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Neural - Glial Interaction in Neuropathic Pain

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1. Introduction

Lesioning of the nervous system can produce a form of pathological pain called "neuropathic pain" that is characterized by sensory deficit, burning sensation, hyperalgesia and allodynia (Cui et al., 2000). The mechanisms underlying neuropathic pain have been studied extensively. Abundant evidence has indicated that aside from the neural component, the non-neural cells of the CNS, such as glial cells, have important roles in the pathogenesis of pain (Coyle, 1998). To a certain extent, glial activation is triggered secondary to injury. Glial cells play an important role in the initiation, development and maintenance of persistent neuropathic pain. Both microglia and astrocytes are activated in the spinal cord after nerve injury, and pain is amplified when glia become activated (Mika, 2008). It has been hypothesized that neuropathic pain and morphine tolerance share some common pathological mechanisms (Mayer et al., 1999). Many studies have indicated that neuropathic pain leads to reduced morphine efficacy and the rapid development of morphine tolerance. The glia become activated in response to the repeated administration of morphine, which leads to the release of proinflammatory mediators and may oppose opioid analgesia by altering neuronal excitability (Campbell et al., 2006). It is not clear how opioids activate microglia in the spinal cord, but previous work by Hutchinson's team suggested the possible involvement of toll-like receptor 4 (TLR4) (Tanga et al., 2005). In this study, we tried to understand the role of microglia in morphine tolerance and also examine some possible methods for improving the efficacy of morphine to control neuropathic pain.

2. Basic mechanisms of neuropathic pain

Pain is a sensory system that, under normal conditions, is protective and adaptive. It serves as a warning signal for the body (tissue inflammation and damage) and induces behavioral changes that facilitate wound healing and recuperation and help to prevent further tissue damage (Bridges et al., 2001). Lesioning of the nervous system can produce a form of pathological pain called "neuropathic pain". Neuropathic pain is a debilitating condition that affects millions of individuals worldwide (Colburn et al., 1999; Zimmermann, 2001). It is characterized by sensory deficit, burning sensation, hyperalgesia and allodynia (Coyle, 1998). Changes in signal processing in the nervous system may contribute to or may become the sole cause for hyperalgesia and allodynia (DeLeo & Yezierski, 2001). A lesion in the peripheral nervous system may induce pain, but simply severing dorsal roots seems to have little chance of causing lasting pain (Li et al., 2000).

Combining inflammatory substances with nerve injury enhances pain behavior (Clatworthy et al., 1995), and there is a strong correlation between the presence of mechanical allodynia in different nerve injury models (Cui et al., 2000; Mirzaei et al., 2010). A neuroma forms when the nerve is injured. The spontaneous activity and ectopic sensitivity to mechanical, thermal, and chemical stimuli that originate from the traumatic neuroma have been well documented (Devor, 2006). It has been demonstrated that there is a large increase in the level of spontaneous firing in the afferent neurons linked to the injury site. Abnormal pain after peripheral nerve injury is dependent on the activation of spontaneous and persistent abnormal discharge from ectopic foci at the site of injury (Wall & Gutnik, 1974) and the dorsal root ganglia (DRG) (C. N. Liu et al., 2000). This spontaneous discharge has been termed ectopic discharge and has also been demonstrated in humans suffering from neuropathic pain (Nordin et al., 1984). Pain is exacerbated in part because of a reorganization of spinal cord circuitry in the setting of persistent injury (Basbaum, 1999). This leads to the prolonged hyperexcitability of spinal cord neurons, which alters transmission of the pain message. Enhanced sensitivity to pain may persist long (months and years) after the primary tissue damage has healed (Dworkin et al., 2003; DeLeo & Yezierski, 2001). Chemical and neural changes occur, at the site of tissue injury, at the nerve endings of pain fibers, along their axons, at first –order synapses, and both pre-and post synaptically in the dorsal horn of the spinal cord or in supra-spinal pain-processing areas. This processing, from the normal condition to a pain – facilitatory state, in the dorsal horn of the spinal cord is collectively known as central sensitization (G. Woolf & Salter, 2000). Pain can transform from a symptom to a disease when injury or inflammation is prolonged (Hucho & Levine, 2007; C. J. Woolf & Mannion, 1999). The alteration of central sensory processing by sensitization of the spinal cord seems to be the key step for many sensory abnormalities in the context of neuropathic pain (Gracely et al., 1993; Roberts, 1986). There has been a great deal of research into the mechanisms of chronic pain, with a strong focus on the development of central sensitization. Changes in dorsal horn neuronal excitability can be achieved by increasing the excitatory input or by decreasing the inhibitory tone. This concept of disinhibition has been of considerable interest as a key mediator of the transmission of augmented sensory input to higher CNS regions in neuropathic pain states. The majority of currently used neuropathic pain models display similar alterations in hind-limb cutaneous sensory thresholds following partial injury of a peripheral (usually sciatic) nerve. In particular, the demonstration of hyperalgesia to noxious thermal stimuli and allodynia to cold and mechanical stimuli are used as outcome measures (Bridges et al., 2001; Bennett, 2005). The three most commonly used models are the chronic constriction injury (CCI) of the sciatic nerve (Bennett & Xie, 1988), the partial sciatic nerve ligation model (PNL) (Seltzer et a1., 1990) and the spinal nerve ligation model (SNL) (Kim et al., 1999). We investigated the characteristics of a CCI neuropathic model from behavioral, molecular and electrophysiological perspectives. In our laboratory, the CCI model produced robust behavioral changes in terms of pain sensation. Findings reveal that the CCI procedure produces long-lasting cold and mechano-allodynia as well as hypersensitivity to noxious stimulation (Hamidi et al., 2006). Microscopic studies of the injured nerves have revealed pathological changes distal to the injured site (see Fig. 1). There is massive degeneration of myelinated axons and less marked damage to unmyelinated axons (Basbaum et al., 1991; Manaheji et al., 2005). It is believed that allodynia is a central phenomenon mediated by large myelinated fibers (Yamamoto & Yaksh, 1992). In the injured nerve, the evoked compound action potentials (CAPs) including conduction velocity (CV), amplitude and rising time have become standard tools for the evaluation of peripheral nerve disorders and the investigation of

the function of the sciatic nerve. Recent research has shown that reduced CV can be caused by demyelination in the zone of the lesion (Basbaum et al., 1991). In our study, we found that the injury leads to a decrease in the CV and amplitude as well as an increase in the rising time of the CAPs (see Fig. 2). These changes are more pronounced in the recordings obtained distally to the ligated site. It seems that the sciatic nerve injuries yield changes in behavioral responses that are in accordance with the electrophysiological events that occur only in the distal part of the ligation site (Hamidi et al., 2006). Peripheral nerve injury is associated with inflammatory responses at the site of tissue damage. CNS injury is accompanied by the release of proinflammatory cytokines (Verri et al., 2006). Proinflammatory cytokines, especially tumor necrosis factor-α (TNF- α), interleukin (IL)-1 and IL-6, induce long-term alteration of synaptic transmission in the CNS and play a critical role in the development and maintenance of neuropathic pain (DeLeo & Yezierski, 2001).

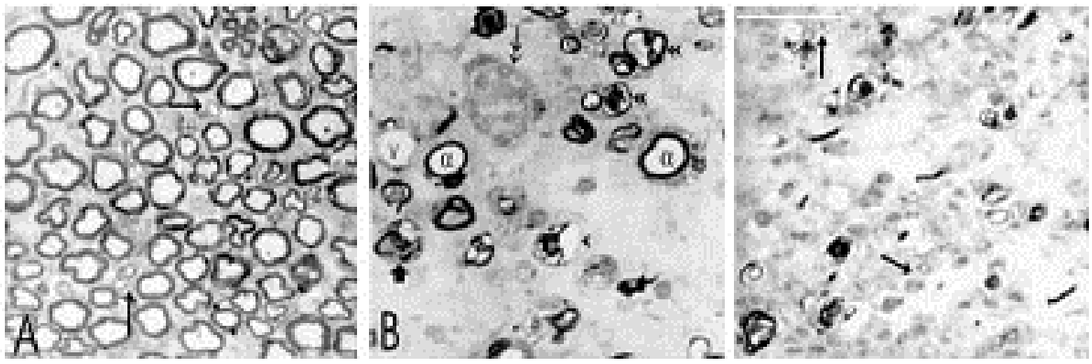

Fig. 1. Photomicrographs of toluidine blue stained semi-thin cross sections from normal sciatic (control or A). CCI 2 or B = two weeks after CCI. CCI 8 or C = eight weeks after CCI. Small myelinated fibers (arrows) are shown in A&C, ruffled basal lamina (double head arrow) in B, Schwann cells or phagocytic cells containing myelin debris (thin arrows) in B, damaged axons (thick arrows)in B. Atrophic axons (double arrow heads) and Schwann cells (arrow head)and blood vessel(V) in B.

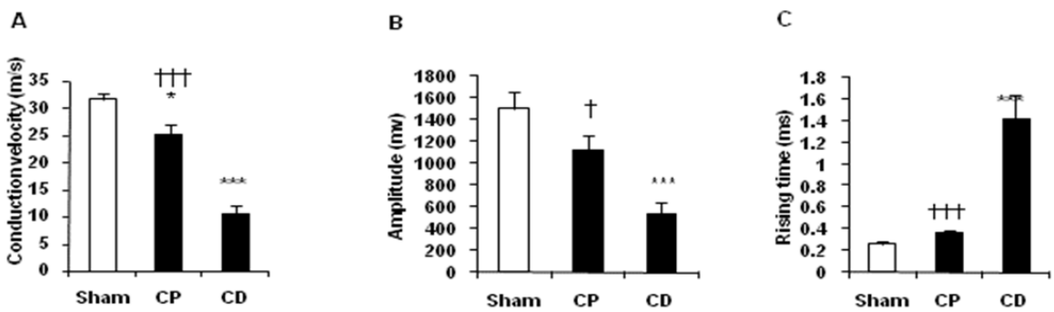

Fig. 2. Histograms of conduction velocity (CV) of the compound action potential (CAP) recorded from the sciatic nerve proximally. Location of stimulation was proximal (CP) or distal (CD) to the level of the constriction. A: The CV decreased in both operated CCI rats compared to the sham animals. B: amplitude of CAPs decreased in both CD and CP groups when compared to the sham animals. C: comparison of the rising time of CAPs represents a significant increased between the CD and CP and the sham animals. Asterisks indicate significant differences between CP and CD with sham. Crosses indicate significant difference between CD and CP.

3. Opioid tolerance in neuropathic pain

The perception of pain is modulated by pain-inhibitory and pain-facilitatory systems. The activation of several areas in the dorsal horn of the spinal cord results in the secretion of modulatory compounds that produce pain suppression (analgesia) or pain facilitation (hyperalgesia). Pain facilitation is mediated by many substances, including cholecystokinin (CCK), prostaglandins, dynorphin, substance P, and sympathetic amines (Mayer et al., 1999; Verri et al., 2006), and can be blocked by NMDA-receptor antagonists (Ben-Eliyahu et al., 1992; Parsons, 2001). Researchers are working to characterize the changes that occur in the nervous system during the development of neuropathic pain in animal models. An understanding of how neuropathic pain develops is necessary to guide the development of new pain therapies. Unfortunately, neuropathic pain is generally resistant to currently available treatments, so treatment options for neuropathic patients are limited, as opioids and other available pharmacological treatments are not able to adequately control associated spontaneous pain (Colburn et al., 1999). Non-steroidal anti–inflammatory drugs, antidepressants and local anesthetic agents are generally ineffective or have substantial drawbacks due to side effects. Generally, these treatments do not protect neurons from stress or death. Recent evidence suggests that NMDA receptor antagonists may have a role in attenuating the features of neuropathic pain. Glutamate concentration increases in the ipsilateral dorsal horn after CCI (Kawamata & Omote, 1996). It has been established that hyperalgesia can be prevented in the CCI model by continual pre- and post-injury i.p. administration of the NMDA receptor antagonist MK-801 (Davar et al., 1991). The endogenous opioid system plays a pivotal role in pain suppression. The administration of exogenous opioid drugs can also activate this system (Shavit et al., 2007). Notably, opioid compounds (e.g., morphine) have been used for centuries to combat many extremely painful conditions. Opioids are among the most effective analgesics for many types of pain (Rashid et al., 2004). However, opioids are reported to have suboptimal therapeutic efficacy against neuropathic pain (Bleeker et al., 2001; Cherny et al., 1994). There have been reports that chronic morphine treatment leading to 'morphine tolerance' may indeed induce the death of neurons (Hameed et al., 2010; Mao et al., 2002). The ineffectiveness of morphine in the context of neuropathic pain may be due to the reduced number of presynaptic opioid receptors due to the degeneration of primary afferent neurons, which is in turn caused by nerve damage. In our study, we treated rats with morphine and MK-801 both separately and together prior to CCI injury. This anti-nociceptive treatment prevents the establishment of altered central processing, which amplifies post-CCI pain. Therefore the application of morphine or MK-801 exerts a minimal effect on allodynia and hyperalgesia phenomena. However, the co-administration of morphine and MK-801 effectively modulates some aspects of neuropathic pain related to behavioral disorders in allodynia induced by extreme cold (Hamidi et al., 2006; Nichols et al., 1997). It has been hypothesized that neuropathic pain shares cellular and molecular mechanisms of neural plasticity with opioid tolerance. Additional evidence for this hypothesis came from a study by (Ossipov et al. 1995), which observed the same result with experimental animal models of neuropathic pain. A reduction in the number of μ-opioid receptors may be an important factor in diminishing the efficacy of morphine and μ-opioid receptor agonists (Przewlocki & Przewlocka, 2001). Partial sciatic nerve injury caused a drastic decrease in μ-opioid receptor expression in the injured DRG

neurons (Rashid et al., 2004). Most previous studies examined the reasons behind the decreased effectiveness of spinal morphine in neuropathic pain, which includes reduced μ-opioid receptor (mOR) expression in the spinal dorsal horn (Porreca et al., 1998). It is well known that mOR expression is greatly decreased in the dorsal root ganglion neurons after peripheral nerve injury (Zang et al., 1998). In contrast, the functional activity of the central and peripheral opioid systems is enhanced by inflammation (Bilevicute-Ljungar et al., 2006). It has been shown that during inflammation, the effect of μ-opioid receptor agonists increases by approximately 10-fold (Cook & Nickerson, 2005). In a study from our laboratory, the effect of persistent arthritis inflammation on spinal μ-opioid receptor expression and variation in hyperalgesia was examined. The results indicated a significant increase in spinal μ-opioid receptor mRNA expression, which was demonstrated by semiquantitative RT-PCR in the first week after arthritis induction. There were also significant ipsilateral changes in thermal hyperalgesia after arthritis. However, in a 21-day study, both μ-opioid receptor mRNA expression and thermal hyperalgesia gradually decreased and achieved levels that were close to normal. It seems that μ-opioid receptor fluctuation may be involved in changes in hyperalgesia during the 21 days after arthritis (see Fig. 3).

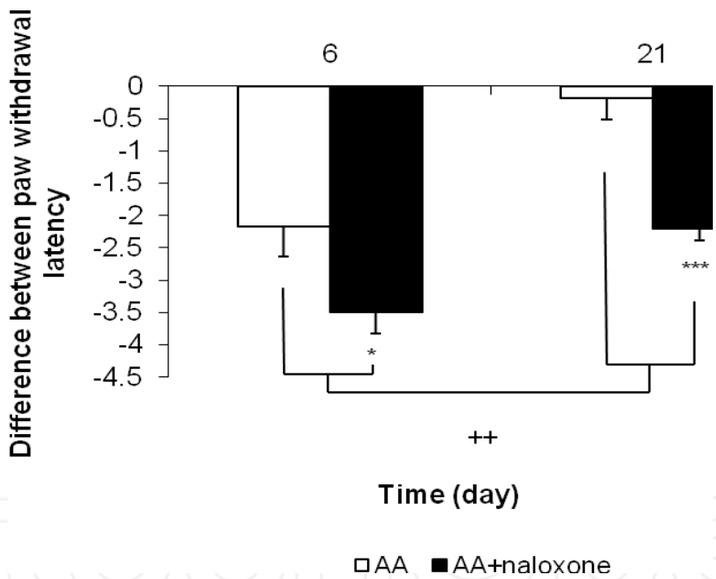

Fig. 3. Comparison of variation in thermal hyperalgesia after naloxone injection on day 6 and 21 days after induction of adjuvant arthritis (AA). (□), AA; (■), AA + naloxone. Data are the mean ±SEM (n= 6-7/ group). $P < 0.001$. *** $P < 0.01$, ** $P < 0.05$, *

Our results demonstrate that opioid receptor mRNA expression and variation in hyperalgesia are time dependent (Zaringhalam et al., 2008). Cytokines may play an important role in this mechanism by up-regulating mOR expression in the CNS. It is believed that excess IL-6 plays a pathogenic role in inflammation. In another set of experiments in our lab, we considered the role of IL-6 in arthritis. IL-6 is a multifunctional cytokine with pro- and anti-inflammatory properties. IL-6 mediates both acute and chronic phases of inflammatory responses and is therefore involved in both the early and late stages

of inflammation (Moller & Villiger, 2006). Our study demonstrated that serum IL-6 and spinal mOR expression increased with concurrent decreases in hyperalgesia during the chronic phase of arthritis. This finding supports the hyperalgesic role of IL-6 during chronic inflammation. Our previous studies demonstrated that IL-6 administration resulted in analgesia, which was blocked by naloxone. This analgesia for sustained inflammatory pain was attributed to a local release of endogenous opioid peptide by immune cells after IL-6 challenge (Tekieh et al., 2011). These results demonstrated an anti-inflammatory effect of serum IL-6 during the chronic phase of arthritis (see Fig. 4). It has been suggested that IL-6 may serve as a regulator of inflammatory pain and may be essential in the immune-opioid pathway (De Jongh et al., 2003). Systemic administration of anti-IL-6 antibody reduced spinal mOR expression and subsequently increased hyperalgesia. IL-6 is an important cytokine for transitioning between acute and chronic inflammation and is involved in different stages of arthritis (Nishimoto & Kishimot, 2006). In another study we revealed an increase in the serum level of IL-6 in CCI animals which was blocked by minocyline and produced antinocicepion (Zanjani et al., 2006). These results suggest that the stages of inflammation in arthritis and the pain behaviors in CCI must be considered to achieve effective anti-hyperalgesic and anti-inflammatory intervention via anti-IL-6 antibody and analgesic effect of minocycline treatment respectively.

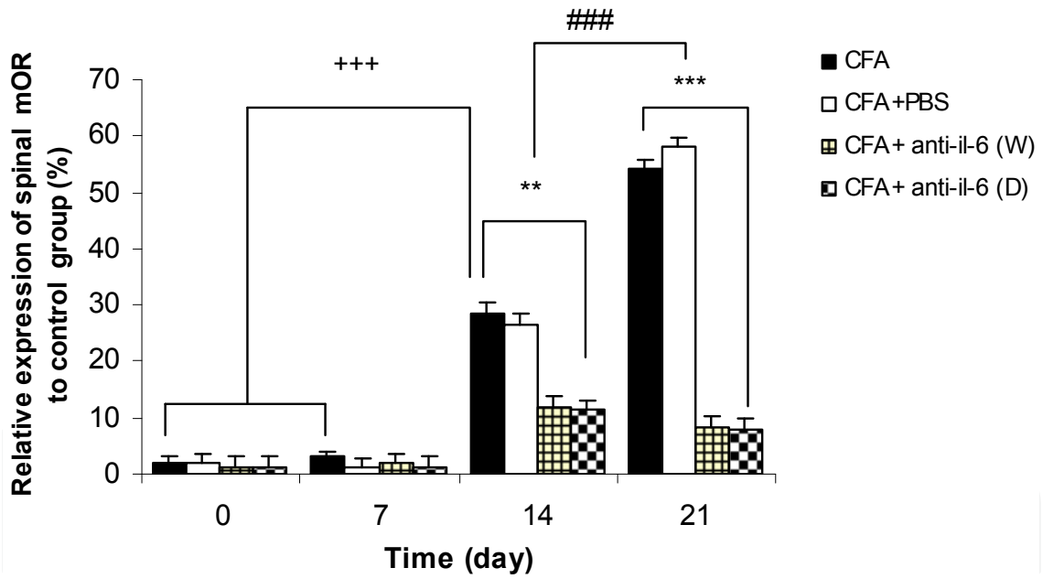

Fig. 4. CFA injection caused significant increased in spinal mOR expression time dependently. Anti- IL-6 antibody administration significantly reduced spinal mOR expression during different stages of AA. Ratio of spinal mOR protein band intensity in AA group significantly decreased at 14th and 21th days after anti-IL-6 antibody treatment compared to AA control group. Data are presented as mean ±SEM (n=6/ group). +++ $P < 0.001$ comparison of ratio of spinal mOR protein band intensity between different days of AA. ** $P < 0.01$, *** $P < 0.001$ comparison of spinal mOR protein band intensity between AA and AA + anti-IL-6 antibody treated rats. ### $P < 0.001$ indicated spinal mOR protein band intensity difference in AA and AA + anti-IL-6 antibody treated rats between 14th and 21th days.

4. Glial and opioid tolerance

As with peripheral mechanisms, much evidence supports the view that the initiation but not the maintenance of neuropathic pain behaviors is associated with immune mechanisms (Xu et al., 2006). Central glial activation is a player in this complicated nociceptive signaling cascade. It has become evident that spinal cord glial cells play a major role in pain facilitation (Campbell & Meyer, 2006; Watkins & Maier, 2002). It is proposed that neuropathic pain leads to reduced morphine efficacy and to the development of morphine tolerance. The results of many studies support the idea that the modulation of glial and neuroimmune activation may be a potential therapeutic mechanism to enhance morphine-induced analgesia (Mika, 2008). The analgesic potency of both systemic and intrathecal morphine is greatly reduced in animal models of neuropathic pain (Idanpaan et al., 1997). Recent evidence suggests that nerve damage evokes a cascade of immune responses and that glia play a crucial role in the maintenance of neuronal homeostasis in the central nervous system (Nakajima & Kohsaka, 2001; Stoll & Jander, 1999). In recognizing that glial cells play a role in chronic pain, one of the most important findings was that P2X receptors resided on glial cells, not on neurons (Sutherland, 2004). P2X receptors, or pain-signaling molecules, have long been associated with pain, but they were perceived to be associated with nerve cells. As a result of this discovery, researchers began inspecting the mechanisms of glial activation more closely (DeLeo, 2006). The mechanisms for this activation might be multifactorial. The glia become activated in response to the repeated administration of morphine, which leads to the release of proinflammatory mediators and may oppose opioid analgesia by altering the level of neuronal excitability. It has been increasingly recognized that spinal cord glial cells such as microglia and astrocytes play a critical role in the induction and maintenance of neuropathic pain by releasing powerful neuromodulators such as proinflammatory cytokines and chemokines. Recent evidence identifies chemokines as new players in pain control (Gao & Ji, 2010). Targeting glial activation is a clinically promising method for the treatment of neuropathic pain (Mika, 2008). Glial cells represent 70% of the cells in the central nervous system (CNS), and microglia represent 5–10% of glial cells under normal conditions. Microglia cells have a small soma bearing thin and branched processes under normal conditions. They are the first non-neural cells to respond to a CNS perturbation such as nerve injury or chronic opioid administration (Raghavendra et al., 2002; Tanga et al., 2004). They play a crucial role in the maintenance of neuronal homeostasis in the central nervous system. It seems that microglia might be responsible for the initiation of neuropathic pain states (Marchand et al., 2005), and their production of immune factors is believed to play an important role in nociceptive transmission (Colburn, 1999; Watkins, et al., 2001). Nerve injury distal to the dorsal root ganglia leads to microglial activation. However, activation after dorsal rhizotomy is much reduced, in keeping with the observation that dorsal rhizotomy leads to less impressive hyperalgesia as compared to spinal nerve lesions involving the identical root (Willis et al., 2006). After activation, microglia cells change morphology from a resting, ramified shape into an active, amoeboid shape (Stoll & Jander, 1999). Activated microglia have dual regulatory functions in the maintenance and facilitation of tissue homeostasis in the CNS. They remove dead cells or dangerous debris by releasing toxic factors and phagocytosis, but they also repair injured cells by releasing neurotrophic factors (Quattrini et al., 1996). The exact mechanism of microglia cell activation may involve the release of algesic factors such as ATP, glutamate and nitric oxide from injured or hyperactive neurons (Inoue, 2006; Watkins & Maier, 2005). Microglial activation can alter the activity of opioid systems, and neuropathic pain is

characterized by resistance to morphine. The major proinflammatory cytokines (IL-1, IL-6 and TNF-α) oppose acute opioid analgesia. Their effects may interact because suppressing the action of any single cytokine unmasks continuing analgesia (Hutchinson et al., 2008). The spinal cellular source of the proinflammatory signal was also of interest. Studies of normal spinal cord document the basal expression of proinflammatory cytokines in glia and to some extent in neurons, suggesting that under acute conditions, both glial and neural stores may be available to oppose opioid analgesia. The potentiation of acute morphine analgesia by minocycline suggests that microglia may prove to be a significant source of mediators that oppose opioid analgesia (Fu et al., 2006). Nevertheless, later reports that studied hyperalgesia in the spinal cord revealed that cytokines were indeed being secreted in a chronic pain state (Wieseler-Frank et al., 2005). These proinflammatory cytokines, specifically tumor necrosis factor (KB-TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), are proteins that are vital in immune-to-brain communication (Sweitzer et al., 2002; Watkins & Maier, 2005; Watkins & Milligan, 2001). It has been found that propentofylline, pentoxifylline, fluorocitrate, ibudilast and minocycline decrease microglial and astroglial activation and inhibit proinflammatory cytokines, thereby suppressing the development of neuropathic pain (Mika, 2008; Raghavendra et al., 2004). Interathecal delivery of the antibiotic minocycline, an inhibitor of microglial activation, attenuates neuropathic pain (Raghavendra et al., 2003). Some glial inhibitors, which are safe and clinically well tolerated, are potentially useful agents for the treatment of neuropathic pain and for the prevention of tolerance to morphine analgesia. Evidence exists for a role of the ATP receptors P2X4 and/or P2X7, both of which are expressed on microglia. The chemokine fractalkine may also be involved, as blockade of its receptor, CX3CR1, attenuates hyperalgesia in neuropathic pain models (Milligan et al., 2005).

Pentoxifylline is a non-specific cytokine inhibitor and an inhibitor of phosphodiesterase that can inhibit the synthesis of TNF-*a*, IL-1*β* and IL-6. Some studies have demonstrated that pentoxifylline influences the development of neuropathic pain behavior in rats and mice (J. Liu et al., 2007; Mika et al., 2007). The local injection of pentoxifylline reduced inflammatory pain by decreasing TNF-*a* (Dorazil-Dudzik et al., 2004). When injected in a preemptive analgesia schema, it reduces postoperative pain in patients (Dobrogowski et al., 2005).The anti-nociceptive effects of pentoxifylline are correlated with a reduced production of TNF-*a*, IL-1*β*, and IL-6 through the inhibition of nuclear factor-*K*B as well as the stimulation of IL-10 expression in the spinal cord and brain (Vale et al., 2004). However, the therapeutic effects of pentoxifylline on developed neuropathic pain remain to be determined by future studies.

Minocycline, a semi-synthetic second-generation tetracycline with adequate penetration into the brain and cerebrospinal fluid (Colovic & Caccia, 2003), has emerged as a potent inhibitor of microglial activation and proliferation, without any known direct action on astrocytes or neurons (Tikka et al., 2001). The effects of minocycline are mediated by microglial cells and are distinct from the antimicrobial actions of this drug (He et al., 2001). The administration of minocycline either systemically or intrathecally attenuated hyperalgesia in rat models of neuropathy. The effect is associated with an inhibition of spinal microglial activation and the attenuated expression of proinflammatory cytokines (Ledeboer et al., 2005; Mika et al., 2007). It is emphasized that minocycline attenuated the development of behavioral hypersensitivity in the rat model of neuropathic pain when the inhibitor was injected preemptively (Raghavendra et al., 2003). However, the analgesic effects of minocycline in a rat model of neuropathic pain result from attenuated expression of IL-1*β*, IL-6, TNF-*a*, IL-1*β*-converting enzyme, TNF-α-converting enzyme, an IL-1β receptor antagonist and IL-10 in the lumbar dorsal spinal cord.

Activation of microglial cells occurs in the dorsal horn, and this activation may play a vital role in initiating central sensitization. The role of this activation in ongoing neuropathic pain is less clear. The sensation of pain begins with a simple thesis: nociceptors encode information about noxious stimuli and propagate these messages to the CNS; then, pain is felt. In the case of neuropathic pain, however, we see that a complex biology is at play (Campbell et al., 2006). Recent studies indicate that preemptive treatment with glial inhibitors seems to be more effective than their administration after glial cells have already been activated (Raghavendra et al., 2003). We observed similar results with minocycline. Preemptive treatment with minocycline in our study attenuated hyperalgesia and allodynia in CCI. We observed that minocycline, which was reported to have a neuroprotective effect in some neurodegenerative diseases, reversed hyperalgesia and allodynia due to sciatic nerve ligation and inhibited interleukin-6 production (see Fig. 5).

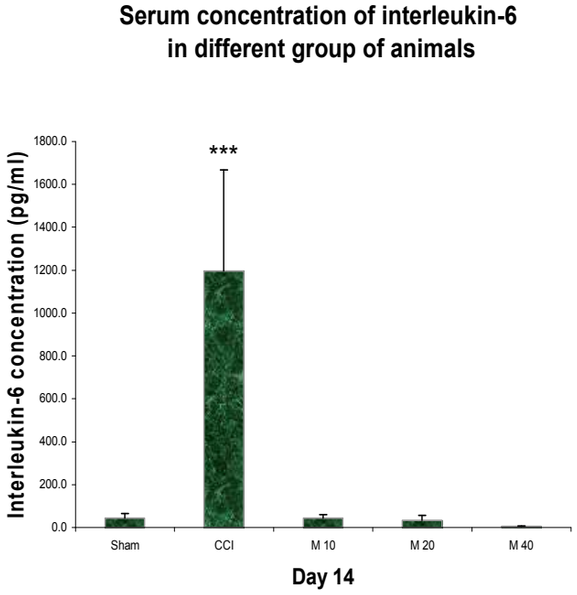

Fig. 5. Serum concentration of interleukin-6 in CCI saline-treated, sham-operated and CCI minocycline – treated rats on day 14 post- ligation. Data are presented as mean ±SEM of 6 rats in each group. *** $P < 0.001$ indicate a statistically significant difference when compared to CCI saline - treated rats. M10 = minocycline 10 mg/kg, M20 = minocycline 20 mg/kg, M40 = minocycline 40 mg/kg

It seems that minocycline could have an anti-inflammatory and analgesic effect in some chronic pain states (Zanjani et al., 2006). As chronic morphine activates spinal cord glia, glial activation causes morphine tolerance, and both neuropathic pain and morphine tolerance share the same mechanism (Mayer et al., 1999), we sought to understand the role of microglia in the morphine tolerance observed following the administration of glial inhibitors (pentoxifylline and minocycline) *after* glial cells have already been activated. We administered Pentoxifylline and Minocyclines i.p. after chronic opioid treatment in a CCI model. Interestingly, the results demonstrated the attenuation of hyperalgesia and allodynia. This suggests a glial contribution in changing nociceptive processing, which could be blocked by glial inhibitor agents and enhance the analgesic effect of morphine. Some studies have suggested that glial-derived fractalkine is an endogenous regulator of morphine analgesia. It is

involved in increasing pain sensitivity, which occurs after chronic opioid treatment (Verge et al., 2004). Several other possible mechanisms involving activated glia have been suggested, such as morphine-induced p^{38} MAPK activation in microglia, changes in the glial regulation of glutamatergic NMDA receptors and the release of excitatory amino acids, prostaglandins and dynorphin (Svensson et al., 2006). Recent works have indicated that microglia are responsible for opioid tolerance and dependence (Guo & Schluesener, 2007). It is not clear how opioids activate microglia in the spinal cord, but previous work by Hutchinson's team suggested the possible involvement of toll-like receptor 4 (TLR4). The results indicate a role for the pattern recognition receptor TLR4 in microglial activation, which provides a link between central sensitization and innate immune responses. Levels of spinal mRNA for TLR4 are increased after L5 SNL (Tanga et al, 2005). TLR4 is involved in neuropathic pain and the dysregulation of opioid actions (Hutchinson et al, 2008). Notably, morphine upregulates TLR4 expression in microglia (Hutchinson et al., 2007). The neuropathic pain arising from CCI is created in part via activation of TLR4, which contributes to microglial activation. These data suggest that TLR4 may prove to be a target worth exploring to improve clinical pain control (Hutchinson et al., 2008).

5. Conclusion

These findings suggest that the analgesic efficacy of opioid is reduced by glial activation, and the release of proinflammatory cytokines may have implications for the treatment of pain. Blocking agents may improve the effectiveness of morphine. Blocking glial activation and the subsequent release of proinflammatory cytokines may minimize the development of opiate tolerance, providing more effective treatment for chronic pain, which is particularly advantageous for the treatment of neuropathic pain.

6. Acknowledgement

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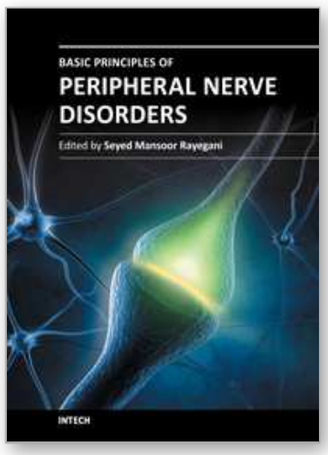

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Peripheral nerve disorders are comprising one of the major clinical topics in neuromusculoskeletal disorders. Sharp nerve injuries, chronic entrapment syndromes, and peripheral neuropathic processes can be classified in this common medical topic. Different aspects of these disorders including anatomy, physiology, pathophysiology, injury mechanisms, and different diagnostic and management methods need to be addressed when discussing this topic. The goal of preparing this book was to gather such pertinent chapters to cover these aspects.

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