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REVIEW

Mode of action of cytokines on nociceptive neurons

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Abstract Cytokines are pluripotent soluble proteins secreted by immune and glial cells and are key elements in the induction and maintenance of pain. They are categorized as pro-inflammatory cytokines, which are mostly algesic, and anti-inflammatory cytokines, which have analgesic properties. Progress has been made in understanding the mechanisms underlying the action of cytokines in pain. To date, several direct and indirect pathways are known that link cytokines with nociception or hyperalgesia. Cytokines may act via specific cytokine receptors inducing downstream signal transduction cascades, which then modulate the function of other receptors like the ionotropic glutamate receptor, the transient vanilloid receptors, or sodium channels. This receptor activation, either through amplification of the inflammatory reaction, or through direct modulation of ion channel currents, then results in pain sensation. Following up on results from animal experiments, cytokine profiles have recently been investigated in human pain states. An imbalance of pro- and anti-inflammatory cytokine expression may be of importance for individual pain susceptibility. Individual cytokine profiles may be of diagnostic importance in chronic pain states, and, in the future, might guide the choice of treatment.

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Introduction

Cytokines and pain in animal models

Cytokines are pluripotent small peptides and proteins that are secreted by a variety of immune cells (e.g., T-lymphocytes, macrophages, natural killer cells) and nonimmune cells (e.g., Schwann cells, fibroblasts). Their main function is the regulation of T cell differentiation from undifferentiated cells to T-helper 1 and 2, regulatory T cells, and T-helper 17 cells (Steinman 2007). Data from animal experiments give unequivocal evidence for the crucial role of cytokines in the initiation and maintenance of pain (Scholz and Woolf 2007; Thacker et al. 2007; Üçeyler and Sommer 2007). Pain modulation by pro- and anti-inflammatory cytokines, has been studied in several animal models. The results imply mostly algesic effects for pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF), interleukin (IL-)1β, and IL-6. In contrast, anti-inflammatory cytokines like IL-4 and IL-10 have analgesic properties. The principal findings supporting the concept that pro-inflammatory cytokines induce and maintain pain are that injury of peripheral nervous tissue leads to a rapid and sustained increase in cytokine expression (Taskinen et al. 2000; Kleinschnitz et al. 2004; Üçeyler et al. 2007d), that the application of pro-inflammatory cytokines (e.g., intraneurally, subcutaneously, intramuscularly) induces pain behavior (Junger and Sorkin 2000; Schäfers et al. 2003b; Zelenka et al. 2005), and that treatment with anti-inflammatory cytokines or inhibitors of pro-inflammatory

cytokines relieves pain (Wagner et al. 1998; Cunha et al. 1999; Sommer et al. 1999, 2001; Vale et al. 2003; Milligan et al. 2005a; Hao et al. 2006).

Cytokines and pain in humans

Recently, human pain disorders were studied for a possible pathogenic role of cytokines. Samples from different body fluids (blood, cerebrospinal fluid, fluid from artificially generated skin blisters) and tissues (skin and nerve biopsy specimens) were investigated. The results are variable, but the main findings are consistent. The trend goes towards an imbalance between algesic pro-inflammatory and analgesic anti-inflammatory cytokines as one potential factor for individual pain susceptibility.

Elevated serum TNF levels were found in patients with fibromyalgia syndrome (FMS) (Maes et al. 1999; Wallace et al. 2001; Gür et al. 2002), while the anti-inflammatory cytokines IL-4 and IL-10 were reduced (Üçeyler et al. 2006). Furthermore, TNF mRNA was detectable in skin samples of patients with FMS but was absent in control skin (Salemi et al. 2003). However, there are also reports describing discrepant results (Amel Kashipaz et al. 2003; Wang et al. 2008). In patients with painful peripheral neuropathies sural nerve biopsy specimens revealed elevated TNF protein levels compared to controls (Empl et al. 2001; Lindenlaub and Sommer 2003). Patients with painful neuropathy also had higher systemic IL-2 and TNF mRNA and protein levels compared to controls and patients with painless neuropathy. In turn, patients with painless neuropathy had higher blood levels of anti-inflammatory cytokines, especially IL-10, compared to patients with painful neuropathy. These results were independent of the underlying etiology (Üçeyler et al. 2007c). Complex regional pain syndrome (CRPS), a pain state covering features of neuropathic and inflammatory pain, was investigated by several groups and again elevated pro-inflammatory cytokine levels were found in different body fluids (Huygen et al. 2002; Alexander et al. 2005; Üçeyler et al. 2007a), while systemic anti-inflammatory cytokine levels were reduced (Alexander et al. 2007; Üçeyler et al. 2007a). Furthermore, treatment with TNF blockers was successful in individual cases with CRPS (Ching et al. 2003; Huygen et al. 2004; Manning 2006; Bernateck et al. 2007). Although there are discrepant results (Wesseldijk et al. 2008) these findings strengthen the notion of an imbalance of pro- and anti-inflammatory cytokines as a factor in the development and maintenance of human pain states, and further research is needed to clarify the underlying mechanisms.

Mode of action of cytokines in pain

Direct actions of cytokines on nociceptors

Neurophysiology and behavior

Changes in pain behavior due to cytokines are paralleled by changes in ectopic activity or sensitivity of nerve fibers: TNF applied to peripheral nerve fibers lowers mechanical activation thresholds in C nociceptors, rapidly (<30 min) evokes ongoing activity in C-fibers, increases plasma permeability and extravasation, and elicits mechanical allodynia (Sorkin et al. 1997; Junger and Sorkin 2000). Intraplantar injection of IL-1β induces transient spontaneous discharges and hyperalgesia within 1 min (Fukuoka et al. 1994). Deletion of the IL-1 receptor type I and transgenic over-expression of the IL-1 receptor antagonist reduce spontaneous ectopic activity following spinal nerve injury (Wolf et al. 2006). IL-1β also sensitizes abdominal visceral afferents of cats to ischemia and histamine (Fu and Longhurst 1999). In a skin-nerve in vitro preparation, brief exposure of the skin to IL-1β facilitates heat-evoked calcitonin gene-related peptide (CGRP) release (Opree and Kress 2000) from peptidergic neurons, which is a direct effect independent of changes in gene expression or receptor up-regulation.

In vitro perfusion of *dorsal root ganglia* (DRG) with TNF elicits neuronal discharges in both A- and C-fibers (Zhang et al. 2002; Schäfers et al. 2003a; Özaktay et al. 2006) and induces allodynia (Homma et al. 2002; Schäfers et al. 2003a; Murata et al. 2006). Application of nucleus pulposus to the DRG also induces spontaneous firing in dorsal horn wide dynamic range neurons, this activation is blocked by TNF antagonists implying that the activity is cytokine mediated (Cuellar et al. 2004). After nerve injury, subthreshold quantities of TNF injected into a DRG result in faster onset of allodynia and increased spontaneous pain behavior, suggesting an increased sensitivity of nerve-injured DRG to TNF (Schäfers et al. 2003a). Markedly increased sensitivity to exogenous TNF is also seen in DRG in vitro, where not only are neurons responsive to lower concentrations of TNF, but firing frequencies are distinctly higher and the duration of the response is longer-lasting after TNF application (Schäfers et al. 2003a). Similar results were obtained in a model of low back pain, where TNF administrated to a compressed DRG enhances ongoing allodynia (Homma et al. 2002), and following mechanical compression of the DRG, where TNF induced neuronal firing is enhanced (Liu et al. 2002). Neutralizing the activity of endogenous TNF in the compressed DRG with soluble TNF receptor reduced allodynia in this model (Homma

et al. 2002). Brief (90 s) applications of IL-1β to DRG yielded a potentiation of heat-activated inward currents and a shift of activation thresholds towards lower temperatures without altering intracellular calcium levels. This IL-1β-induced heat sensitization is mediated by activation of protein kinases. IL-1 receptor is expressed on DRG neurons, such that IL-1β can act directly on sensory neurons to increase their susceptibility to noxious heat (Obreja et al. 2002).

Application of TNF to the *dorsal root* induces spontaneous discharges at the time of application, but decreased neural activity at later time points and results in increased mechanical sensitivity of the receptive fields (Özaktay et al. 2002). Application of TNF to the dorsal root also evoked spontaneous discharges in dorsal horn wide dynamic range neurons (Onda et al. 2002). This synergized with root traction to cause neuropathic pain behavior and neuropathological changes (Igarashi et al. 2000). Animals treated with either neutralizing antibodies to TNF directly on the nerve root or with systemic TNF antagonists show a marked reduction of both the neuronal activity and the pain behavior implicating a role for TNF in the process (Onda et al. 2003). IL-1β applied to dorsal roots decreased neural activity of A-delta and C-fibers within 3 h, but increased mechanosensitivity of the peripheral receptive fields 90 min after application (Özaktay et al. 2002) (Fig. 1).

In *spinal cord* there is a similar association between TNF neuronal sensitization and pain behavior: intrathecal administration of TNF enhances responses to C-fiber stimulation and increases both wind-up and the post-discharge response of deep dorsal horn neurons. Importantly, TNF alters excitability throughout the central nervous system via its effects on glutamate transporters: TNF decreases expression of the glutamate transporter gene EAAT2/GLT-1 (Sitcheran et al. 2005) and decreases glutamate uptake by other glial transporters such as GLAST (Korn et al. 2005). Decreased glutamate uptake via these transporters has been associated with increased pain behavior due to changes in spinal processing (Weng et al. 2005; Niederberger et al. 2006).

Signal transduction

TNF exerts its actions via its receptors, TNF receptor (TNFR) 1 and the lower affinity TNFR2 (MacEwan 2002). In the naive system, stimulation of TNFR1, but not TNFR2 induces pain-associated behavior in vivo and ectopic activity in Aβ- and Aδ-fibers in vitro. After nerve injury, TNFR2 contributes in the presence of TNFR1 activation (Schäfers et al. 2008). Response latencies of several minutes or less for the initial excitatory effects of TNF in the nervous system require that the mechanisms are post-translational. The literature provides evidence for TNF activation of different kinases: topical application of TNF to rat nerve root increases phosphorylation of extracellular signal-related kinase (ERK) with an onset time of several hours (Takahashi et al. 2006), while acute (5–15 min) application of TNF to cultured DRG neurons induces phosphorylation of c-Jun terminal kinase (JNK) and proteinkinase p38 (p38), but not ERK (Pollock et al. 2002), suggesting different roles for all three families of mitogen activated protein kinases (MAPK). Activated kinases may modify channel subunits via phosphorylation and thus alter their biophysical properties and/or stabilization within the postsynaptic density. Both of these effects may modulate neuronal responses to physiological and pathological stimuli.

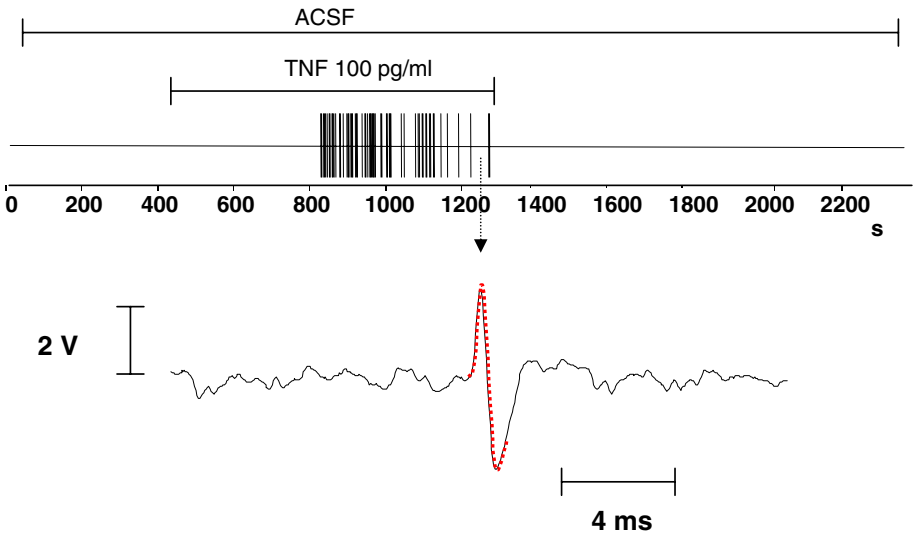

Fig. 1 In vitro extracellular dorsal root recording. After electrical stimulation, activity was recorded from an Aδ-fiber while the DRG was perfused first with ACSF and then with exogenous TNF (here, 100 pg/ml). Computer-based matching of the electrically evoked templates (*dotted line*) to the spikes (*continuous line*) obtained during the course of baseline, TNF perfusion, and washout allows information on separate fibers to be collected simultaneously

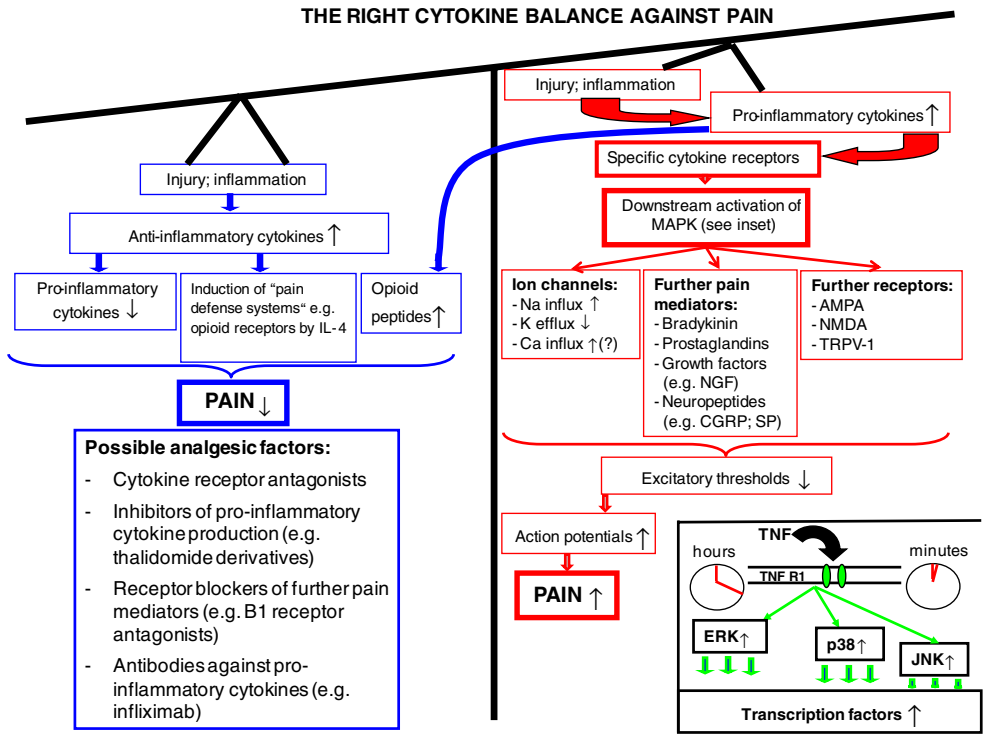

Fig. 2 Overview of selected pathways leading from cytokines to pain and to analgesia. *AMPA* α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor, *B1 receptor* bradykinin receptor 1, *Ca* calcium, *CGRP* calsitonin gene related peptide, *ERK* extracellular signal-regulated kinase, *IL-4* interleukin 4, *JNK* Janus kinase, *K* potassium, *MAPK* mitogen activated protein kinase, *Na* sodium, *NGF* nerve growth factor, *NMDA* N-methyl-D-aspartate receptor, p38 = a MAPK, *SP* substance P, *TNF* tumor necrosis factor-alpha, *TRPV1* transient receptor potential vanilloid 1, *TNF R1* tumor necrosis factor-alpha receptor 1

Ion channels

Earlier studies suggested that TNF trimers themselves may bind to membranes in a pH-dependent manner, insert into cell membranes and form cation channels, resulting in increased Na^+ influx (Kagan et al. 1992; Baldwin 1996). However, this idea has been discounted as studies with a lectin-deficient TNF mutant provide evidence that TNF does not form channels itself, but rather interacts with endogenous ion channels or with plasma membrane proteins that are coupled to channels (van der Goot et al. 1999).

Cytokines and Na^+ currents

Up to date, there is minimal literature concerning cytokine-induced effects on receptor-activated or voltage-gated ion channels, especially in the context of pain. Recently, TNF was shown to rapidly enhance Na^+ currents (Czeschik et al. 2008), another study found TNF-induced tetrotodoxin-resistent (TTX-R) Na^+ currents in DRG neurons via activation of TNFR1 and p38 MAPK (Jin and Gereau 2006). This enhancement of TTX-R Na^+ currents by TNF is suggested to be mediated by an increase in total TTX-R conductance rather than a shift in the voltage-dependence of activation or of steady-state inactivation and may induce TNF-dependent mechanical allodynia (Jin and Gereau 2006). In trigeminal ganglia neurons, short (5 min) exposure to IL-1β inhibits voltage-dependent Na^+ currents in an IL-1 receptor dependent manner (Liu et al. 2006). Longer (24 h) IL-1β exposures increased total Na^+ current in trigeminal ganglia neurons (Liu et al. 2006), this was suppressed by selective inhibitors of protein kinase C and G-protein-coupled signaling pathways. In epithelial cells, IL-1β decreases the expression of Na^+ channel subunits (Roux et al. 2005; Choi et al. 2007). In retinal ganglion neurons, IL-1 decreases inward Na^+ currents and outward K^+ currents independent of IL-1 receptor I activation (Diem et al. 2003) (Fig. 2).

Cytokines and K^+ currents

In addition, cytokine modulation of K^+-channels might contribute to regulation of action potentials: sustained exposure to TNF can have a slow, post-transcriptional effect on K^+-induced hyperpolarization as increased levels of TNF result in synthesis of prostaglandin E_2 (PGE_2) (Dinarello et al. 1986) which inhibits K^+ currents (Weinreich and Wonderlin 1987; Nicol et al. 1997). However, in a recent pilot study voltage-gated potassium channel currents were not influenced by TNF in DRG neurons (Czeschik

et al. 2008), further studies are needed to investigate this topic in more detail. More data are available from other experimental systems: application of TNF acutely reduces the outward K^+ current in identified Aplysia neurons (Sawada et al. 1991), retinal ganglion cells (Diem et al. 2001), and cortical neurons (Houzen et al. 1997). In retinal ganglion neurons, this is possibly linked to phosphatidylinositol 3-kinase (PI3 K) dependent Akt phosphorylation (Diem et al. 2001). In cultured cortical astrocytes, TNF induces a protein-kinase C-dependent reduction in K^+ conductance (inward rectifying K^+ currents, KIRs), which affects the capacity of glial cells to buffer extracellular K^+ released by neuronal firing and disturbs glutamate uptake leading to increased neuronal vulnerability (Koller et al. 1998). In human microglia cells, acute TNF exposition leads to the expression of an outward rapidly activating and not inactivating TEA-sensitive outward K^+ current in one-third of cells (McLarnon et al. 2001). In contrast to astrocytes, KIRs are not affected in microglia cells. IL-1β increases neuronal excitability in rat subfornical organ neurons, activates a nonselective cation current and inhibits delayed rectifier K^+ currents in a receptor-dependent manner (Desson and Ferguson 2003). In glomus cells of the carotid body, IL-1β decreases the outward K^+ current (Shu et al. 2007), whereas in bone marrow stroma cells IL-1β markedly increases the open time of K^+ channels (Chen and Wu 1999).

Cytokines and Ca^{2+} currents

Cytokine-induced modulation of voltage gated Ca^{2+} currents has been the subject of even fewer investigations: L-type Ca^{2+}-currents are increased by extended (24 h or greater), but not acute incubation of hippocampal neuronal cell cultures with TNF (Furukawa and Mattson 1998). In DRG neurons, voltage dependent Ca^{2+} channel (VDCC) currents were decreased voltage-dependently by TNF (Czeschik et al. 2008). Similarly, IL-1β rapidly inhibited VDCC activity in acutely dissociated hippocampal CA1 neurons (Plata-Salaman and Ffrench-Mullen 1992; Plata-Salaman and ffrench-Mullen 1994), in cortical neurons (Zhou et al. 2006), in adrenal chromaffin cells (Morita et al. 2004) and in ventricular myocytes (Schreur and Liu 1997). The lack of inhibition of neuronal VDCCs following exposure to other cytokines (IL-6, epidermal growth factor, basic fibroblast growth factor) or bacterial lipopolysaccharide indicates a specific action by IL-1β (Plata-Salaman and ffrench-Mullen 1994). In cortical neurons, a reduced expression of Ca^{2+} channel protein is suggested to underlie the inhibitory effect of IL-1β on Ca^{2+} channel activity (Zhou et al. 2006). IL-1β induced inhibition of VDCCs and the resulting Ca^{2+}-influx may impact on its ability to reduce neurotransmitter release (Rada et al. 1991; Murray et al. 1997), impairs long-term potentiation in the hippocampus (Katsuki et al. 1990; Cunningham et al. 1996; Schneider et al. 1998) and modulates synaptic transmission in the neocortex (D'Arcangelo et al. 1997).

Actions through other receptors

Cytokines and TRPV1 TNF enhances TRPV1-mediated currents in DRG neurons (Nicol et al. 1997), probably via the neuronal production of prostaglandins and TNF applied to isolated skin enhances heat-evoked CGRP release from nociceptor terminals (Opree and Kress 2000). IL-1β can also affect TRPV1 receptors (Piper et al. 1999): brief IL-1β application sensitizes TRPV1 currents (Obreja et al. 2002), whereas longer incubation of DRG neurons with IL-1β did not affect capsaicin-induced currents (Nicol et al. 1997).

Cytokines and ionotropic glutamate receptors In hippocampal neurons, TNF increases cell surface expression of the amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor subunit GluR1 (Beattie et al. 2002). This is accompanied by a concomitant decrease in membrane GluR2 and is thought to be the result of rapid insertion of Ca^{2+}-permeable AMPA/kainate channels and decreased Ca^{2+} impermeable AMPA receptors into the membrane (Ogoshi et al. 2005). The increase in AMPAR surface expression is triggered by TNFR1 and requires PI3K activity (Stellwagen et al. 2005). Changes in AMPAR subtype density may be involved in synaptic scaling during activity blockade rather than in the control of long-term potentiation or long-term depression (Stellwagen and Malenka 2006). TNF also increases cytosolic Ca^{2+} responses to AMPA and KCl in hippocampal neurons (De et al. 2003).

In vitro and in vivo evidence suggest the existence of a functional interaction between IL-1β and NMDAR: IL-1β reduces the frequency of AMPA-dependent spontaneous excitatory postsynaptic currents (sEPSC) and miniature excitatory postsynaptic currents (mEPSCs) (Yang et al. 2005), but enhances NMDAR-mediated current (Viviani et al. 2003; Yang et al. 2005). Recently, TNF and IL-1β were shown to increase AMPA and NMDA-induced currents in lamina II superficial dorsal horn neurons (Kawasaki et al. 2008). In this study, also sEPSC were increased by these cytokines. Interestingly, spontaneous inhibitory postsynaptic currents (sIPSCs) were reduced by IL-1β, as well as GABA and glycine induced currents. Together, these data show a strong role of proinflammatory cytokines in enhancing synaptic transmission and neuronal activity in the dorsal horn.

Actions of cytokines through other mediators

Beside direct actions on nerve endings and ion channels, cytokines exert their effects through several other pain

mediators. These interactions are not completely understood, but there is evidence for an important role of cytokines as initiators of downstream cascades.

Neuropeptides

Substance P (SP) is a pro-algesic neuropeptide that is released from sensory neurons. Together with neurokinin A, neurokinin B, neuropeptide K, and neuropeptide Y it is a member of the tachykinin family. Physiologically SP acts as a neurotransmitter, neuromodulator, or trophic factor via its G-protein linked neurokinin receptor type 1 (Liu et al. 2007). Mice deficient of SP display reduced pain behavior (Cao et al. 1998), and neurokinin receptor antagonists have analgesic effects in pain models (Coudore-Civiale et al. 1998). Noxious cutaneous thermal stimulation induces the release of SP into the spinal cord (Allen et al. 1997). The neuropeptide CGRP is a potent vasodilatator and is also involved in the induction of pain, a pathophysiological role is assumed in migraine (Durham 2006) and in CRPS (Birklein et al. 2001). The secretion of both SP and CGRP can be induced by cytokines. For instance, IL-1β modulates sensory neuron transmission via increased release of SP (Malcangio et al. 1996; Inoue et al. 1999) and CGRP (Fukuoka et al. 1994; Hou et al. 2003). IL-6 contributes to the expression of SP in sensory neurons (Murphy et al. 1999) and TNF induces the production of SP in sympathetic ganglia (Ding et al. 1995). Sustained treatment of primary afferent neurons with IL-1β leads to an increase in SP secretion via the cyclooxygenase system (Inoue et al. 1999). TNF and IL-1β facilitate heat-evoked CGRP release (Opree and Kress 2000). Intramuscular injection of TNF increases the CGRP levels in muscle tissue (Schäfers et al. 2003c). Interestingly, endogenous TNF which is produced in injured nerves, is transported anterogradely to muscle (Schäfers et al. 2002), where it might induce CGRP release.

Bradykinin

The nonapeptide bradykinin is one of the most potent algesic peptides. It is formed from kininogenes by cleavage of kallikrein and acts via two receptors: the kinin B1 and B2 receptors (Calixto et al. 2000). While the kinin B2 receptor is expressed constitutively and disappears during inflammation, the kinin B1 receptor is inducible by inflammation (Regoli et al. 1993; Moreau et al. 2005). If bradykinin is injected subcutaneously into normal tissue it leads to hyperalgesia by activation of kinin B2 receptors. The role of the kinin B1 receptor in the induction of pain is controversial. While mice lacking the kinin B1 receptor display hypoalgesia and altered inflammatory responses (Pesquero et al. 2000), a recent study found that the kinin B1 receptor, but not the kinin B2 receptor is responsible for inflammatory hyperalgesia mediated by TNF and IL-1β (Cunha et al. 2007). Bradykinin sensitizes peripheral nociceptor terminals and potentiates glutamatergic synaptic transmission in the spinal cord (Wang et al. 2005). By disinhibition of the TRPV1 receptor, bradykinin can sensitize nociceptors (Di Marzo et al. 2002) and increase the proportion of sensory neurons that respond to capsaicin or protons (Stucky et al. 1998). IL-1β but not TNF alpha induces B1 receptors, which then mediate thermal hyperalgesia (Perkins and Kelly 1994). In turn, bradykinin induces the secretion of TNF and IL-1β from macrophages (Tiffany and Burch 1989). The increase of the expression of bradykinin receptors plays a major role in inflammatory hyperalgesia (Dray and Perkins 1993; Dray 1997). This upregulation is facilitated by cytokines like IL-1β (Marceau 1995).

Prostaglandins

Prostaglandins are produced from membraneous arachidonic acid by the action of the cyclooxygenase 1 and 2 (COX1, COX 2) and are potent mediators of nociceptor sensitisation. It is assumed that inflammatory pain is preceded by cytokine–cytokine interactions leading to the secretion of prostaglandins and sympathetic amines (Cunha et al. 1992, 2005; Verri et al. 2006). TNF, IL-1β, and IL-6 are potent inducers of prostaglandins. The intraplantar injection of IL-1β, for instance, leads to reduced paw withdrawal latencies in a prostaglandin dependent way (Dayer et al. 1985; Ferreira et al. 1988). TNF induces the release of both prostaglandins and sympathetic amines (Cunha et al. 1992). Sympathetic amines are also inducible by IL-8 and the resulting hyperalgesia can be alleviated by atenolol (Cunha et al. 1991). The TNF induced increase in capsaicin sensibility in rat DRG neurons is also mediated by prostaglandins (Nicol et al. 1997).

Nerve growth factor

NGF is a prototype of growth factors and directly sensitizes sensory neurons and increases the production of SP and CGRP (Donnerer et al. 1992), both of which have pro-inflammatory properties and induce hyperalgesia. TNF and IL-1β induce NGF in inflamed tissue (Manni and Aloe 1998). IL-1β triggers the secretion of NGF from macrophages, which then leads to hyperalgesia via leucotrienes. Intramuscular injection of TNF also upregulates NGF (Schäfers et al. 2003c), which is excitatory to mechanosensitive group IV muscle afferents (Hoheisel et al. 2005).

Opioid peptides

Under inflammatory conditions the production of opioid peptides is increased in the DRG and they are axonally

transported to the periphery (Hassan et al. 1993; Mousa et al. 2001). In vitro, IL-1β induces the secretion of opioid peptides from lymphocytes, and the injection of IL-1β into the inflamed paw of a rat has hypoalgesic effects (Schäfer et al. 1994). In vivo, the release of opioid peptides is enhanced by IL-1β, IL-6, and TNF and this induces peripheral analgesia (Czlonkowski et al. 1993).

The role of anti-inflammatory cytokines

Anti-inflammatory cytokines are increasingly considered in the orchestra of pain mediating and alleviating agents. The pleiotropic glycoprotein IL-4 is one promising candidate. IL-4 is produced by activated $CD4^+$ T cells, mast cells, eosinophils and basophils and directs the immune response towards the T-helper 2 direction. Furthermore, IL-4 inhibits the activation of macrophages, one main source of pro-inflammatory cytokines. In animal studies IL-4 showed analgesic actions, for instance in the acetic acid induced writhing response in mice and in the zymosan-induced knee-joint incapacitance of rats (Cunha et al. 1999; Vale et al. 2003). Furthermore, IL-4 gene therapy attenuates mechanical allodynia and thermal hyperalgesia induced by spinal nerve ligation in mice (Hao et al. 2006). The link between IL-4 and analgesia might involve the endogenous opioid system. IL-4 induces the transcription of μ opioid receptors in human primary blood cells, immune cell lines and dendritic cells, and primary rat neuron cultures (Kraus et al. 2001). Furthermore, the expression of δ opioid receptors also is partly mediated by IL-4 (Börner et al. 2004). A polymorphism in the IL-4 responsive element of the μ opioid receptor gene reduces IL-4 inducibility (Hoehe et al. 2000; Kraus et al. 2001).

IL-10, a nongycosilated protein derived from activated T cells, B-cells, macrophages, mast cells and keratinocytes is also a potent analgesic cytokine. IL-10 mRNA is upregulated within 1 h in the sciatic nerve after lesion (Jander et al. 1996; Taskinen et al. 2000; Kleinschnitz et al. 2004; George et al. 2005; Üçeyler et al. 2007d) and a second delayed peak is observed after 45 days (Okamoto et al. 2001), which may indicate a role in nerve regeneration and possibly in the remission of hyperalgesia. IL-10 protein levels, however, decrease in the injured nerve within 1 day with a prolonged recovery period (George et al. 2000), indicating lack of IL-10 in spite of increased gene expression or increased turnover. The application of IL-10 before treatment reduces the hyperalgesic response upon intraplantar injection of carrageenan and of pro-inflammatory cytokines (Poole et al. 1995). This effect is also seen in IL-10 administration prior to nerve injury (Wagner et al. 1998). The intrathecal application of IL-10 protein, IL-10 DNA via viral vectors, and of naked DNA resulted in sustained pain reduction after chronic constriction injury to the sciatic nerve in rats (Milligan et al. 2005b; 2006).

Open questions

There are still many open questions concerning the mode of action of cytokines in pain. For example, the relative impact of direct (i.e., ion channel mediated) versus indirect (mediated via amplification of inflammation) and of peripheral versus central mechanisms is not known. Furthermore, although there are now data on how a cytokine (TNF) can modulate a TTX-resistant sodium channel, such data are as yet mostly lacking for other cytokines, chemokines, and ion channels.

In the complex field of immune mediators and their influence on pain, cytokines are only one element in a large pool of algesic substances. The combination of several mediators, resulting in "inflammatory soup" appears to be more powerful in activating nociceptors than individual factors (Kessler et al. 1992; Ma et al. 2006; Maingret et al. 2008). The exact position of cytokines in this context remains to be defined. Furthermore, a direct comparison between mediators like for example, TNF and a B1 agonist on C-fiber activity in vitro, has not been performed.

Despite the central role of cytokines in pain, several factors have to be considered that limit the appraisal of their role. Up to now only few and selected pro- and anti-inflammatory cytokines have been investigated in animal models and clinical trials. Besides, the role of cytokine receptors and receptor associated proteins must be taken into account, as well as the interactions between pro- and anti-inflammatory cytokines and their physiological antagonists, like soluble receptor molecules. The use of cytokine or cytokine receptor knockout animals is a frequently applied tool to study cytokine action, however, interactions between the pleiotropic cytokines may mask effects and other cytokines may take over the knocked out cytokine's functions. Cytokines are pluripotent proteins that are physiologically involved in numerous regulatory circuits. Therefore, a therapeutic knockdown of the protein function in the entire organism or the substitution of a cytokine might have deleterious effects. To minimise adverse effects it is, therefore, important to choose a target as specific and as localized as possible. The latter option would be particularly attractive in focal human pain states for which an impact of locally produced cytokines is assumed. Small fiber neuropathy with acral burning pain would be one example, with preliminary data indicating local upregulation of pro-inflammatory cytokines in patient skin (Üçeyler et al. 2007b).

Conclusions

Cytokines are a very crucial element in the neuroimmune circuits relevant to pain by inducing further pain mediators. In clinical studies there is growing evidence for the importance of a balanced cytokine expression as a protective factor against pain. Increasing evidence suggests that cytokines also have to be regarded as novel neuromodulators, specifically interacting with receptors and ion channels and thus regulating neuronal excitability, synaptic plasticity, and injury. Nevertheless, we are far from providing an exhaustive description of the pathways leading from a cytokine-receptor interaction to pain (Fig. 2), and further efforts will have to be made to better define this complex network.

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