogenic oedema after intradermal injection of Phoneutria nigriventer venom or saphenous nerve stimulation could be abolished by the tachykinin NK_1 receptor antagonist, SR140333 (Palframan et al., 1996; Towler and Brain, 1998), and that pancreatic-induced oedema was blocked by the tachykinin NK_1 receptor antagonist, CP96345 (Grady et al., 2000).

Concerning the pain component, although the NK_1 receptor antagonists, CP99994, MK869 and LY303870,

have been proven to reduce pain in guinea pig neuropathic models, in clinical trials they have weak effects or are ineffective (Dionne et al., 1998; Goldstein et al., 2000; Reinhardt, 1998). Recently, this has been discussed extensively (Hill, 2000; Urban and Fox, 2000). As these antagonists seem to have antidepressive and anxiolytic effects, the use of NK_1 receptor antagonists in the late chronic phase of complex regional pain syndrome type 1 could be more beneficial as substances to treat psychiatric disorders better than as analgesic drugs (Argyropoulos and Nutt, 2000; Lieb et al., 2000).

Another, most promising, approach is the development of capsaicin-like substances, which exert anti-inflammatory properties after repetitive application. Regarding this, the topical use of ricinoleic acid has been described in oedema models for neurogenic inflammation in guinea pigs and mice (Vieira et al., 2000). A contribution of CGRP to inflammatory processes underlying complex regional pain syndrome type 1 has become plausible, although so far, it is not clear whether this substance is involved in the complex cross-talk resulting in initial, secondary and chronic phases observed in this mechanism. Intravenous injection of the antagonist, CGRP8-37, however, attenuated the first phase and almost abolished the secondary phase in thermally induced inflammation (Lofgren et al., 1998).

4.2. Substances which affect cytokines

Focussing on complex regional pain syndrome type 1 as an inflammatory skin disease, some clinical aspects are similar to those seen in atopic dermatitis, allergic contact hypersensitivity and psoriasis. T-lymphocytes play a critical part in the interplay of cells involved in the inflammatory reaction. Topical application of ABT-281, a macrolactam inhibitor of both T helper type 1 and 2 associated cytokine biosynthesis, has been proven to be much more effective than topical corticosteroids in dinitrochlorobenzene-induced contact hypersensitivity in pigs (Mollison et al., 1999). Another possible way to interfere in the balance of T helper type 1 and 2 associated cytokine biosynthesis is the use of immune response modifiers such as imiquimod. So far, this substance has been successfully used in the treatment of virally caused genital warts. The main effect attributed to this drug is the preferential induction of IFNγ and interleukin-12 (Miller et al., 1999; Sauder, 2000). Although the exact mechanism of action of imiquimod is unknown, its selective immunomodulating properties are promising, since not only the expression of inflammatory cytokines such as interleukin-1α, interleukin-1β, interleukin-6 and interleukin-8 was not induced (Manlove-Simmons et al., 2000) but also the overexpression of atopic disease associated cytokines interleukin-4 and interleukin-5 was inhibited (Wagner et al., 1999). In patients with psoriatic arthritis, three intravenous infusions of the chimeric monoclonal antibody to tumour necrosis factor α (infliximab) significantly improved clinical manifestations (Van den Bosch et al., 2000). This was confirmed in a patient with refractory inflammatory bowel disease and severe psoriasis after a single infusion of infliximab (Oh et al., 2000). The beneficial effect of infliximab was first observed in Crohn's disease and extensively described thereafter (Van Hogezand and Verspaget, 1998; Present et al., 1999; Van Deventer, 1999). Since then the long-term effects of infliximab have shown an acceptable safety profile (Schaible, 2000) and the drug is not associated with typical immunosuppressive sequelae, such as infections and malignancy, or with autoimmune disorders (Hanauer, 1999). In children and adolescents, the rapid return of disease activity requires additional dosing strategies for the particular subpopulation (Hyams et al., 2000). Therapy with chimeric anti-tumour necrosis factor α was successfully used in rheumatoid arthritis as disease-modifying antirheumatic drug (Maini et al., 1999; Luong et al., 2000), although concomitant therapy with other immunosuppressives such as methotrexate was indicated (Pincus et al., 1999). As new and future therapies for rheumatoid arthritis, and perhaps also for complex regional pain syndrome type 1, targeting of cytokines by the blockade of interleukin-1, interleukin-2 or interleukin-6 has been suggested (Breedveld, 1999; Simon and Yocum, 2000). The anti-inflammatory activity of interleukin-10, which reverses the cartilage degradation, and that of interleukin-4, which reduces prostaglandin production, are currently being tested for their clinical efficacy (Breedveld, 1999), but seem less promising than infliximab and concomitant therapy.

4.3. Substances which affect eicosanoids

In general, NSAIDs are agents of first choice for the treatment of inflammation in humans. With chronic use of normal doses of NSAIDs in most patients, side-effects varying from gastrointestinal complaints to severe hepatotoxicity or renal toxicity have been reported (Bjorkman, 1999; Rainsford, 1999). The discovery of a second cyclooxygenase has triggered the search for new anti-inflammatory drugs. This second enzyme, cyclooxygenase-2, is effectively absent from healthy tissues but its levels rise dramatically during inflammation. Cyclooxygenase-2 can be induced in migratory cells by bacterial lipopolysaccharide, cytokines and growth factors.

Since the finding of differential sites of action of NSAIDs on constitutive cyclooxygenase-1 (COX-1), which synthesise prostaglandins that protect the stomach and kidney from damage, and the beneficial therapeutic effects on inhibition of inducible cyclooxygenase-2, much effort has gone into the development of cyclooxygenase-selective NSAIDs (Mitchell et al., 1993; Davies, 1997; Mitchell and Warner, 1999; Warner et al., 1999). As cycloxygenase-2 is induced by inflammatory stimuli, such as cytokines, and produces prostaglandins that contribute to the pain and

Table 3
Antagonists and enzyme inhibitors to be explored for use in complex regional pain syndrome type 1

	Antagonists and inhibitors
Neuropeptides	CGRP8-37
	CP 99994
	MK 869
	LY 303870
	capsaicin
Cytokines	anti-tumour necrosis factor α
	interleukin-10
Eicosanoids	meloxicam
	nimesulide
	rofecoxib
	celecoxib

swelling of inflammation, selective cyclooxygenase-2 inhibitors should be anti-inflammatory without side effects on the kidney and stomach (Vane and Botting, 1998).

Based on the current literature, the most selective cyclooxygenase-2 inhibitors which could be used successfully for chronic treatment in complex regional pain syndrome type 1 to suppress inflammation and provide analgesia are meloxicam (Davies and Skjodt, 1999; Schoenfeld, 1999; Tsubouchi et al., 2000) and nimesulide (Bernareggi, 1998; Bjarnason and Thjodleifsson, 1999; Blain et al., 2000; Shah et al., 1999). With respect to the most commonly observed gastrointestinal injury and death as associated outcome with NSAIDs, however, one should consider not only the cyclooxygenase-1 and cyclooxygenase-2 specificity of the drug to be used chronically, but also their gastrointestinal tract-sparing effects. Medications currently available on prescription for rheumatoid arthritis could also be used for complex regional pain syndrome type 1. Both cyclooxygenase-2 selectivity and proven fewer side-effects suggest rofecoxib and celecoxib as first choice NSAIDs (Bensen, 2000; Blain et al., 2000; Silverstein et al., 2000; Urban, 2000) (Table 3).

5. Conclusion

Evaluation of all clinical aspects observed in complex regional pain syndrome type 1 leads to the conclusion that there is at least some talk of neurogenic inflammation in the affected extremity. Throughout the body, inflammation is normally associated with increasing temperature, oedema, redness, pain and loss of function. All these phenomena are seen at some point during complex regional pain syndrome type 1. Therefore, there could be a prominent role, specially just for mediators of inflammation responsible for one or more of the manifestations of the disease, and that consequently offer a new class of pharmaceutical compounds to be developed and applied in this disabling disease.

In general, involvement of inflammatory mediators could be considered when the following conditions are confirmed: (i) generation at the site of the injury, (ii) injection of these substances provokes comparable clinical manifestations, (iii) specific antagonists or synthesis inhibitors have beneficial effects. Based on the presently available literature covering all these aspects of complex regional pain syndrome type 1, the following concluding remarks could be made.

Firstly, none of the neuropeptides, cytokines nor eicosanoids have been definitely found in increased amounts at the site of the injury in complex regional pain syndrome type 1. Secondly, injection of substance P worsens the complaints. Only indirect evidence was obtained from applications of other mediators in other, similar diseases. Finally, specific antagonists or synthesis inhibitors have not yet been studied, pending more findings about mediators involved in this particular disease. In general, early application of corticosteroids is beneficial, although the common and unselective NSAIDs have slight analgesic effects and negligible effects on inflammation.

In conclusion, the wide range of mediators normally involved in inflammatory events should be shown to exist in complex regional pain syndrome type 1 before the use of readily available immunosuppressives can be recommended.

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