Review

TNF-α and neuropathic pain - a review

Lawrence Leung*1,2,3 and Catherine M Cahill1,4,5

Abstract
Tumor necrosis factor alpha (TNF-α) was discovered more than a century ago, and its known roles have extended from within the immune system to include a neuro-inflammatory domain in the nervous system. Neuropathic pain is a recognized type of pathological pain where nociceptive responses persist beyond the resolution of damage to the nerve or its surrounding tissue. Very often, neuropathic pain is disproportionately enhanced in intensity (hyperalgesia) or altered in modality (hyperpathia or allodynia) in relation to the stimuli. At time of this writing, there is as yet no common consensus about the etiology of neuropathic pain - possible mechanisms can be categorized into peripheral sensitization and central sensitization of the nervous system in response to the nociceptive stimuli. Animal models of neuropathic pain based on various types of nerve injuries (peripheral versus spinal nerve, ligation versus chronic constrictive injury) have persistently implicated a pivotal role for TNF-α at both peripheral and central levels of sensitization. Despite a lack of success in clinical trials of anti-TNF-α therapy in alleviating the sciatic type of neuropathic pain, the intricate link of TNF-α with other neuro-inflammatory signaling systems (e.g., chemokines and p38 MAPK) has indeed inspired a systems approach perspective for future drug development in treating neuropathic pain.

Introduction
Despite intense research over the last 30 years, debate is still ongoing regarding the nature of neuropathic pain, including controversy as to whether such pain is peripheral or central in origin, and as to whether its etiology is inflammatory or non-inflammatory. Increasing evidence has provided better understanding of the roles of both immune and pro-inflammatory mediators (e.g., the interleukins, TNF-α, complement components, ATP and the chemokines) in the mechanisms of both peripheral and central neuropathic pain [1-4]. This review will concentrate on current knowledge and experimental models regarding the role of TNF-α, among other cytokines, in neuropathic pain; with an appraisal of available potential therapeutic targets related to TNF-α and directions for future developments in this area.

Neuropathic pain as an example of an inflammatory pain model
Neuropathic pain is characterized by disproportionate hypersensitivity to stimuli (hyperalgesia), abnormal pins-and-needles or electric-shock-like sensations (hyperpathia) and, finally, nociceptive responses to non-noxious stimuli (allodynia). It is a pathological type of pain that persists despite resolution of the inciting damage to the nerve and the surrounding tissues. From a behavioral standpoint, nociception is an adaptive tool for better survival, while neuropathic pain is considered maladaptive. The prevalence of neuropathic pain ranges from 1% in UK [5] to 1.5% in the US [6] to 17.9% in Canada [7]. Weir Mitchell [8] is often credited with the first descriptive account of neuropathic pain from nerve injuries seen in the US Civil War, using terms that range from “burning”, “mustard red hot”, “red-hot file rasping the skin” to “with intensity ranging from most trivial burning to a state of torture”. Clinically, the top three most common types of neuropathic pain are post-herpetic neuralgia, trigeminal neuralgia and diabetic neuropathy [9]. Neuropathic pain is among the most difficult types of chronic pain to treat, which not only significantly impairs patients’ quality of life [10] but also adds to the burden of direct and indirect medical cost for our society [10,11]. Conceptually, neuropathic pain consequent to peripheral nerve injury results from an increased excitability of the neurons as a result of sensitization. The debate is still on-going as to whether this sensitization occurs in the peripheral or central compartments of the nervous system, or both. Experimentally, various animal models of peripheral neuropathic pain have been developed: chronic constriction injury (CCI) of the sciatic nerve with loose ligatures [12-15];
partial sciatric nerve injury with tight ligatures [15-17];
total sciatric nerve ligation [15,18]; sciatric nerve transac-
tion [19-21] and anatomy of lumbar roots entering the
sciatric nerve [22,23]. Despite the various degrees and
modes of nerve damage in these models, there is a com-
mon sequel--post-injury inflammatory changes leading to
mast cell degranulation [24], and recruitment of both
macrophages [25] and polymorphonuclear neutrophils
[26]. However, in CCI models thermal hyperalgesia still
occurs when ligatures are loosely placed around the sci-
atic nerve without actual mechanical damage [27]. This
finding supports the hypothesis that it is the inflamma-
tory microenvironment [28] and the release of mediators
[29], rather than the nerve injury per se, that is pivotal for
the development of neuropathic pain. Clatworthy et al.
[30] further demonstrated that suppression of the inflam-
matory response with dexamethasone reduces thermal
hyperalgesia, while enhancing the inflammatory response
using Freud’s adjuvant was seen to aggravate the level of
pain hypersensitivity. His work set the stage for continu-
ing research on immune and pro-inflammatory media-
tors in neuropathic pain over the past two decades. An
updated list of such mediators, by no means exhaustive,
includes the eicosanoids [31-34], bradykinins [35,36],
serotonin [37-39], ATP/ADP [40-42], neurotrophins [43-
46], cytokines [47-52], chemokines [53,54], and reactive
oxygen species [21,55,56]. These mediators are not exclu-
sive to cells of immune/inflammatory origin, but are also
produced by Schwann cells [57-59] and spinal glial cells
[42,60-63], thereby potentially mediating the mechanisms
of neuropathic pain.

Cytokines in neuropathic pain

Cytokines are low molecular weight glycoproteins that
are secreted mainly, but not exclusively, by immunologi-
cal cells such as T-cells, macrophages and neutrophils.
Other cells that secrete cytokines include keratinocytes
and dendritic cells of the skin [64] and Schwann cells and
glial cells of the central nervous system [65,66]. They act
as intercellular mediators regulating the functions and
differentiation of neighboring cells and are produced in
response to disease, inflammation, or tissue damage.
Cytokine synthesis is prompt and their actions are often
localized with a relatively short half-life. This distin-
guishes them from hormones which are constantly pro-
duced with longer-lasting and more distant effects. The
first cytokine was discovered by Beeson in 1948 [67] as a
pyrogenic compound extracted from ploysmorphonuclear
leucocytes, later known as IL-1β. Since then, many other
cytokines have been discovered, and these fall into five
main categories: interleukins, interferons, tumor necrosis
factors, growth factors and chemokines. Together, these
factors contribute to the pathogenesis of neuropathic
pain [47,68]. In particular, tumor necrosis factor alpha
(TNF-α) [69,70], interleukin-1 (IL-1) [47,71,72] and inter-
leukin-6 (IL-6) [49,73] have been associated with the
development of neuropathic pain in various animal mod-
els [74]. In this review, we shall limit our scope to TNF-α.

Tumor necrosis factor alpha (TNF-α): a neuropathic pain-
related cytokine

In 1891, the success story of William Coley in using
supernatant extract of heat-killed mixtures of Streptococ-
cus pyogenes and Serratia marcescens bacteria to treat
tumors may in fact be the first discovery of tumor necro-
sis factor [75]. It was not until 1975 that an endotoxin-like
substance was described in activated macrophages with
tumor-regression activity and was given the name of
tumor necrosis factor alpha, TNF-α [76]. TNF-α belongs
to a superfamly of ligand/receptor proteins called the
tumor necrosis factor/tumor necrosis factor receptor
superfamily proteins (TNF/TNFR SFP). TNF-α possess a
trimeric symmetry with a structural motif called the TNF
homology domain (THD), which is shared with all other
members of the TNF proteins. This THD binds to the
cysteine-rich domains (CRDs) of the TNF receptors
(TNFRs), and variations of these CRDs lead to heteroge-
neity of the TNFRs [77]. TNFRs are either constitutively
expressed (TNFR1, p55-R) or inducible (TNFR2, p75-R)
[78]. In the context of neuropathic pain, using the stan-
dard model of chronic constriction injury (CCI) of sciatic
nerve in rats, TNF-α has been detected at the injury site
and shows temporal up-regulation [79-81]; here TNF-α is
located mainly in macrophages [82] and Schwann cells
[70,83] by immuno-reactive staining. Similarly, there is
local up-regulation of both TNFR1 and TNFR2 as injured
neurons undergo Wallerian degeneration, albeit at differ-
ential rates [84]. Similar results are found in humans,
where nerve biopsies from patients with painful neuropa-
thy show higher levels of TNF-α expression, especially in
Schwann cells [85]. Intra-scatic injection of TNF-α in
rats reproduces pain hypersensitivity that is similar to
that of neuropathic pain in humans [69,86], and this is
reversible with neutralizing antibodies to TNFR [86], in
particular TNFR1 [50]. TNF-α enhances the tetrodo-

toxin-resistant (TTX-R) Na⁺ current in cultured DRG
cells from wild-type but not from TNFR1-knockout mice,
and such current is abolished by a p38-MAPK inhibitor;
implying that TNF acts via TNFR1 and activates TTX-R
Na⁺ channels via the p38 MAPK system [87]. Further
studies using TNFR1/TNFR2 knock-out mice have sug-
gested a neurotoxic role for TNFR1 versus a neuroprotec-
tive role of TNFR2 [88]. However, there is still debate
regarding the relative roles of TNFR1 and TNFR2 in
chronic pain: in mice with tumor-induced thermal hyper-
algiesa, deletion of the TNFR2 gene reduces the painful
response hence signifying a role for TNFR2 [89]; whilst in rats with spinal root injury, TNFRI elicits excitatory responses in DRG of adjacent uninjured roots and TNFR2 excites DRG neurons from injured roots [90]. In the inflammatory models of carrageenan-induced and zymosan-induced pleurisy in rat models, TNF-α has been found to have a lead role in activating a cascade of other cytokines, notably IL-1β, IL-6 and IL-8 [91]. A similar local cascade has been demonstrated in a model of neuropathic pain following nerve injury [83].

The role of TNF-α in peripheral mechanisms of neuropathic pain

TNF-α plays a role in the peripheral mediation of neuropathic pain. Clinically, HIV therapy and chemotherapy produce peripheral neuropathy with massive release of TNF-α in serum [92] and TNF-α used as a clinical anticancer treatment leads to peripheral neuropathy [93]. Traditional CCI of sciatic nerve in rats results in raised levels of TNF immunoreactivity in dorsal root ganglia (DRG) of both injured and uninjured ipsilateral adjacent afferents [94], as well as of contralateral uninjured counterparts [95], which can only be partly explained by retrograde axonal transport [96]. There is also a corresponding up-regulation of TNFR1 and TNFR2 in both nerve and DRG [97], with a temporal pattern of increased TNF mRNA expression, first in sciatic nerve, and then in DRG [98]. When nucleus pulposus extract of coccygeal intervertebral disc is applied to lumbar DRG of rats, neuropathic pain is induced but is abolished by co-application of TNFR1, implying a direct role of TNF as a local mediator [99]. Exogenous TNF-α injected into DRG of CCI roots is transported both anterograde to the site of injury and retrograde into the dorsal horn [100], precipitating allodynia in both the ligated and adjacent uninjured nerves [101]. TNF-α is known to lead to apoptosis via TNFR1 [102,103] and the caspase signaling pathway [103]. Caspase inhibitors can attenuate peripheral neuropathy experimentally induced by HIV therapy or chemotherapy in rats [104]. A recent study compared crush injury of L5 spinal nerve (distal to DRG) with L5 nerve roots (proximal to DRG) in rats and found that distal crush injury resulted in more neuronal apoptosis and enhanced TNF-α expression and caspase levels, correlating with higher neuropathic pain [105], lending more support to a TNF-α-apoptosis-caspase signaling paradigm for peripheral neuropathic pain. In addition to enhancing TTX-R Na+ channels in nociceptive DRG neurons [87], TNF-α can also increase membrane K+ ion conductance in a non-voltage-gated fashion [106] leading to overall neuronal hyper-excitability and hence leading to neuropathic pain.

The role of TNF-α and glia in central mechanisms of neuropathic pain

In late 1990s, TNF-α was proposed to be one pro-inflammatory cytokine with a pivotal role in the “immune-to-brain” pathway of communication for pain, and in models of sickness response in general [51,107]. In classic CCI models in rats, increased levels of TNF-α are found in hippocampus [108,109], locus coeruleus [109,110] and red nucleus [111] of brain. Recent data have suggested that TNF-α mediates central mechanisms of neuropathic pain through glial systems. In the central nervous system, glial cells outnumber neurons by as much as 50-fold, and include three relevant types: astrocytes, oligodendrocytes and microglia. Oligodendrocytes not only provide the myelin sheaths that insulate the neurons, they also contribute to the actual expansion of neuronal caliber and reorganization of neurofilaments [112]. Astrocytes are the most abundant glial cells and possess the most diverse functions: they can modulate synaptic functions by forming a tripartite synapse with pre-synaptic, post-synaptic and extra-synaptic astrocytic contacts with up to 10,000 other neurons [113,114] using glutamate and adenosine as neurotransmitters [115]. It has been suggested that spinal astrocytes may play a role in sensitization of chronic pain via activation of the p38-MAPK system [116,117], and may even synapse with microglia, with pre-synaptic neuronal processes and with post-synaptic neuronal structures to form a tetrapartite configuration [118]. Astrocytes also regulate maturation of neurons and synaptogenesis, hence playing a pivotal role in modulation of neural plasticity [119]. Microglia constitute 15-20% of the total glial population and serve as an immune invigilator for the central nervous system. They originate from mesodermal precursor cells of hemopoietic lineage. In response to nerve injury and inflammation, microglia transform into macrophage-like cells [120] that express major histocompatibility complex antigens and secrete pro-inflammatory cytokines, including TNF-α, IL-1 and IL-6 [121,122]; CCL2 and CX3CL1 [53,123], and ATP, which mediate their effects via the p38-mitogen-activated protein kinase (p38-MAPK) system [41,124,125].

Back in 1991, it was shown that classic CCI leads to hypertrophy of astroglia in the dorsal horn of spinal cord as reflected by increased immunostaining of glial fibrillary acidic protein [126]. Since then, other subcutaneous and intraperitoneal inflammatory pain models [127] have also been shown to induce glial activation. In newborn rats, where microglia are immature, intrathecal lipopolysaccharide (LPS) fails to evoke the allodynia response that is invariably seen in adult rats [62], suggesting a necessary role for functional microglia in the pathogenesis of neuropathic pain. Along with various other mediators, TNF-
α has been shown to be present on the surfaces of astrocytes by immunofluorescence staining, where TNF-α auto-stimulates its own production via G-protein coupled receptor (CXCR4) and TNF-α converting enzyme. The result is a cascade of events leading typically to production of IL-1, IL-6, nitric oxide and ATP [121,128], all of which contribute to enhanced neuronal activity leading to pathological pain. Wei et al [129] demonstrated increased levels of TNF-α and IL-1β in the rostral ventromedial medulla (RVM) of rats after CCI of the infraorbital nerve, with a corresponding enhancement of phosphorylation of the NR1 subunit of NMDA receptors, which is thought to be coupled to the receptors for both TNF-α and IL-1β. Injection of TNF-α and IL-1β into RVM increases NR1 phosphorylation of NMDA receptors and produces hyperalgesia, which is reversed by an NMDA antagonist. Wei’s work sparked off research into NMDA receptors as a possible target for treating neuropathic pain; unfortunately, progress has been discouraged by the ubiquitous expression of NMDA receptors in the human central nervous system, which renders NMDA receptor blockade for analgesia an impossible task without concomitant alterations in cognition, memory and learning.

**TNF-α, neural plasticity and neuropathic pain**

Originally identified in hippocampus as a substrate for memory storage and learning, the synaptic mechanisms of long term potentiation (LTP) in glutamergic neurons [130] have since been demonstrated as well in other parts of the central nervous system; in particular, in the dorsal horn of the spinal cord, where they may lead to abnormal nociception and neuropathic pain [131,132]. Normal nociceptive signals are conveyed by both Aδ and C-fibers; of which the latter make synapses with second-order neurons in the spinal dorsal horn. The LTP phenomenon has been well characterised in C-fibers of rat dorsal horn with tetanic stimulation [133,134] and also with acute nerve injury [135]. High-frequency stimulation leads to an LTP pattern of cutaneous allodynia and hyperalgesia in humans [136] with a typical early LTP time course [137]. As the signalling mechanism of LTP unfolds, TNF-α is found to play an important role. Endogenous glial TNF-α can modulate synaptic plasticity by increasing the expression of AMPA receptors in cultured rat hippocampal slices [138] for homeostatic regulation of synaptic strength in an activity-dependent fashion [139]. However, TNF-α given at non-physiological levels often inhibits LTP in similar models of cultured rat hippocampus [140,141]. As regards to C-fibers in the spinal dorsal horn, exogenous TNF-α produces LTP in C-fiber evoked field potentials only in the presence of nerve injury, and this LTP is blocked by inhibitors of NF-kappa B, JNK and p38-MAPK [142]. In the absence of nerve injury, TNF-α can neutralise the action of src-family kinase inhibitors by restoring LTP in C-fiber evoked potentials as normally induced by high-frequency stimulation (HFS).

**TNF-α, ATP and p38-MAPK**

Since the 1950s, release of ATP has been detected from nerve endings [143,144] and a role for ATP in nociception was implicated when it was shown to induce pain in human blister bases [145]. ATP excites cutaneous afferent neurons of animal models in a fashion similar to that of other neurotransmitters like 5-HT and acetylcholine [146], and can act proximally to excite DRG neurons [147]. Around the same time, Burnstock and his colleagues [148,149] first characterized purinergic receptors into P1 (sensitive to adenosine, ADO), P2X and P2Y receptors (sensitive to ATP and ADP). Molecular cloning studies have identified four sub-types of P1 (A1, A2A, A2B, and A3), seven sub-types of P2X (P2X1 to P2X7) and 8 sub-types of P2Y receptors (P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P2Y13, P2Y14) [150]. Each subtype has a different distribution in neuronal and glial cells, interacting with each other in an intricate manner. In terms of signaling functions, P1 and P2Y receptors are G-protein coupled receptors, while P2X receptors are ligand-gated ion channels [151]. Within the context of neuropathic pain, P2X3, P2X4 and P2X7 receptors are thought to play a role; and in particular, P2X3 may act via the TTX-R voltage-gated sodium channel Na+, 1.9 [152].

Earlier studies using nerve injury models in rats revealed either an increase [153] or decrease [154] of P2X3 immuno-reactivity in the DRG neurons, depending on the type of nerve injury. When expression of P2X3 receptors in DRG is reduced using anti-sense oligonucleotides [155] or siRNA [156], development of mechanical hyperalgesia is mitigated after classic CCI. Furthermore, administration of anti-sense oligonucleotides to knock down P2X3 receptors can reverse established neuropathic pain that re-emerges after cessation of the anti-sense treatment [157], suggesting a dynamic modulatory role of P2X3 receptors. Following a similar approach, Tsuda et al [158] demonstrated an increase in P2X4 receptor expression after chronic nerve injury, and showed that both pharmacological blockade and anti-sense oligonucleotide treatment abrogates the development of mechanical allodynia. Later studies have suggested that P2X4 receptor stimulation leads to secretion of brain-derived neurotrophic factor (BDNF) in spinal microglia, and that this BDNF is involved in mediating neuropathic pain [40,159,160], possibly via activation of the p38-MAPK system [161]. P2X4 receptors are associated with TNF-α production in microglia through the p38-MAPK system [162,163], as an inhibitor of MAPK system will suppress
production of TNF-α mRNA and an inhibitor of p38 will prevent nucleocyttoplasmic transport of TNF-α mRNA [162]. Independent of ATP, the p38-MAPK system seems to be essential for the action of TNF-α via TTX-R Na+ channels [87]. As an entity itself, microglial p38-MAPK has been implicated in the pathogenesis of neuropathic pain in studies using various in vivo models of peripheral nerve [164,165] and spinal cord injury [166,167]. For example, spinal nerve ligation in rats leads to allodynia with concomitant rises in TNF-α and p38 phosphorylation; treatment with inhibitors of either TNF-α or p38 results in reduction of allodynia and, finally, TNF-α blockade can in turn suppress p38 activation [168]. Studies using HSV-mediated gene transfer in nerve injury animal models have shown induced expression of soluble p55 TNFR (sTNFR2) in DRG neurons, resulting in decreased phosphorylation of p38 and reduced allodynia, again suggesting a causal link between TNF-α and the p38-MAPK system.

TNF-α as potential drug target for chronic pain—the possibilities

Due to the unique trimeric structure shared between the TNF ligand and the TNF receptor (both belonging to the TNF/TNFR SPF), the transmembrane portion of TNF molecule (mTNF), besides being a ligand, is capable of acting as a receptor for a soluble form of TNF (sTNF) in a “reverse-signaling” manner [169], which then inhibits phosphorylation of p38 and hence expression of TNF protein. This unique phenomenon makes it possible to use gene therapy with a herpes simplex virus vector carrying a p55 sTNFR gene to transfect DRG neurons of rats [170]. As a result, over-expressed p55 sTNFR (sTNFR2) binds to the mTNF of DRG and down-regulates overall production of TNF by reverse signaling, significantly reducing the allodynia and hyperalgesia responses to CCI [170,171]. Following a similar logic, a fusion protein (ELP-sTNFR2) has been developed wherein a soluble form of TNFR2 (sTNFR2) is conjugated to a temperature-sensitive elastin-like polypeptide (ELP), which can be thermally triggered to form a deposit around the perineural site of injection [172]. This fusion protein has been reported to be able to mitigate levels of TNF-α in DRG of injured nerve in rat models [173]. Indeed, many studies have demonstrated that local or spinal administration of agents that antagonize TNF-α will attenuate pain behaviors in neuropathic animal models [174-177]. Mechanical allodynia in the rat model of central neuropathic pain due to T13 spinal cord hemisection is attenuated by immediate, but not delayed, intrathecal administration of etanercept (a fusion protein blocker of TNF-α) at 1-4 weeks post spinal cord injury [178]. Propentofylline is a methylxanthine that inhibits lipopolysaccharide (LPS)-induced release of both TNF-α and IL-1β in a dose-dependent manner in glial cultures [179] and abates allodynia in rat spinal nerve transection models by modulating glial activation [180,181]. Propentofylline was initially evaluated for treating dementia [182], but was eventually withdrawn from further clinical studies due to patent issues [183], and its efficacy in animal neuropathic pain models has yet to be tested in humans. Thalidomide, once banned in 1963 due to its teratogenicity, is now regaining favor in neuropathic pain research due to its ability to cross the BBB and its inhibitory effects on TNF-α (in vitro and in-vivo) and on IL-1/IL-6 (in-vitro only) [184,185]. In the rat model of CCI, systemic thalidomide reduces the hyperalgesia response coincident with reductions in TNF-α levels, unchanged levels of IL-1/IL-6 and increased levels of IL-10 [186,187]. Clinically, there have been sporadic reports of success in using thalidomide to treat complex regional pain syndromes [188]. However, the balance of thalidomide’s efficacy versus safety in treating in chronic and neuropathic pain needs further clinical study [189], especially in view of its paradoxical neurotoxicity [189,190]. Methotrexate is a well-known drug for treating cancer that is derived from glumatic acid. It is capable of crossing the BBB [191] and has anti-rheumatoid and anti-inflammatory actions through its inhibition of production of TNF-α via adenosine nucleotides [192,193] and its ability to antagonize the actions of IL-1 [194]. Intrathecal administration of methotrexate reduces classic CCI-induced allodynia in rats [195] but its value in treating neuropathic pain is severely offset by its propensity per se to induce astrocytic proliferation [196] and hence neurotoxicity [197,198].

The role of TNF-α in chronic pain seems irrefutable in view of abundant data from various neuropathic animal models, and with the actual isolation of TNF-α from neuropathic nerves [85] and perineural fat from radiculo-pathic nerve roots [199] in humans. An initial pilot study using subcutaneous etanercept to treat patients admitted to the hospital with acute severe sciatica showed improved pain scores [200]. Similarly, an open-label study with infliximab (an antibody to TNF-α) revealed promising results [201]. Subsequent randomized controlled trials failed to support the benefits of systemic anti-TNF-α treatment [202-205], but a recent report did show positive benefits of epidurally administered etanercept in the treatment of sciatica [206]. To date we are unaware of any randomized controlled clinical trials of infliximab or etanercept in treating other types of neuropathic pain. AV411(ibudilast), a trial drug that was originally developed as a non-selective phosphodiesterase inhibitor for treating bronchial asthma, has been studied in phase I and phase 2a clinical trials in the US and in Australia for treatment of diabetic neuropathic pain [207], based on findings that AV411 also suppresses glial cell activation and reduces the production of pro-inflammatory cytok-
ines (IL-1β, TNF-α, IL-6) in rat neuropathic pain model [208].

**Perspective on future studies**

TNF-α is undoubtedly a titan in the research of neuropathic pain, and is by no means the only one in the arena. It is a pivotal member of the cytokine mediator system that is intrinsic to the pathogenesis of neuropathic pain both at peripheral and central levels (See Fig 1). Together with other mediators like interleukins, nerve growth factors, chemokines and interferons, it forms a network that interacts with downstream signaling mechanisms like the NMDA, ATP and MAPK systems. We now know that removing TNF-α from the picture will not abolish neuropathic pain as has already been demonstrated by the failure of TNF-α antagonists in clinical trials for sciatica [202-205]. Emerging data have guided research towards a collective role for glia-derived mediators and their coupled signaling pathways in the modulation of neuropathic pain [122,127,209,210]. The paradigm is shifting from a

---

**Figure 1** The roles of TNF-α as recognized at different levels of the nervous system in neuropathic pain induced by nerve injury: (1) at site of nerve injury; (2) at dorsal root ganglion; (3) at dorsal horn of the spinal cord; and (4) at the brain and higher centres.
single compound towards a system as a potential target for novel drug development for treating neuropathic pain [211-214]. Examples include the chemokine system [215], the MAPK system [216], and the glial system as a whole [217].

Abbreviations

S-HT: 5-hydroxytryptamine (Serotonin); ADO: Adenosine; ADP: Adenosine diphosphate; ATP: Adenosine triphosphate; BBB: Blood-brain barrier; BDNF: Brain-derived neurotrophic factor; CCI: Chronic constrictive injury; CCL2: Chemokine (C-C motif) ligand-2; CX3CL1: Chemokine (C-X3-C motif) ligand 1; CXCR4: CX chemokine receptor-4; DRG: Dorsal root ganglion; CRDs: Cysteine rich domains; ELPl: Elastin-like polypeptide; ERK: Extracellular signal-regulated kinases; HFS: High Frequency stimulation; HSV: Herpes simplex virus; IL-1: Interleukin-1; IL-1B: Interleukin-1 beta; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; JNK: c-Jun N-terminal kinase; LPS: Lipopolysaccharide; LTP: Long Term Potentiation; MAPK: Mitogen activated protein kinase; NSAIDs: Non-steroidal anti-inflammatory drugs; siRNA: Small interfering RNA; RVM: Rostral ventro medial medulla; THD: TNF homology domain; mTNF: Transmembrane portion of TNF; sTNF: Soluble form of TNF; TNF-α: Tumor necrosis factor alpha; TNFR: Tumor necrosis factor receptor; sTNFRII: Soluble p55 TNF receptor; TNFRSF: Tumor necrosis factor receptor super family receptor; TXR-T: Tetrodotoxin resistant.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LL wrote the manuscript, CMC provided comments and proof-reading. Both authors have read and approved of the final version of the manuscript.

Author Details

1Centre for Neurosciences Studies, 18, Stuart Street, Queen's University, Kingston, Ontario K7L 3N6, Canada and 5Department of Medicine, 220 Bagot Street, Queen's University, Kingston, Ontario K7L 5E9, Canada.

Received: 20 October 2009 Accepted: 16 April 2010

References

1. Campbell JN, Meyer RA: Mechanisms of neuropathic pain. Neuropharmacology 2006, 52:77-92.
2. McMahon SB, Cafferty WB, Marchand F: The role of immune and inflammatory cells as pain mediators and modulators. Exp Neurol 2005, 192:444-462.
3. Marchand F, Pinetti M, McMahon SB: Role of the immune system in chronic pain. Nat Rev Neurosci 2005, 6:521-532.
4. Moalem G, Tracey DJ: Immune and inflammatory mechanisms in neuropathic pain. Brain Res Rev 2006, 51:240-264.
5. Bowsher D: Neurogenic pain syndromes and their management. Br Med Bull 1991, 47:544-666.
6. Carter GT, Galer B: Advances in the management of neuropathic pain. [Phys Med Rehabil Clin N Am 2001] - PubMed result, Phys Med Rehabil Clin N Am 2001, 12:447-459.
7. Toth C, Lander J, Wiebe S: The prevalence and impact of chronic pain with neuropathic pain symptoms in the general population. Pain Med 2009, 10:918-929.
8. Mitchell SW: Injuries of nerves and their consequences. Philadelphia, Lippincott; 1872.
9. Hall GC, Carroll D, Parry D, McQuay HJ: Epidemiology and treatment of neuropathic pain: the UK primary care perspective. Pain 2006, 122:156-162.
10. McDermott AM, Toelle TR, Rowbotham DJ, Schaefer CP, Dukes EM: The burden of neuropathic pain: results from a cross-sectional survey. Eur J Pain 2006, 10:127-135.
11. O'Connor AB: Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. Pharmacoeconomics 2008, 27:95-112.
12. Bennett GJ, Xie YK: A peripheral mononeuropathy in rat that produces d... [Pain 1988] - PubMed result. Pain 1988, 33:87-107.
13. Xie Y, Zhang J, Petersen M, LaMotte RH: Functional changes in dorsal root ganglion cells after chronic nerve constriction in the rat. J Neurophysiol 1995, 73:1811-1820.
14. Kingery Ws, Castelotte JM, Wang EE: A loose ligature-induced mononeuropathy produces h... [Pain 1993] - PubMed result. Pain 1993, 55:297-304.
15. Kim KJ, Yoon YW, Chung JM: Comparison of three rodent neuropathic pain models. Exp Brain Res 1997, 113:200-206.
16. Shi Y, Seltzer Z: A-fibers mediate mechanical hyperalgesia and allo... [Neurosci Lett 1999] - PubMed result. Neurosci Lett 1999, 11562-67.
17. Seltzer Z, Dubner R, Shi Y: A novel behavioral model of neuropathic pain disorders produced in rats by partial sciatic nerve injury. Pain 1990, 43:205-218.
18. Nuytten D, Kupers R, Lammens M, Dom R, et al.: Further evidence for myelinated as well as unmyel... [Exp Brain Res 1992] - PubMed result. Exp Brain Res 1992, 91:73-78.
19. Puke MJ, Xu JX, Wiesenfeld-Hallin Z: Intrathecal administration of chloride suppresses... [Neurosci Lett 1991] - PubMed result. Neurosci Lett 1991, 133:199-202.
20. Miao P, Madec K, Gong Y, Shen H, Eiseinstein MD, Melanson M, Gu X, Leong C, Klowak M, Namaka M: Axotomy-induced up-regulation of tumor necrosis factor-alpha in the dorsal root ganglia. Neurol Res 2008, 30:623-631.
21. Guerdes RP, Araujo AS, Janner D, Bello-Klein A, Ribeiro MF, Partata WA: Increase in reactive oxygen species and activation of Akt signaling pathway in neuropathic pain. Cell Mol Neurobiol 2008, 28:1049-1056.
22. Li L, Xian CJ, Zhong JH, Zhou XF: Effect of lumbar 5 ventral root transaction on pain behaviors: a novel rat model for neuropathic pain without anatomy of primary sensory neurons. Exp Neurol 2002, 175:23-54.
23. Xu JT, Xian WJ, Zang Y, Wu CY, Liu XG: The role of tumor necrosis factor-alpha in the neuropathic pain induced by Lumbar 5 ventral root transaction in rat. Pain 2006, 123:306-321.
24. Olsson Y: Degranulation of mast cells in peripheral nerve injuries. Acta Neurol Scand 1987, 43:369-374.
25. Perry VH, Brown MC, Gordon S: The macrophage response to central and peripheral nerve injury. A possible role for macrophages in regeneration. J Exp Med 1987, 165:1218-1223.
26. Daemen MA, Kuvers HA, Kistslaar PJ, Slaff DW, Bullens PH, Wildenberg FA Van den: Neurogenic inflammation in an animal model of neuropathic pain, Neurol Res 1998, 20:41-45.
27. Maves TJ, Pehman PS, Gebhart GF, Meller ST: Possible chemical contribution from chronic gut sutures produces disorders of pain sensation like those seen in man. Pain 1993, 54:57-69.
28. Sommer C, Galbraith JA, Heckman HM, Myers RR: Pathology of experimental compression neuropathy producing hyperesthesia. J Neuropathol Exp Neurol 1993, 52:223-233.
29. Friesen JL, Baling M, Fried K: Distribution and axonal relations of macrophages in a neuroma. Neuroscience 1993, 55:1003-1013.
30. Clowson ML, Liebich PA, Castro GA, Walters ET: Role of peri-axonal inflammation in the development of thermal hyperalgesia and guarding behavior in a rat model of neuropathic pain. Neurosci Lett 1995, 184:5-8.
31. Schaefer M, Marziniak M, Sorokin LS, Yaksh TL, Sommer C: Cyclooxygenase inhibition in nerve-injury- and TNF-induced hyperalgesia in the rat. Exp Neurol 2004, 185:160-168.
32. Ma W, Du W, Eisenach JC: Role for both spinal cord COX-1 and COX-2 in maintenance of mechanical hypersensitivity following peripheral nerve injury. Brain Res 2003, 937:94-99.
33. Synofzik JP, Hu D, Walker JS, Tracey DJ: Hyperalgesia due to nerve injury: role of prostaglandins, Neuroscience 1999, 94:587-594.
34. Okubo M, Yamanaka H, Kobayashi K, Noguchi K: Leukotriene synthases and the receptors induced by peripheral nerve injury in the spinal cord contribute to the generation of neuropathic pain. Glia 2009, 57(5):599-610.
35. Rashid NH, Inoue M, Matsumoto M, Ueda H: Switching of bradykinin-mediated nociception following partial sciatic nerve injury in mice. J Pharmacol Exp Ther 2004, 308:1158-1164.
36. Petcu M, Dias JP, Ongali B, Thibault G, Neugebauer W, Couture R. Role of kinin B1 and B2 receptors in a rat model of neuropathic pain. Int Immunopharmacol 2008, 8:188-196.

37. Berrocoso E, De Benito MD, Mico JA. Role of serotonin 5-HT1A and opioid receptors in the antiallodynic effect of tramadol in the chronic constriction injury model of neuropathic pain in rats. Psychopharmacology (Berl) 2007, 193:97-105.

38. Faerber L, Drechsler S, Ladenburger S, Geschwindmeier H, Fischer W. The neuronal 5-HT3 receptor network after 20 years of research—evolving concepts in management of pain and inflammation. Eur J Pharmacol 2007, 560:1-8.

39. Rahman W, Suzuki R, Webber M, Hunt SP, Dickenson AH. Endogenous spinal 5-HT attenuates the behavioural hypersensitivity to mechanical and cooling stimuli induced by spinal nerve ligation. Pain 2006, 123:264-274.

40. Inoue K. P2X receptors and chronic pain. Purinergic Signal 2007, 3:135-144.

41. Inoue K, Tsuda M, Koizumi S. ATP- and adenosine-mediated signaling in the central nervous system: chronic pain and microglia: involvement of the ATP receptor P2X4. J Pharmacol Sci 2004, 94:112-114.

42. Inoue K, Tsuda M, Tozaki-Saitoh H. Modification of neuropathic pain sensation through microglial ATP receptors. Purinergic Signal 2007, 3:311-316.

43. Wilson-Gerwing TD, Stucky CL, McComb GW, Verge VM. Neuronal 5-HT3 receptor network after 20 years of research—evolving concepts in management of pain and inflammation. Eur J Pharmacol 2007, 560:1-8.

44. Rahaman W, Suzuki R, Webber M, Hunt SP, Dickenson AH. Depletion of endogenous spinal 5-HT attenuates the behavioural hypersensitivity to mechanical and cooling stimuli induced by spinal nerve ligation. Pain 2006, 123:264-274.

45. Inoue K. P2 receptors and chronic pain. Purinergic Signal 2007, 3:135-144.

46. Chien CC, Fu WM, Huang HI, Lai YH, Tsai YF, Guo SL, Wu TJ, Ling QD. ATP- and adenosine-mediated signaling in microglia: a key mediator of microglial activation in neuropathic pain states. Exp Neurol 2008, 213:303-314.

47. Ma W, Quirion R. Neuronal 5-HT3 receptor network after 20 years of research—evolving concepts in management of pain and inflammation. Eur J Pharmacol 2007, 560:1-8.

48. Faerber L, Drechsler S, Ladenburger S, Geschwindmeier H, Fischer W. The neuronal 5-HT3 receptor network after 20 years of research—evolving concepts in management of pain and inflammation. Eur J Pharmacol 2007, 560:1-8.

49. Arruda JL, Colburn RW, Rickman AJ, Rutkowski MD, DeLeo JA. Changes in plasma cytokines associated with delayed wallerian degeneration: differential effects of cytokine infusion. J Neuroimmunol 2007, 189:83-89.

50. Leung and Cahill. J Neurol 2005, 252:261-268.

51. Watkins LR, Maier SF, Goehler LE. Immune activation: the role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. Pain 1995, 68:298-302.

52. Lattre-Mollere E, Mauborgne A, Masson J, Bourgoin S, Kayser V, Hamon M, Pohl M. Differential implication of proinflammatory cytokine interleukin-6 in the development of cephalic versus extracerephalic neuropathic pain in rats. J Neurosci 2008, 28:3289-3290.

53. Ma W, Quirion R. Cytokine-mediated effects on pain behavior. In: Duncker K, editor. Pain and its treatment. Stuttgart: Thieme; 1998. p. 107-116.

54. Bechler L, Drechsler S, Ladenburger S, Geschwindmeier H, Fischer W. The neuronal 5-HT3 receptor network after 20 years of research—evolving concepts in management of pain and inflammation. Eur J Pharmacol 2007, 560:1-8.

55. Gao X, Kim HK, Chung JM, Chung K. Reactive oxygen species (ROS) are involved in enhancement of NMDA-receptor phosphorylation in animal models of pain. Pain 2007, 131:262-271.

56. Siniscalco D, Fuccio C, Giordano C, Ferraraccio F, Palazzo E, Luongo L, Rossi F, Roth KA, Maione S, de Novellis V. Role of reactive oxygen species and spinal cord apoptotic genes in the development of neuropathic pain. Pharmacol Res 2007, 55:158-166.
production and nerve regeneration on thermal and mechanical hypersensitivity, Brain Res 1998, 784:154-162.

83. Shamash S, Reichert F, Rotshenker S, Sorkin LS. Inflammatory mediators in experimental inflammatory reaction. Yakugaku Zasshi 1996, 116:455-462.

84. Yang L, Lindholm K, Konishi Y, Li R, Shen Y. Tumor necrosis factor receptor subtypes reveals hippocampal neuron death and survival through different signal transduction pathways. J Neurosci 2002, 22:3025-3032.

86. Jin X, Gereau RW. Acute p38-mediated modulation of tetrodotoxin-resistant sodium channels in mouse sensory neurons by tumor necrosis factor-alpha. J Neurosci 2006, 26:246-255.

87. Jin X, Gereau RWt. Axonal transport of TNF-alpha in painful and spared myelinated nerve fibers: evidence with focus on bFGF/JNK pathway. Brain Res 2008, 122:293-298.

88. Yang L, Lindholm K, Konishi Y, Li R, Shen Y. Tumor necrosis factor receptor subtypes reveals hippocampal neuron death and survival through different signal transduction pathways. J Neurosci 2002, 22:3025-3032.

90. Shubayev VI, Myers RR. Caspase signalling in neuropathic and inflammatory pain in the rat. Eur J Neurosci 2004, 20:2898-2902.

91. Sekiguchi M, Sekiguchi Y, Konno S, Kobauchi H, Homma Y, Ikuchi S. Comparison of neuropathic pain and neuronal apoptosis following nerve root or spinal nerve compression. Eur Spine J 2009, 18:1978-1985.

92. Czeschik JC, Hagenacker T, Schafers M, Busselberg D. TNF-alpha differentially modulates ion channels of nociceptive neurons. Neurosci Lett 2006, 434:293-296.

93. Drory VE, Lev D, Groozman GB, Gutmann M, Klausner JM. Induction of TNF receptor I-mediated apoptosis in nerve root and spinal nerve compression. Eur Spine J 2009, 18:1978-1985.

94. Leung and Cahill in inflammatory mediators in experimental inflammatory reaction. Yakugaku Zasshi 1996, 116:455-462.

95. Shubayev VI, Myers RR. Caspase signalling in neuropathic and inflammatory pain in the rat. Eur J Neurosci 2004, 20:2898-2902.

96. Leung and Cahill in inflammatory mediators in experimental inflammatory reaction. Yakugaku Zasshi 1996, 116:455-462.
131. Rygh LJ, Svendsen F, Fiskja A, Haugen F, Hole K, Tjolsen A: Long-term potentiation in spinal nociceptive systems—how acute pain may become chronic. Psychoneuroendocrinology 2003, 30:950-964.

132. Ikeda H, Kintoshi T, Murase K: Synaptic plasticity in the spinal dorsal horn. Neurosurg Rev 2009, 64:133-136.

133. Liu XG, Sandkuller J: Long-term potentiation of C-fiber-evoked potentials in the rat spinal dorsal horn is prevented by spinal N-methyl-D-aspartic acid receptor blockade. Neurosci Lett 1995, 191:43-46.

134. Liu X, Sandkuller J: Characterization of long-term potentiation of C-fiber-evoked potentials in spinal dorsal horn of adult rat: essential role of N1K1 and N2K2 receptors. J Neurophysiol 1997, 78:1973-1982.

135. Zhang HM, Zhou LJ, Hu XD, Hu NW, Zhang T, Liu XG: Acute nerve injury induces long-term potentiation of C-fiber evoked field potentials in spinal dorsal horn of intact rat. Sheng Li Xue Bao 2004, 56:591-596.

136. Klein T, Mageri W, Hofp HC, Sandkuller J, Treede RD: Perceptual correlates of nociceptive long-term potentiation and long-term depression in humans. J Neurosci 2004, 24:964-971.

137. Klein T, Mageri W, Treede RD: Perceptual correlate of nociceptive long-term potentiation (LTP) in humans shares the time course of early-LTP, J Neurophysiol 2006, 96:3551-3555.

138. Pickering M, Cumesky D, O'Connor JJ: Actions of TNF-alpha on glutamatergic synaptic transmission in the central nervous system. Exp Physiol 2005, 90:663-670.

139. Cancredi V, Dr'angeli G, Grossi F, Taroni P, Palmieri G, Tarroni P, Santoni A, Eusebi F. Tumor necrosis factor alters synaptic transmission in rat hippocampal slices. Neurosci Lett 1992, 146:176-178.

140. Liu YL, Zhou LJ, Hu NW, Xu JT, Wu CY, Zhang T, Li YY, Liu XG. Tumor necrosis factor-alpha induces long-term potentiation of C-fiber evoked field potentials in spinal dorsal horn in rats with nerve injury: the role of NF-kappa B, JNK and p38 MAPK. Neuropharmacology 2007, 52:708-715.

141. Holton FA, Holton P: The capillary dilator substances in dry powdered root of St John's wort, a possible role of adenosine triphosphate in chemical transmission from nerve endings. J Physiol 1954, 126:1-140.

142. Holton P: The liberation of adenosine triphosphate on antidromic stimulation of sensory nerves. J Physiol 1959, 145:494-504.

143. Bleehen T, Keele CA: Observations on the algogenic actions of adenosine compounds on the human blister base preparation. Pain 1977, 3:367-377.

144. Bleehen T: The effects of adenosine nucleotides on cutaneous afferent nerve activity. Br J Pharmacol 1978, 62:573-577.

145. Jahn CE, Jessell TM: ATP excites a subpopulation of rat dorsal horn neurones. Nature 1983, 304:730-733.

146. Burnstock G: Purinergic nerves and receptors. Prog Biochem Pharmacol 1980, 16:141-154.

147. Burnstock G, Kennedy C: Is there a basis for distinguishing two types of P2-purinoceptors? Gen Pharmacol 1985, 16:433-440.

148. Burnstock G: Purinergic signalling and disorders of the central nervous system. Nat Rev Drug Discov 2008, 7:575-590.

149. Burnstock G: Physiology and pathophysiology of purinergic neurotransmission. Physiol Rev 2007, 87:559-797.

150. Amaya F, Wang H, Costigan M, Allchorne AJ, Hatcher JP, Egerton J, Steven T, Morisset V, Groen DJ, Gunthorpe MJ, et al.: The voltage-gated sodium channel Nav(1.9) is an effector of peripheral inflammatory pain hypersensitivity. J Neurosci 2006, 26:12852-12860.

151. Novakovic SD, Kasatoski LC, Oglesby IB, Smith JA, Eglen RM, Ford AP, Hunter JC: Immunocytochemical localization of P2X3 purinoceptors in sensory neurones in naive rats and following neuropathic injury. Pain 1999, 82:273-282.

152. Bradley B, Burnstock G, McMahon SB. The expression of P2X3 purinoceptors in sensory neurons: effects of axotomy and glial-derived neurotrophic factor. Mol Cell Neurosci 1998, 12:256-268.

153. Barclay J, Patel S, Dom G, Wetherspoon G, Moffatt S, Eunson L, Abbedal F, Natt F, Hall J, Winter et al.: Functional downregulation of P2X3 receptor subunit in rat sensory neurones reveals a significant role in chronic neuropathic and inflammatory pain. Neurosci Lett 2002, 329:81-84.
administration of methotrexate reduces mechanical allodynia in an

Reversal of the antiinflammatory effects of methotrexate by the

nucleotidase gene-deficient mice

Cronstein BN:

term effects on spinal cord dorsal horn met-enkephalin

on vascular pathology and hyperalgesia caused by chronic

constriction injury of rat nerve.

Pain 1989, 43:38-43.

The antiinflammatory mechanism of methotrexate

The effect of thalidomide treatment on vascular pathology and hyperalgesia caused by chronic

constriction injury of rat nerve.

Pain 1989, 43:38-43.

Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation.

Exp Mol Pathol 1990, 53:211-222.

Montesinos MC, Takedachi M, Thompson LF, Wilder TP, Fernandez P, Cronstein BN. The antiinflammatory mechanism of methotrexate depends on extracellular conversion of adenine nucleotides to adenosine by ecto-5'-nucleotidase: findings in a study of ecto-5'-

nucleotidase gene-deficient mice. Arthritis Rheum 2007, 56:1440-1445.

el-Badawi MG, Fatani JA, Bahakim H, Abdalla MA: Light and electron microscopic observations on the cerebellum of guinea pigs following low-dose methotrexate. Exp Mol Pathol 1990, 53:211-222.

Montesinos MC, Takedachi M, Thompson LF, Wilder TP, Fernandez P, Cronstein BN. The antiinflammatory mechanism of methotrexate depends on extracellular conversion of adenine nucleotides to adenosine by ecto-5'-nucleotidase: findings in a study of ecto-5'-

nucleotidase gene-deficient mice. Arthritis Rheum 2007, 56:1440-1445.

Goll V: Does thalidomide have an analgesic effect? Current status and future directions. Curr Pain Headache Rep 2007, 11:38-43.

Moreira AL, Sampaio EP, Zmuidzinas A, Frindt P, Smith KA, Kaplan G. Thalidomide reduces tumour necrosis factor alpha and interleukin 12 production in patients with chronic active type dementia: overview of phase I and phase II clinical trials. J Neuropathol Exp Neurol 2001, 60:112-125.

Thalidomide neurotoxicity. Arch Dermatol 1984, 120:338-341.

Tawilki VL, Nutile-McMenemy N, Lacroix-Fralish ML, Deleo JA. Efficacy of propofol, a glial modulating agent, on existing mechanical allodynia following peripheral nerve injury. Brain Behav Immun 2007, 21:238-246.

Mielke R, Moller HJ, Erkinniemi T, Rosenkranz B, Rother M, Kttner B: Propofol treatment in the field of vascular dementia and Alzheimer-type dementia: overview of phase I and phase II clinical trials. Alzheimer Dis Assoc Disord 1998, 12(Suppl 2):S29-35.

Frampton M, Harvey RJ, Kirchner V. Propofol treatment for dementia. Cochrane Database Syst Rev 2003,CD002853.

Bauditz J, Wedel S, Locchi H. Thalidomide reduces tumour necrosis factor alpha and interleukin 12 production in patients with chronic active Crohn’s disease. Gut 2002, 50:196-200.

Moreira AL, Sampaio EP, Zmuidzinas A, Finndt P, Smith KA, Kaplan G. Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. Exp Mol Pathol 1990, 53:211-222.

Sommer C, Marzinak M, Myers RR. The effect of thalidomide treatment on vascular pathology and hyperalgesia caused by chronic constriction injury of rat nerve.

Pain 1989, 74:83-91.

George A, Marzinak M, Schafers M, Toyka KV, Sommer C. Thalidomide treatment in chronic constractive neuropathy decreases endoneural tumor necrosis factor-alpha, increases interleukin-10 and has long-term effects on spinal cord dorsal horn met-enkephalin. Pain 2006, 88:267-275.

Mackey S, Feinberg S. Pharmacologic therapies for complex regional pain syndrome. Curr Pain Headache Rep 2007, 11:38-43.

Goll V: Does thalidomide have an analgesic effect? Current status and future directions. Curr Pain Headache Rep 2007, 11:38-43.

Cite this article as: Leung and Cahill. 

