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Role of interleukin-1β during pain and inflammation

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Abstract

The cytokine cascade in pain and inflammatory processes is a tremendously complex system, involving glial, immune, and neuronal cell interactions. IL-1β is a pro-inflammatory cytokine that has been implicated in pain, inflammation and autoimmune conditions. This review will focus on studies that shed light on the critical role of IL-1β in various pain states, including the role of the intracellular complex, the inflammasome, which regulates IL-1β production. Evidence will be presented demonstrating the importance of IL-1β in both the induction of pain and in the maintenance of pain in chronic states, such as after nerve injury. Additionally, the involvement of IL-1β as a key mediator in the interaction between glia and neurons in pain states will be discussed. Taken together, the evidence presented in the current review showing the importance of IL-1β in animal and human pain states, suggests that blockade of IL-1β be considered as a therapeutic opportunity.

1. Interleukin-1

Interleukin-1 α and β are prototypic proinflammatory cytokines that exert pleiotrophic effects on a variety of cells and play key roles in acute and chronic inflammatory and autoimmune disorders. There are two IL-1 receptors, IL-1 type 1 receptor (IL-1RI) and IL-1 type 2 receptor (IL-1 RII). IL-1α and IL-1β signal through IL-1RI. Binding to IL-1RII does not lead to cell signaling and it is therefore considered a decoy receptor. Upon binding of IL-1 to IL-1RI, a second receptor termed IL1 receptor accessory protein (IL-1RAcP) gets recruited at the cell membrane to form a high affinity binding receptor complex leading to intracellular signaling. A third IL-1 family member, IL-1 receptor antagonist (IL-1ra), binds to IL-1 receptors and prevents the interaction of IL-1 with its receptors, acting as a natural IL-1 inhibitor (reviewed in Dinarello, 1996 and Braddock and Quinn, 2004) This review will focus on the role of IL-1β in painful and inflammatory conditions.

IL-1β has important homeostatic functions in the normal organism, such as in the regulation of feeding, sleep, and temperature (reviewed in Dinarello, 1996). However, overproduction of IL-1β is implicated in the pathophysiological changes that occur during different disease states, such as rheumatoid arthritis, neuropathic pain, inflammatory bowel disease, osteoarthritis, vascular disease, multiple sclerosis, and Alzheimer's disease (reviewed in Dinarello, 1996; Braddock and Quinn, 2004, and Dinarello, 2004). IL-1β can be released from keratinocytes, fibroblasts, synoviocytes, endothelial, neuronal, immune cells such as macrophages and mast cells, and glial cells such as Schwann cells, microglia and astrocytes (Watkins et al., 1995; Copray et al., 2001; Shamash et al., 2002; Sommer and Kress, 2004;

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Perrin et al., 2005; Clark et al., 2006; Guo et al., 2007; Thacker et al., 2007). One area of research that has shed new light into IL-1β's role in inflammation and pain during disease state is the processing of IL-1β by Caspase-1 via the inflammasome.

2. Inflammasome

The inflammasome is an intracellular multi-protein complex that is emerging as an important regulator of inflammation (Fig. 1). The inflammasome acts as an activating scaffold for proinflammatory Caspases. One such Caspase, Caspase 1, cleaves and activates pro-IL-1β and pro-IL-18 (reviewed in Martinon and Tschopp, 2007). IL-33 has also been shown to be a possible Caspase 1 substrate (Schmitz et al., 2005). Inflammasomes play important roles in the innate immunity pathway and are active players in inflammatory disorders. As shown below, there is also evidence that they are involved in painful conditions.

Inflammasomes contain NOD-like receptor (NLR) proteins, and are named based on which NLR protein is present. The NLRP3, also known as NALP3 or CIAS1, inflammasome is probably the best studied (reviewed in Tschopp et al., 2003 and Mariathasan and Monack, 2007). The NLRP3 protein contains four distinct domains, a Pyrin domain (PYD) at the N-terminus, followed by a NACHT domain (named after NAIP, CIITA, HET-E, and TP1), a NACHT-associated domain (NAD) and a Leucine-rich repeats (LRR) domain at the C-terminus (Reviewed in Church et al., 2008). It is thought that NLRP3 acts as a sensor for cell injury and microbial components and once activated it binds through the PYD region to the ASC (apoptosis-associated speck-like protein containing a CARD domain) adaptor protein, which contains a PYD domain at the N-terminus and a CARD domain at the C-terminus. Besides binding to ASC, NLRP3 is also bound through its NACHT domain to the FIIND domain at the N-terminus of the Cardinal protein (Agostino et al., 2004). The ASC and Cardinal proteins, through their CARD domains, in turn bind to the CARD domain of pro-Caspase 1, causing proteolytic cleavage yielding activated Caspase 1. Cleaved Caspase 1 can then process pro-IL-1β to its bioactive IL-1β form (Agostino et al., 2004). Besides Caspase 1, there is evidence that metalloproteases (MMPs) cleave IL-1β, therefore Caspase 1-independent pathways may also play roles in pain transmission (Kawasaki et al., 2008a).

3. IL-1β in gout and other autoinflammatory diseases

Recently, gouty arthritis has taken center stage in the inflammasome field. Gout is one of the most painful acute conditions known to man and has been described since Egyptian times (reviewed in Nuki and Simkin, 2006). Gout is an autoinflammatory disorder that is caused by hyperuricemia. Articular deposits of monosodium urate (MSU) crystals lead to gouty arthritis, which causes acute gout attacks. These attacks present clinically as a highly inflammatory arthritis with intense redness, warmth and pain surrounding an affected joint that lasts for a few days and are associated with systemic symptoms such as fever, leukocytosis and elevated markers of inflammation. Most patients will have recurring attacks and chronic tophaceus gout can occur in untreated gout (reviewed in Dalbeth and Haskard, 2005, Masseoud et al., 2005, and Terkeltaub, 2006).

For the past 20 years, it had been known that IL-1β was produced by human white blood cells stimulated by MSU crystals (Malawista et al., 1985; Di Giovine et al., 1987), but the mechanism of how the crystals increased IL-1β production was not known until the seminal work of Martinon et al. (2006). In this paper, it was demonstrated that the inflammatory effects of the MSU crystals worked through the NLRP3 inflammasome. The authors showed that there was a deficiency in the activation of IL-1β by MSU crystals in macrophages isolated from mice deficient in various components of the inflammasome. Additionally, in an in vivo model of MSU crystal-induced peritonitis, there was a reduction in the neutrophil

influx in NLRP3, ASC, or Caspase 1-deficient mice as well as in IL-1R1-deficient mice (Martinon et al. 2006).

The importance of the IL-1 pathway, and not IL-18, was demonstrated by Chen et al. (2006), who showed that IL-1R1 deficient mice, and not IL-18R deficient mice, had an impairment of neutrophil influx in the MSU crystal peritonitis model. Additionally, pharmacological blockade of IL-1 pathway was shown to reduce neutrophil influx in the MSU crystal peritonitis model with blocking antibodies to IL-1 and IL-R1 or with the recombinant protein version of IL-1ra, Anakinra. This neutrophil influx decrease was not observed with an anti-TNF blocking antibody (Chen et al., 2006; So et al., 2007). Furthermore, in a small human pilot study involving 10 gouty arthritis patients, Anakinra rapidly relieved the inflammatory symptoms of gout (So et al., 2007). Anakinra is an FDA approved drug for the treatment of rheumatoid arthritis (reviewed in Braddock and Quinn, 2004 and Dinarello, 2004).

Besides the role of the inflammasome in acute gouty arthritis, there is a growing body of literature that shows that multiple auto-inflammatory diseases may result from mutations within genes that encode for different components of the inflammasome, leading to over production of IL-1β (reviewed in Stojanov and Kastner, 2005 and Church et al., 2008). For example, there are mutations within the NLRP3 gene that are associated with several hereditary periodic-fever syndromes, such as familial cold urticaria and Muckle–Wells, that lead to periodic fevers, joint inflammation and pain among other symptoms (Hoffman et al., 2001; reviewed in Hull et al., 2003). These NLRP3 gene mutations are thought to lead to excessive production of IL-1β (Agostino et al., 2004; Gattorno et al., 2007). The importance of the overproduction of IL-1β was recently demonstrated in small human pilot clinical trials showing that the recombinant protein version of IL-1ra, Anakinra, ameliorated clinical symptoms in periodic-fever syndromes (Hawkins et al., 2004, Hoffman et al., 2004). Additionally, Rilanocept (IL-1 Trap) was recently approved by the FDA for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle–Wells Syndrome (MWS) after successfully completing human clinical trials (Hoffman et al., 2008; Gold-bach-Mansky et al., 2008). The IL-1 Trap is a recombinant dimeric fusion protein that contains in a single chain the extracellular domains of IL-1RI and IL-1RAcP fused to the human Fc portion of an IgG protein (Economides et al., 2003; reviewed in Braddock and Quinn, 2004).

4. IL-1β in the periphery and pain

IL-1β is a potent mechanical and thermal hyperalgesic agent when injected into any number of peripheral tissues (Ferreira et al., 1988; Fukuoka et al., 1994; Watkins et al., 1994; Safieh-Garabedian et al., 1995; Cunha et al., 2000; Zelenka et al. 2005). Intraplantar injection of inflammatory agents, such as carrageenan, lipopolysaccharide (LPS) bacterial endotoxin, or complete Freund's adjuvant (CFA), produce mechanical or thermal hyperalgesia associated with an upregulation of IL-1β and other inflammatory cytokines in the inflamed tissue and in the dorsal root ganglia (DRG) (Safieh-Garabedian et al., 1995, 2002; Woolf et al., 1997; Cunha et al., 2000; Samad et al., 2001; Chessell et al. 2005; Menetski et al. 2007).

One mechanism of action for IL-1β is through upregulation of other pro-nociceptive mediators. For example, administration of IL-1ra significantly reduced mechanical hyperalgesia produced by a CFA intraplantar injection as well as CFA-induced upregulation of Nerve Growth Factor (NGF), a neurotrophic factor known to play a crucial role in a variety of acute and chronic pain states (Safieh-Garabedian et al., 1995). Interestingly, anti-NGF pre-treatment was able to reduce the CFA-induced hyperalgesia but not the elevation in IL-1β (Safieh-Garabedian et al., 1995) suggesting indirect mechanisms may be

responsible for the changes in behavior. This upregulation of NGF by IL-1β occurred at both the transcriptional and post-transcriptional levels (Lindholm et al., 1987, 1988; Vige et al., 1991). IL-1β can additionally signal through complex signaling cascades that lead to the release and/or activation of other nociceptive molecules such as Prostaglandin, Interleukin-6, Substance-P, and MMP9 (Inoue et al. 1999; Samad et al., 2001; Economides et al., 2003; Kawasaki et al., 2008a).

Despite the anti-NGF results, there is also evidence that IL-1β's actions can occur directly on nociceptors. RT-PCR and in situ hybridization studies have demonstrated that IL-1R1 is expressed in sensory neurons (Copray et al. 2001, Obreja et al., 2002). IL-1β is known to modulate neuronal excitability by affecting neuronal receptors such as TRPV1, sodium channels, GABA receptors, and NMDA receptors (reviewed in Schäfers and Sorkin, 2008). As evidence of IL-1β's direct actions on nociceptors, it has been shown that IL-1β in a nerve-skin in vitro preparation can excite nociceptive fibers in as little as 1 min (Fukuoka et al., 1994). Additionally, IL-1β has been shown to cause an increase in the heat-evoked release of Calcitonin Gene Related Peptide (CGRP) from rat cutaneous nociceptors in vitro (Opree and Kress, 2000). In a separate study, brief application of IL-1β to isolated neurons yielded a potentiation of heat-activated excitatory inward currents (I_{heat})(Obreja et al., 2002).

5. IL-1β's role during neuropathic pain

Neuropathic pain arises from dysfunction of the nervous system. The interplay between the immune and nervous systems is thought to be critical for the development and maintenance of neuropathic pain, and the proinflammatory cytokines, including IL-1β, appear to be contributory to the pain state (reviewed in Scholz and Woolf, 2007, and Uceyler and Sommer, 2008). Low back pain is a common and debilitating painful disorder which can arise from nerve injury. In degenerate and herniated human intervertebral discs, IL-1β expression is higher than in non-degenerate intervertebral disc controls (LeMaitre and Hoyland, 2007). In various animal models of neuropathic pain, IL-1β expression is increased in the injured sciatic nerve, DRG, and spinal cord (Rotshenker et al., 1992; Hashizume et al 2000; Lee et al., 2004; Perrin et al., 2005; Ruohonen et al., 2005; Uceyler et al., 2007; Kawasaki et al., 2008a). Immediately after peripheral nerve injury, Schwann cells are activated and macrophages are recruited to the injury site and both secrete IL-1β (reviewed in Scholz and Woolf, 2007) . The ipsilateral upregulation of IL-1β at the site of injury in the sciatic nerve has been detected as early as 1 h post-surgery in the chronic constriction injury (CCI) model in mice (Uceyler et al., 2007). In a rat transected sciatic nerve model, upregulation of IL-1β has been detected as long as 35 days post-surgery (Ruohonen et al., 2005).

In the CCI model in mice, sciatic nerve epineural injections of IL-1R1 neutralizing antibodies were shown to reduce both thermal hyperalgesia and mechanical allodynia, suggesting a role for the upregulated IL-1β in the induction of neuropathic pain (Sommer et al. 1999; Schafers et al., 2001). Additionally, in the same CCI model, mechanical allodynia was reduced by intrathecally administered IL-1β neutralizing antibody (Kawasaki et al., 2008a) suggesting that neuropathic pain is mediated by IL-1β activity at several sites. That IL-1β may act in concert with other mediators is suggested by the observation that in another neuropathic pain model, the L5 spinal nerve transection in rats, the combination of intrathecal (i.t.) injections of IL-1ra and soluble TNF Receptor (sTNFR) dose-dependently attenuated mechanical allodynia (Sweitzer et al., 2001). Using genetically-engineered models, it was shown that both IL-1R1 knockout mice and mice genetically overexpressing IL-1ra in astrocytes had reduced thermal hyperalgesia and mechanical allodynia in the L5 spinal nerve transection model, and reduced autotomy in a complete sciatic denervation

model. Additionally, both lines of engineered mice had a reduction in the amount of spontaneous ectopic activity in isolated DRG, a phenomenon previously associated with the development of neuropathic pain (Wolf et al., 2006).

Recently, new mechanisms of neuropathic pain have been revealed involving a complex pathway with MMP9, MMP2 and IL1-β. Kawasaki et al., 2008a showed that in the CCI model cleavage of IL-1β by MMP subtypes contributed to different phases of neuropathic pain behavior. After nerve injury, MMP-9 induced neuropathic pain through IL-1β cleavage and microglial activation at early times, whereas MMP-2 maintained neuropathic pain through IL-1β cleavage and astrocyte activation at later times. This well-orchestrated sequential activation of microglia followed by activation of astrocytes in the spinal cord during neuropathic pain has been previously documented (reviewed in Scholz and Woolf, 2007). Additionally, IL-1β was shown to activate MMPs, suggesting a circular regulation between MMPs and IL-1β (Kawasaki et al., 2008a). Therefore, IL-1β is likely part of a complex signaling cascade involving MMPs in the CCI model.

6. IL-1β in the CNS and pain

As suggested by the spinal cord data mentioned previously, the involvement of cytokines in persistent pain is not limited to peripheral sensitization. Proinflammatory cytokines and their receptors have been found in the CNS. For example, IL-1β's receptor IL-1R1 has been localized to the spinal dorsal horn and brain (Samad et al., 2001, Guo et al., 2007; Zhang et al., 2008).

Direct injection of IL-1β into the CNS has been shown to produce hyperalgesia and enhanced neuronal responses in animals (Oka et al., 1993; Oka et al., 1994; Watkins et al., 1994; Reeve et al., 2000). For example, intracerebroventricular (i.c.v.) injection of IL-1β has been shown to decrease response latency in the hot plate test in rats (Oka et al., 1993). A separate study showed that an i.t. injection of IL-1β led to a decrease in hind paw withdrawal thresholds in the von Frey test (Reeve et al., 2000). To assess the effects of IL-1β in neuronal responses, Oka et al. (1994) microinjected IL-1β in the lateral cerebral ventricle of rats. This resulted in potentiated responses of wide dynamic range neurons in the trigeminal subnucleus caudalis to noxious pinching of the facial skin. However, the same dose of IL-1β did not affect the responses of low threshold mechanoreceptive neurons to skin brushing, suggesting some specificity of action. The IL-1β-induced enhancement of nociceptive neuron responses was completely abolished by pretreatment with IL-1ra (Oka et al., 1994). In a separate study, Reeve et al. (2000) showed that an i.t. administration of rat IL-1β produced enhanced dorsal horn neuronal activity, including enhancement of responses to C-fiber stimulation, wind-up and after-discharges.

In addition to the evidence cited above suggesting that CNS administration of IL-1β can induce pain states, data have been generated which suggest that IL-1β acting in the CNS can contribute to nociceptive responses in animal models of pain. For example, i.t. delivery of IL-1ra has been demonstrated to relieve HIV-1 gp120-induced mechanical allodynia and thermal hyperalgesia in the hind paw (Milligan et al., 2001). In addition, Zhang et al. (2008) showed that IL-1ra given by an i.t. injection decreased inflammatory hyperalgesia in the hind paw induced by a CFA injection. While the source of increased IL-1β in the CNS is not clear, IL-1β has been shown to be present in the spinal cord and brain following a CFA hind paw injection (Samad et al., 2001; Raghavendra et al., 2004; Zhang et al., 2008). Work with IL-1β and other cytokines has led to the notion that the central cytokine cascade could be an important contributor to the development of persistent pain states (Samad et al., 2001; Guo et al., 2007; Kawasaki et al., 2008b; Zhang et al., 2008).

7. IL-1β in central glia-neuronal interaction

Injury-induced central neuronal hyperexcitability, or central sensitization, has been identified as an important mechanism underlying persistent pain. Evidence suggests that glia, particularly astroglia, are intimately involved in the control of neuronal activity (Jourdain et al., 2007; Parri and Crunelli, 2007). Convergent evidence suggests that inflammatory cytokines act as mediators between glia and neurons and assume roles as neuromodulators (reviewed in Watkins and Maier, 2003).

Inflammatory cytokines are known to be released by activated glia and have been implicated in persistent hyper-algesia (DeLeo and Yezierski, 2001; Watkins et al., 2003). Injection of CFA into the masseter muscle of the rat produces muscle inflammation and hyperalgesia. After CFA injection, rats exhibited an increased responsiveness and reduced response threshold to mechanical stimuli, characteristic of mechanical hyperalgesia and allodynia (Sugiyo et al., 2005; Watanabe et al., 2005). Masseter inflammation induced glial activation in the spinal trigeminal nucleus, as indicated by increased immunoreactivity of glial fibrillary acidic protein (GFAP, astroglial marker), astroglial gap junction protein connexin 43 and CD11b, a marker of activated microglia (Guo et al., 2007). Activation of glia by masseter inflammation was accompanied by an increase in IL-1β levels. Interestingly, IL-1β was selectively induced in astroglia as shown by double immunofluorescence staining: IL-1β colocalized with GFAP, but not CD11b and Neu-N, a neuronal marker (Guo et al., 2007). Similar selective induction of IL-1β in astrocytes was also observed in a bone cancer pain model and after intracerebral hemorrhage (Zhang et al., 2005; Wasserman and Zhu, 2007). These results suggest that astrocytes are a source of IL-1β release under these conditions. Further evidence indicated that both inflammation-induced astroglial activation and IL-1β were dependent on nerve input and were inhibited by the glial modulator propentofylline, suggesting that glial activation is upstream and critical to cytokine induction in the CNS after inflammation (Guo et al., 2007).

Studies have also indicated that IL-1β is produced in microglia in the CNS (Clark et al. 2006; Van Dam et al., 1995). Application of LPS to an ex vivo dorsal horn slice preparation induced rapid secretion of IL-1β from activated spinal micro-glial cells (Clark et al., 2006). Additionally, an i.t. injection of LPS in the lumbar spinal cord produced mechanical hyper-algesia in the rat hindpaw that was attenuated by the concomitant i.t. injection of IL-1ra (Clark et al., 2006). These data suggest a critical role of IL-1β and activated microglia in enhancing nociceptive transmission in spinal cord inflammation.

8. IL-1β signaling, NMDA receptor phosphorylation, and persistent pain

Neuronal glutamate receptors, particularly ionotropic NMDA receptors, play major roles in activity-dependent synaptic plasticity and persistent pain (reviewed in Woolf and Salter, 2000, Guo et al., 2006, and Ji and Woolf, 2001). NMDA receptors are heteromers of NR1/NR3 and NR2 subunits (reviewed in Paoletti and Neyton, 2007). Several amino acid residues on the intracellular C-termini of the NR1 and NR2 proteins are phosphorylated upon activation of protein kinases. These phosphorylation sites of the NMDA receptor subunits facilitates its trafficking, modulates channel kinetics and enhances function (Chen and Huang, 1992; Tingley et al., 1997; Yu et al., 1997; Brenner et al., 2004). The NMDA receptor phosphorylation is increased after tissue or nerve injury and this correlated with increased pain sensitivity (Guo et al., 2002; Zou et al., 2002; Brenner et al., 2004; Caudle et al., 2005).

Recent studies have indicated that the signal transduction cascade involving IL-1β and NMDA receptors are linked in the ascending nociceptive circuit (Viviani et al., 2003; Yang et al., 2005; Guo et al., 2007; Zhang et al., 2008; Kawasaki et al., 2008b). The glial inhibitor

fluorocitrate and IL-1ra inhibited inflammatory hyperalgesia and inflammation-induced NMDA receptor phosphorylation. Additionally, IL-1R1 and the NR1 subunit of the NMDA receptor were shown to colocalize in neurons (Guo et al. 2007, Zhang et al., 2008). In another set of experiments, direct application of IL-1β to an in vitro brain stem slice preparation induced an enhanced NMDA receptor phosphorylation in regions involved in trigeminal nociceptive processing. The effect of IL-1β on NMDA receptor was selective since another prototype inflammatory cytokine, TNFα, did not affect P-ser896-NR1 levels at the dose tested. This IL-1β-induced NR1 phosphorylation was blocked by IL-1ra, but not by fluorocitrate, the glial inhibitor, suggesting that the effect of IL-1β on NMDA receptor is downstream to glial activation (Guo et al. 2007). Taken together, these findings provide evidence that IL-1β leads to NMDA receptor phosphorylation through IL-1R1 signaling to facilitate pain transmission.

9. Conclusions

In summary, a growing number of studies show that peripheral injury activates both neuronal and non-neuronal or glial components of the peripheral and central cellular circuitry. The subsequent interactions between the injury site, neurons, and glia cells lead to increased excitability and persistent pain. Proinflammatory cytokines are also induced after injury, and may act on neurons to facilitate central sensitization and hyperalgesia. Recent findings implicate IL-1β in painful and inflammatory processes at multiple levels, both peripherally and centrally. IL-1β may explain how glial cells affect CNS neuronal activity and promote hyperalgesia. The mediation of interactions between cells at the injury site, such as glia and neurons, by IL-1β may facilitate synaptic activity and pain transmission, and contribute to the development of chronic pain. Taken together, these findings suggest that IL-1β inhibition could represent a broad-acting and efficacious method for managing pain and inflammation across a wide variety of conditions.

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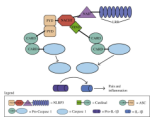

Fig. 1.

NLRP3 inflammasome: The NLRP3 protein is thought to be activated by both intracellular and extracellular signals and acts as a central component of a protein complex containing ASC, Cardinal, and Pro-Caspase1. The activation of the inflammasome leads to cleavage of the Pro-caspase 1 to its active form, which results in the production of the active mature form of IL-1β.