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Intrathecal Studies on Animal Pain Models

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1. Introduction

Spinal and epidural anesthesia have been widely used in clinical settings for the management of peri-operative, neuropathic and cancer pain (Dureja et al., 2010; Hong, 2010; Mercadante, 1999). They provide another route for the analgesic administration in addition to oral or systemic absorption. Since the pain pathway initiate with primary and secondary neurons located in dorsal root ganglion and spinal cord, respectively, the ***intrathecal*** (spinal) route may provide an effective alternative for less drug dosage and fewer side effects, compared with systemic administration.

In recent decades, many animal pain models have been developed to explore the possible mechanisms involved in the pathogenesis of clinically relevant pain statuses, such as postoperative (Brennan et al., 1996), neuropathic (Kim & Chung, 1992), inflammatory (Wheeler-Aceto et al., 1990) and cancer pain (Clohisy & Mantyh, 2003). These studies not only help to extent our understanding on pain mechanisms but also provide novel promising agents or targets for the management of different pain situations (Mogil et al., 2010). In this chapter, we present various animal pain models, emphasizing on *intrathecal* studies, and potential therapeutic molecular targets and analgesics found in latest years. In addition, the related neurotoxicity studies and morphine-induced tolerance will be mentioned.

2. Intrathecal animal pain studies

The first mentioned *intrathecal* study using rat animal model was reported by Yaksh, beginning with the study of *intrathecal* morphine (Yaksh et al., 1977). For *intrathecal* drug administration, a polyethylene catheter is inserted *intrathecally* in rats during inhalation anesthesia (LoPachin et al., 1981). The catheter is passed caudally from the cisterna magnum to the level of lumbar enlargement. Since the development of *intrathecal* catheterization, lots of studies explored the pharmacology and pain pathways using *intrathecal* space as a route of drug administration, either in basic researches or clinical studies. The *intrathecal* studies on various pain models provide a lot of promising analgesics for the management of different pain statuses.

2.1 Postoperative pain model

The postoperative or incisional pain model was proposed by Brennan in 1996 (Brennan et al., 1996). A 1-cm longitudinal incision is made through skin, fascia and muscle of the plantar aspect of the hindpaw in anesthetized rats. The lesion produced reliable and

quantifiable mechanical allodynia and thermal hyperalgesia around the wound and spontaneous nociceptive behaviors for about one week, which mimics the clinical course of postoperative pain. Selective denervations of the rat hindpaw prior to foot incision reveal both the sural and tibial nerves are responsible for the nociception transmission from the incision. This model helps to better understand mechanisms of sensitization caused by surgery and provide promising therapeutics for postoperative pain management (Kang & Brennan, 2009).

2.2 Inflammatory formalin pain model

The formalin test involves subcutaneous injection of 5% formaldehyde (50 μl) at the plantar surface of the rat hindpaw, using a 27-gauge needle. After injection, the rat displays characteristic nociceptive behaviors, flinching, shaking, biting and licking of the injected paw. Two phases of nociceptive behaviors are observed after formalin injection as described previously (Abbott et al., 1995). Phase 1 is initiated within seconds after injection and it lasts for about 5–10min. After several minutes quiescent, a second phase of flinching occurs and peaks at 25–35 min after injection.

The formalin-induced nociceptive response in rats is believed to be an inflammatory pain and involves central sensitization in the spinal cord (Abbott et al., 1995). The hindpaw injection of formalin induces tissue injury leading to acute (phase 1) and facilitated (phase 2) states of pain. The phase 2 response is believed to be a persistent input-induced nociceptive behavior mediated through central sensitization (Coderre & Melzack, 1992). LTP of C-fiber-evoked field potentials in the spinal superficial dorsal horn has been reported in the formalin-injected rats (Sandkuhler & Liu, 1998). *Intrathecal* injection of T-type Ca^{2+} channel blockers (mibefradil and Ni^{2+}) has been reported to attenuate formalin-induced pain behaviours, either phase 1 or 2, indicating the important role of T-type Ca^{2+} channel in the spinal central sensitization (Cheng et al., 2007). Other chemical irritants, such as complete Freund's adjuvant (CFA), carrageenan or capsaicin, could also be used to be injected subcutaneously into the plantar surface of rat hindpaw to induce pain behaviors (Duarte et al., 2011; Thorpe et al., 2011; Yu et al., 2011).

2.3 Nerve injury-induced neuropathic pain model

Nerve injuries due to trauma, chemotherapy, diabetic mellitus or tumor invasion may induce neuropathic pain, which is usually refractory to conventional analgesic agents, including opioids and non-steroid anti-inflammatory agents. For the past decades, several animal models have been developed to mimic the clinical conditions and explore the possible mechanisms underlying neuropathic pain. Among these neuropathic pain models, nerve injury-induced neuropathic pain (NINP) models, such as spinal nerve ligation, spared nerve injury and chronic constriction injury, are most often studied (Ji & Strichartz, 2004).

Several targets have been proposed to be involved in the pathogenesis of NINP, such as NMDA receptors (Szekely et al., 2002) and ion channels (Rogers et al., 2006). Recently, new molecules have been emerging as promising targets for the treatment of NINP, such as purinergic receptors (Donnelly-Roberts et al., 2008), cannabinoid receptors (Lynch & Campbell, 2011), transient receptor potential V1 (TRPV1) receptor (Facer et al., 2007), chemokine receptors (White et al., 2007), acid-sensing ion channel (Mazzuca et al., 2007; Poirot et al., 2006), annexin 2 light chain p11 (Foulkes et al., 2006) and matrix metalloproteinase (Kawasaki et al., 2008a).

The L5/6 spinal nerve ligation neuropathic pain model was reported by Kim and Chung in 1992 (Kim & Chung, 1992). This model involves a tight ligation of L5 and L6 spinal nerves of animals under anesthesia. The nociceptive behavioral assessments also consist of von Frey hair test (Chaplan et al., 1994) and radiant heat test (Hargreaves et al., 1988) for the quantification of mechanical allodynia and thermal hyperalgesia, respectively, on the affected hindpaw. Compared with postoperative pain model and formalin inflammatory pain model, this model induced chronic nociceptive behaviors lasting for several weeks. This chronic pain model helps to reveal the possible mechanisms involved in the development and maintenance of nerve injury-induced pain, either the neuronal components or glial components.
Spared nerve injury pain model was developed by Decosterd and Woolf in 2000 (Decosterd & Woolf, 2000). An adaptation of spared nerve injury surgery was later developed in the mouse (Bourquin et al., 2006). This model involves a lesion of two of the three terminal branches of the sciatic nerve (tibial and common peroneal nerves) leaving the remaining sural nerve intact. The spared nerve injury model differs from the L5/6 spinal ligation pain model in that the co-mingling of distal intact axons with degenerating axons is restricted, and it permits behavioral testing of the non-injured skin territories adjacent to the denervated areas. The mechanical (von Frey and pinprick) sensitivity and thermal (hot and cold) responsiveness is increased in the ipsilateral sural territory.

2.4 Cancer pain model

Cancer pain significantly affects the diagnosis, quality of life and survival of patients with cancer. Tumor growth may produce inflammation in tumor bearing tissues, which will release inflammatory mediators to stimulate nociceptors. Tumor growth may also compress the peripheral nerves in tumor bearing tissues, inducing nerve injury. Therefore, cancer pain is likely to share mechanisms of inflammatory pain and neuropathic pain, although this pain may have distinct mechanisms (Ghilardi et al., 2010). Whether inflammation or nerve injury dominates during tumor growth may depend on the interactions between tumor cells and surrounding tissues (Cain et al., 2001).
In recent years, several laboratories have developed cancer pain models by inoculation of tumor cells into a hindpaw of mouse (Constantin et al., 2008). Animals inoculated with melanoma cells into the plantar of the hindpaw show marked pain hypersensitivity and peripheral nerve degeneration (Gao et al., 2009a). We have used this melanoma cancer pain model to test the anti-tumor growth and analgesic effects of JNK inhibitor (Gao et al., 2009a). Other cancer pain models include breast, prostate and bone cancer pain models (Bloom et al., 2011; Ghilardi et al., 2010; Jimenez-Andrade et al., 2010). These cancer pain models may possess different pathophysiologies for pain induction. For example, intramedullary injection of breast cancer cells could induce periosteal sprouting of CGRP(+) sensory fibers and pain, both of which could be blocked by anti-nerve growth factor (NGF) (Bloom et al., 2011). Inhibitor of NGF receptor TrkA has been shown to attenuate bone cancer pain and tumor-induced sprouting of sensory nerve fibers (Ghilardi et al., 2010). Similarly, NGF also plays an important role in the induction of prostate cancer-induced sensory fiber sprouting and bone pain (Jimenez-Andrade et al., 2010).

3. Potential therapeutic molecular targets for pain management

Voltage-gated ion channels and glial cells have all been found to be promising therapeutic targets for pain management. Voltage-gated ion channels are a class of transmembrane ion

channels that are activated by changes in membrane potential; these types of ion channels are especially critical in excitable cells, including neuronal, cardiac and skeletal cells (Szu-Yu Ho & Rasband, 2011), or even cancer cell migration (Cuddapah & Sontheimer, 2011). Since voltage-gated ion channels are important for neuronal excitability, conduction and transmission, they have long been the targets of interest in the field of pain research.

3.1 Voltage-gated Na^+ channels

Voltage-gated Na^+ channels are essential for the initiation of action potentials which are crucial for nerve conduction. Their activation and inactivation are strongly gated by the membrane potential of neuronal cells, but their properties can also be modulated by G-proteins or protein kinases (Kakimura et al., 2010). Voltage-gated Na^+ channels are constituted by the pore-forming α−subunit and auxiliary β-subunits. Up to now, nine α−subunits (Nav1.1-1.9) and four β-subunits (β1-4) have been identified (Catterall et al., 2005). The Na^+ channels can be either sensitive (Nav1.1, Nav1.2, Nav1.3, Nav1.6) or resistant (Nav1.4, Nav1.5, Nav1.7, Nav1.8, Nav1.9) to tetrodotoxin (TTX), a toxin found in the liver of puffer fish. Neuronal cells contain most of the Na^+ channel subtypes but Nav1.4 and Nav1.5, respectively, are mainly in skeletal and cardiac muscles (Jarecki et al., 2010). Nav1.1, Nav1.3, Nav1.6, Nav1.7, Nav1.8 and Nav1.9 have been found in adult dorsal root ganglion (DRG) sensory neurons and these isoforms can be important for the firing properties of sensory neurons (Hunanyan et al., 2011). After spared nerve injury in rats, altered neuronal electrogenesis in DRG neurons, such as accelerated re-priming of TTX-sensitive Na^+ currents, was observed and may be due to a complex regulation of voltage-gated Na^+ channels (Berta et al., 2008; Wang et al., 2011).

Several lines of evidence indicate that Nav1.7, and Nav1.8 are involved in pain regulation, especially NINP (Lampert et al., 2010). Nav1.7 and Nav1.8 channels have been shown to accumulate in neuroma endings in humans with neuropathic pain (Kretschmer et al., 2002). This accumulation may be due to a loss of myelin inhibition or target determined transfer of Na^+ channels (Aurilio et al., 2008). Loss of Nav1.7 function may lead to complete insensitivity to pain in humans (Cox et al., 2010). Compounds possessing Nav1.7 blocking effects have been reported to reverse nerve injury-induced mechanical allodynia (Tyagarajan et al., 2010). Nav1.8 is increased in sciatic nerve after nerve injury and *intrathecal* antisense oligoneucleotide directed against Nav1.8 is effective in neuropathic pain models (Joshi et al., 2006). A μΩ-conotoxin MrVIB was found to be a preferential Nav1.8 blocker and could reverse partial sciatic nerve ligation-induced mechanical allodynia and thermal hyperalgesia, when given *intrathecally* (Ekberg et al., 2006). Intraperitoneal administration of A-803467, a selective Nav1.8 blocker, has been reported to attenuate nerve injury-induced mechanical allodynia (Jarvis et al., 2007). Nonetheless, Nassar et al. found that mice lacking Nav1.7 and Nav1.8 still develop neuropathic pain after spinal nerve ligation (Nassar et al., 2005). Recent studies also revealed a role of Nav1.3 (Mo et al., 2011) and Nav1.9 (Leo et al., 2010) in the development of neuropathic pain. For normal nerve conduction, Nav1.1 family is involved (Catterall et al., 2010). Therefore, the selective Nav1.3, Nav1.7, Nav1.8 and Nav1.9 channel blockers will have clinical potential in the treatment of neuropathic pain since they do not affect normal neuronal conduction.

Besides the pore-forming α-subunit, β2 subunit was reported to be up-regulated in injured and non-injured sensory neurons after peripheral nerve injuries (Pertin et al., 2005) and the development of spared nerve injury-induced mechanical allodynia is attenuated in β2-null mice (Lopez-Santiago et al., 2006), suggesting the important role of β2 subunit in NINP. The

involvement of Na^+ channel β2 subunit in neuropathic and inflammatory pain has been extensively reviewed (Brackenbury & Isom, 2008).

In addition to changes in protein expression, phosphorylation-induce change of conductance or gating property of Na^+ channels may also lead to enhanced neuronal excitability and NINP (Aurilio et al., 2008). The activation of presynaptic delta-opioid receptor by enkephalin has been reported to prevent the increase in neuronal $Na_V1.7$ in DRG through inhibition of PKC and p38 (Chattopadhyay et al., 2008). Tumor necrosis factor-α (TNF-α), a pro-inflammatory cytokine involved in NINP formation (Schafers et al., 2003), was found to enhance TTX-resistant Na^+ currents in isolated DRG neurons *via* a TNF receptor 1- and p38-dependent mechanism (Jin & Gereau, 2006). The Na^+ currents of isolated sensory neurons can be enhanced by protein kinase A and protein kinase C (Gold et al., 1998; Mo et al., 2011), both of which are involved in NINP (Gao et al., 2005; Song et al., 2006). Phosphorylation of TTX-S and TTX-R sodium channels involving both serine/threonine and tyrosine sites has been reported to contribute to painful diabetic neuropathy (Hong et al., 2004). Further studies are required to reveal the exact role of Na^+ channel phosphorylation in the pathogenesis of NINP.

3.2 Voltage-gated Ca^{2+} channels

Voltage-gated Ca^{2+} channels are involved in neuron excitability, neurotransmitter release, synaptic transmission and gene expression (Dolmetsch et al., 2001). Ca^{2+} channels are constituted by the pore-forming α-subunit and auxiliary subunits, β- and α2δ subunits. They are classified into Cav1, Cav2 and Cav3 families based on their structure homology, but are categorized as L- (Cav1.1, Cav1.2 and Cav1.3), P/Q- (Cav2.1), N- (Cav2.2), R- (Cav2.3), and T- (Cav3.1, Cav3.2 and Cav3.3) type based on their sensitivity to specific blockers, activation/inactivation characteristics and current conductance (Catterall et al., 2002). Various Ca^{2+} channel blockers have been tested in the postoperative, inflammatory and neuropathic pain models (Cheng et al., 2007). The potential use of Ca^{2+} channel blockers for neuropathic pain treatment and roles of Ca^{2+} channels in ascending pain pathway have been well reviewed (Yaksh, 2006; Zamponi et al., 2009).

3.2.1 N-type Ca^{2+} channels

N-type Ca^{2+} channels are distributed in the dorsal root ganglia and spinal dorsal horn. It is generally believed that N-type Ca^{2+} channels are involved in the neurotransmitter release of spinal dorsal horn (Smith et al., 2002). Substance P, one of the neurotransmitter of primary sensory neurons, has been found to be mostly co-localized with N-type Ca^{2+} channels in the spinal dorsal horn (Westenbroek et al., 1998).

Several lines of evidence indicate that N-type Ca^{2+} channels play an important role in NINP. Mice lacking N-type Ca^{2+} channels exhibit reduced signs of neuropathic pain after spinal nerve ligation (Saegusa et al., 2001). *Intrathecal* small interference RNA knockdown of N-type Ca^{2+} channels reversed sciatic nerve constriction-induced tactile allodynia and thermal hyperalgesia (Altier et al., 2007).

New non-peptide compounds with N-type Ca^{2+} channel blocking property have been recently developed in pharmaceutical companies for the treatment of neuropathic pain (Knutsen et al., 2007). A highly reversible ω-conotoxin FVIA, a potent N-type Ca2+ channel blocker with fewer side effects, was found to possess analgesic effect in the formalin test and neuropathic pain models (Lee et al., 2010). Recent findings suggest that diminished Ca^{2+}

influx through N-type Ca^{2+} channels may contribute to sensory neuron dysfunction and pain after nerve injury (McCallum et al., 2011).

3.2.2 T-type Ca^{2+} channels

T-type Ca^{2+} channels are low-voltage activated Ca^{2+} channels. It can serve as an initiator to trigger the opening of high-voltage activated ion channels. In spinal dorsal horn, it may be involved in spontaneous neurotransmitter release and long term potentiation (LTP) (Ikeda et al., 2003). LTP, a form of synaptic plasticity, in the spinal dorsal horn is believed to contribute to the central sensitization of pain transmission (Ji et al., 2003), a wiring phenomenon usually observed in neuropathic pain (Romanelli & Esposito, 2004).

Among three subtypes of T-type Ca^{2+} channels, $Ca_V3.1$, $Ca_V3.2$ and $Ca_V3.3$, $Ca_V3.2$ mRNAs are mostly abundant in the spinal dorsal horn and are limited to the superficial layers (Talley et al., 1999). *Intrathecal* injection of the antisense oligonucleotide targeted to the α1-subunit of $Ca_V3.2$, but not $Ca_V3.3$ or $Ca_V3.1$, produced analgesic effect in both acute and neuropathic pain states (Bourinet et al., 2005), suggesting that $Ca_V3.2$ is much more involved in spinal nociceptive pathway than $Ca_V3.1$ and $Ca_V3.3$.

Subtype-specific blockers of T-type Ca^{2+} channels are not commercially available. However, mibefradil, a non-selective T-type Ca^{2+} channel blocker, when given systemically or intraplantarly, can reverse mechanical allodynia and thermal hyperalgesia induced by L5/6 spinal nerve ligation (Dogrul et al., 2003). Our recent work on *intrathecal* T-type Ca^{2+} channel blockers (mibefradil or Ni^{2+}) revealed their effectiveness in the second phase of formalin test (Cheng et al., 2007). In these years, small molecules with potent blocking effect on T-type Ca^{2+} channels, such as KYS05090, have been developed (Doddareddy et al., 2007; Seo et al., 2007). Recent studies revealed spinal T-type Ca^{2+} (Cav3.2 and Cav3.3 but not Cav3.1) channels may play an important role in the pathogenesis of chronic compression of DRG-induced neuropathic pain (Wen et al., 2010). In addition, Cav3.2-dependent activation of extracellular signal-regulated kinase in the anterior nucleus of paraventricular thalamus was found to contribute to the development of acid-induced chronic mechanical hyperalgesia (Chen et al., 2010).

3.2.3 P/Q- and R-type Ca^{2+} channels

Compared with N-type Ca^{2+} channel, it seems P/Q type is much less important in NINP. Only one study using transgenic mice revealed its involvement in chronic constriction injury-induced mechanical allodynia (Luvisetto et al., 2006). The hypoalgesic behaviors of P/Q-type Ca^{2+} channel mutant mouse suggest P/Q-type Ca^{2+} channel has a pro-nociceptive role (Fukumoto et al., 2009). As for R-type Ca^{2+} channel, its blocker SNX-482 could inhibit C-fiber and Aδ-fiber-mediated neuronal responses after L5/6 spinal nerve ligation, when administered ***intrathecally*** (Matthews et al., 2007). Moreover, the responses to innocuous mechanical and thermal stimuli were more sensitive to SNX-482 in nerve-ligated rats than control animals (Matthews et al., 2007). These findings suggest spinal R-type Ca^{2+} channel could be a potential therapeutic target for NINP. Blocking the R-type Ca^{2+} channel has been reported to enhance morphine analgesia and reduce morphine-induced tolerance (Yokoyama et al., 2004).

3.2.4 α2δ subunit of Ca^{2+} channels

α2δ subunit is one of the modulatory subunits of Ca^{2+} channels, which could modulate the membrane targeting and conductance of α1 subunit of Ca^{2+} channel (Felix, 1999). Four

isoforms (α2δ-1~4) were identified (Qin et al., 2002). The α2δ-1 subunit is up-regulated in dorsal root ganglion and dorsal spinal cord after peripheral nerve injury (Li et al., 2004). *Intrathecal* injection of α2δ-1 antisense oligonucleotide could block this up-regulation in spinal dorsal horn and diminish injury-induced tactile allodynia (Li et al., 2004). Over expression of α2δ-1 in spinal dorsal horn neurons could enhance Ca^{2+} currents, exaggerate dorsal horn neuronal responses to external stimuli and increase the nociceptive responses in neuropathic pain models (Li et al., 2006).

α2δ subunit is the specific binding site in the central nervous system of gabapentin and its analogue pregabalin (Klugbauer et al., 2003), both of which have been shown to be effective in preclinical and clinical studies of neuropathic pain (Cheng & Chiou, 2006). Gabapentin was first designed as a chemical analogue of γ-aminobutyric acid, an inhibitory neurotransmitter, to treat spasticity and was later found to have anticonvulsant and antinociceptive activities in various seizure and pain models. A point mutation of the arginine 217 of α2δ-1 subunit, which is critical for gabapentin binding (Wang et al., 1999), was found to cause a loss of gabapentin-induced analgesia (Field et al., 2006). Recently, chronic *intrathecal* infusion of gabapentin was found to prevent nerve ligation-induced mechanical allodynia and thermal hyperalgesia without causing obvious neuropathological changes in spinal cord and cauda equine (Chu et al., 2011).

Gabapentin has been found to attenuate morphine-induced tolerance (Lin et al., 2005) and this finding may encourage the combined use of gabapentin with morphine in the treatment of neuropathic pain. It is interesting to note that α2δ-1 subunit was identified to be a receptor involved in excitatory synapse formation and gabapentin may act by blocking new synapse formation (Eroglu et al., 2009).

3.3 Voltage-gated K^+ channels

The opening of K^+ channel may lead to cell repolarization and make the neuron less excitable and down-regulation of K^+ channel in nociceptive neurons may decrease pain threshold. There are 12 different families of voltage-gated K^+ channels (Kv1 to Kv12) and all Kv channels are tetramers of α subunits (Ocana et al., 2004). A-type K^+ channel (A-channels) is a group of Kv channels that are activated transiently and inactivated rapidly. Five A-channels Kv1.4, Kv3.4, Kv4.1, Kv4.2, and Kv4.3 were found in mammals (Chien et al., 2007; Mienville et al., 1999; Serodio et al., 1996). Except for Kv3.4 with high-voltage activation, the other four are activated at low voltages (Coetzee et al., 1999). Kv1.4 proteins in the somata of DRG neurons are greatly reduced in the L5/6 spinal nerve ligation pain model (Rasband et al., 2001). The expression of Kv1.4 is also reduced in the small-/medium sized (Aδ-/C-) trigeminal ganglion neurons after temporomandibular joint inflammation (Takeda et al., 2008). Gene expressions of Kv1.2, Kv1.4, and Kv4.2 are down-regulated in the DRG following sciatic nerve transection (Park et al., 2003). Recent study also revealed the Kv1.2 expression is decreased in DRG neurons from rats with irritable bowel syndrome, a visceral pain model (Luo et al., 2011). The expression of Kv3.4 and Kv4.3 in DRG neurons were found to be also decreased after spinal nerve ligation and ***intrathecal*** injections of antisense oligodeoxynucleotides against Kv3.4 or Kv4.3 in naïve rats could induce mechanical hypersensitivity (Chien et al., 2007). New compounds with A-type K^+ channel opening activity, such as KW-7158 (Sculptoreanu et al., 2004), may prove to be effective for the treatment of NINP.

The Kv7 channel (also known as KCNQ) opener retigabine has been reported to be effective in sciatic chronic constrict injury (Blackburn-Munro & Jensen, 2003) and L5 spinal nerve

ligation (Dost et al., 2004) pain models. It is important to note that the antiallodynic effect of retigabine could be inhibited by linopirdine, a selective KCNQ channel blocker, indicating the involvement of KCNQ channel opening in the effect of retigabine (Dost et al., 2004). When directly applied to the spinal cord, retigabine inhibited the Aδ and C fiber-mediated response of dorsal horn neurons to noxious stimuli (Passmore et al., 2003). Recently, the selective cyclooxygenase-2 (COX-2) inhibitor celecoxib was found to enhance Kv7.2-7.4, Kv7.2/7.3 and Kv7.3/7.5 currents expressed in HEK 293 cells, providing a novel mechanism for its antinociceptive effect (Du et al., 2011b). Based on these reports, further efforts may be needed to develop subtype-specific K^+ channel openers and to test their effects in NINP models.

Just as voltage-gated Na^+ channels, K^+ channels could also be modulated by phosphorylation (Sergeant et al., 2005). The Kv4.2 current of spinal dorsal horn neurons could be inhibited by extracellular signal-regulated kinase (ERK)-induced phosphorylation (Hu et al., 2003). Genetic elimination of Kv4.2 increases excitability of dorsal horn neurons and sensitivity to tactile and thermal stimuli (Hu et al., 2006). This modulation of Kv4.2 by ERK may underlie the induction of central sensitization, a cellular mechanism of NINP (Ji et al., 2003). The role of Kv channels in different trigeminal neuropathic and inflammatory pain models was recently reviewed (Takeda et al., 2011).

3.4 Other K^+ channels

In addition to Kv channels, there are other K^+ channels that are important for pain modulation, such as G-protein coupled inwardly rectifying (GIRK or Kir3), ATP-sensitive (K_{ATP} or Kir6), Ca^{2+}-activated (KCa) and two-pore (K_{2P}) K^+ channels (Gutman et al., 2003). Activation of K_{ATP} channels was recently found to antagonize nociceptive behavior and hyper-excitability of DRG neurons from rats (Du et al., 2011a). Following partial sciatic nerve ligation, elevated tyrosine phosphorylation (pY12) of Kir3.1 was observed in the spinal superficial dorsal horn of wild type, but not Kir3.1 knock-out, mice (Ippolito et al., 2005). This phosphorylation may suppress channel conductance and accelerate channel deactivation (Ippolito et al., 2002), leading to enhanced neuronal excitability and could possibly contribute to the genesis of NINP. It is interesting to note that induced expression of Kir2.1 in chronically compressed DRG neurons can effectively suppress the neuronal excitability and, if induced at the beginning of the chronic compression, prevent the development of compression-induced hyperalgesia (Ma et al., 2010).

The TREK-1 channel is a member of mechano-gated K_{2P} family, one of the targets of inhalation anesthetics (Patel et al., 1999). TREK-1 is highly expressed in small sensory neurons and extensively co-localized with TRPV1 (Alloui et al., 2006). Mice with a disrupted TREK-1 gene are more sensitive to painful heat and low threshold mechanical stimuli and display an increased thermal and mechanical hyperalgesia in conditions of inflammation (Alloui et al., 2006). On the other hand, the TREK-1 null mice showed decreased sensitivity to acetone (less cold allodynia) after sciatic nerve ligation (Alloui et al., 2006). The chemotherapy drug oxaliplatin, which induces cold hypersensitivity, could lower the expression of TREK-1 (Descoeur et al., 2011). Future studies are needed to elucidate the role of TREK-1 channels in NINP. Similar as TREK-1, TREK-2 is also a member of the K_{2P} family. TREK-2 provide the major background K^+ conductance in cell body of small to medium-sized DRG neurons (Mathie, 2007), which are the major component of nociceptors. Based on these findings, it is also intriguing to investigate the role of TREK-2 in NINP (Huang & Yu, 2008).

Changes in the expression and function of voltage-gated ion channels in the pain pathway may contribute to the development and maintenance of NINP. Manipulations aiming at voltage-gated ion channels may provide novel strategies for the treatment of NINP. In addition to ion channel modulators, recent studies also reveal the promising roles of glial inhibitors, such as minocycline, and morphine in the management of NINP.

3.5 Microglia and astrocyte activation in nerve injury-induced neuropathic pain

During the last decade, the neuroimmune system, such as spinal glial cells, has been found to be critical for the development and maintenance of nerve injury-induced neuropathic pain (Watkins et al., 2007). Nerve injury not only induces morphological changes of microglia but also biochemical changes to induce pain. Nerve injury results in a up-regulation of P2X4 receptor (Tsuda et al., 2003) and CX3CR1 receptor in spinal cord microglia (Verge et al., 2004; Zhuang et al., 2007). *Intrathecal* blockade of P2X4 and CX3CR1 signaling attenuates NINP (Tsuda et al., 2003; Zhuang et al., 2007). The chemokine receptor CCR2 and the Toll-like recepotor-4 (TLR4) are also important for the formation of neuropathic pain *via* microglial activation (Abbadie et al., 2003; Tanga et al., 2005). Phosphorylation of p38 in microglia via activation of P2X4 receptor could increase the synthesis and release of the neurotrophin BDNF and pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α), all of which could enhance nociceptive transmission in the spinal cord (Coull et al., 2005; Ji & Suter, 2007; Kawasaki et al., 2008b; Wang et al., 2010)

Our study using continuous *intrathecal* infusion of minocycline, a microglia inhibitor, revealed its effectiveness in attenuating the development of nerve injury-induced pain and no obvious spinal neurotoxicity was observed after the infusion (Lin et al., 2007). Other glial modulators, such as AV-411 (Ledeboer et al., 2006) and pentoxifylline (Mika et al., 2007), also possessed analgesic effect in NINP models. In addition to glial activation, compliment activation was recently found to participate in spinal nerve ligation-induced pain (Levin et al., 2008). Similar with gabapentin, minocycline could also attenuate morphine-induced tolerance (Cui et al., 2008) and this made itself a promising drug to be co-administered with morphine in the treatment of neuropathic pain. It is worthwhile to note that the attenuation effect of minocycline on morphine-induced tolerance is associated with inhibition of p38 activation in spinal microglia caused by chronic morphine (Cui et al., 2008).

In contrast to microglia, which is important for the development phase of NINP (Ji & Suter, 2007), astrocytes activation was critical for the maintenance phase of NINP (Zhuang et al., 2006). JNK-induced MCP-1 production and JAK-STAT3 pathway in spinal cord astrocytes was found to contribute to the maintenance of NINP (Gao et al., 2009b; Tsuda et al., 2011). The role of astrocyte activation and kinases involved in glial activation after nerve injury have been well reviewed (Gao & Ji, 2010; Ji et al., 2009).

4. Morphine in nerve injury-induced neuropathic pain

Morphine is the main drug used in pain clinics, especially in cancer pain. Recent animal studies also revealed the effectiveness of morphine in NINP models (Mika et al., 2007; Zhang et al., 2005). However, acute and chronic use of morphine can induce hyperalgesia and analgesia tolerance (Mao et al., 1994), which often lead to increased drug consumption and unwanted side-effects.

4.1 Glial non-opioid/p38 pathway in morphine-induced analgesia and tolerance

Using the tail flick test, Tseng's group has shown that morphine could induce anti-analgesia, which could be prevented by *levo*-, *dextro*naloxone **(a non-opioid ligand)** and p38 inhibitor *via* a glial non-opioid mechanism (Wu et al., 2006a; Wu et al., 2006b; Wu et al., 2005). From the works of Tseng's group, it could be summarized that 1) both *dextro*- and *levo*-morphine and lipopolysaccharide (LPS), a toll-like receptor (TLR)-4 agonist, could induce anti-analgesia, which could be prevented by *dextro*-, *levo*-naloxone and p38 inhibitor; 2) the anti-analgesia-inducing potency is: *dextro*-morphine > *levo*-morphine, and the reversal potency is: *levo*-naloxone > *dextro*-naloxone, which may imply the different binding affinities of *dextro*/*levo*- morphine and naloxone to the putative non-opioid receptor or TLR-4 (Hutchinson et al., 2007).

Inspired by the studies of Hong's group showing naloxone could attenuate LPS-induced microglial activation and neuronal damage (Liu et al., 2000), Watkin's group further tested the possible involvement of the putative nonopioid/TLR-4 pathway in NINP. They found *dextro*-naloxone, *levo*-naltrexone, and LPS-antagonist possess analgesic effects in chronic constriction neuropathic pain model (Hutchinson et al., 2007). Taken together with the role of glial p38 activation in NINP (Jin et al., 2003) and morphine-induced tolerance (Cui et al., 2006), it is possible that the putative glia non-opioid/TLR-4 pathway is important for the development of NINP and morphine-induced tolerance (Cui et al., 2006).

4.2 Intrathecal studies on morphine tolerance

Morphine has long been used *intrathecally* in the management of cancer and non-cancer chronic pain (Plummer et al., 1991; Roberts et al., 2001). However, the long-term use of morphine is associated with severe side-effects and tolerance (Osenbach & Harvey, 2001). Recently, many studies have revealed that *intrathecal* morphine could induce glial activation and neuro-inflammation in the spinal cord (Muscoli et al., 2010; Zhang et al., 2011). Several therapeutic targets have been found, including cytokine receptors, kappa-opioid receptors, N-methyl-D-aspartate receptors, and Toll-like receptors (Hameed et al., 2010; Lewis et al., 2010). Recently, tumor necrosis factor (TNF)-α antagonist etanercept was found to reverse morphine-induced tolerance and block morphine-induced neuroinflammation in the microglia (Shen et al., 2011). *Intrathecal* gabapentin and minocycline could also enhance the antinociceptive effects of morphine and attenuate morphine-induced tolerance (Habibi-Asl et al., 2009; Hutchinson et al., 2008; Lin et al., 2005). These promising agents may be co-administered with *intrathecal* morphine to improve the pain management for cancer patients (Christo & Mazloomdoost, 2008; Mercadante et al., 2004).

5. Intrathecal neurotoxicity studies

For a drug to be tested *intrathecally* in clinical trials, it is imperative to examine its neurotoxic effects first in animals (Bennett et al., 2000; Smith et al., 2008). For instance, *intrathecal* lidocaine has been found to induce neuropathological changes in the spinal cord and cauda equina (Kirihara et al., 2003). Other analgesics, such as adenosine, sufentanil, alfentanil and morphine have all been tested *intrathecally* in animal studies to examine their potential neurotoxicity (Chiari et al., 1999; Sabbe et al., 1994; Westin et al., 2010). Recently, chronic *intrathecal* infusion of minocycline or gabapentin has been reported to cause no grossly neurotoxicity in animal studies (Chu et al., 2011; Lin et al., 2007), supporting the *intrathecal* use of these agents for pain management.

6. Conclusion

Intrathecal space has been a route for spinal anesthesia and analgesics. This space also provides us a way to explore the possible mechanisms involved in pain transmission. Since pain is a major world-wide issue in clinical settings, more and more *intrathecal* animal studies have been undertaken to explore the possible mechanisms involved in the formation of different pain statuses and help to develop promising analgesics to alleviate the suffering of pain patients. These efforts will eventually help to provide better pain managements in clinical settings.

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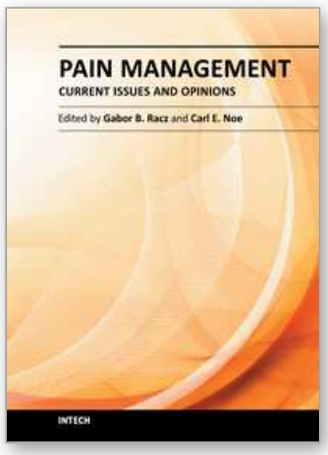

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Pain Management - Current Issues and Opinions is written by international experts who cover a number of topics about current pain management problems, and gives the reader a glimpse into the future of pain treatment. Several chapters report original research, while others summarize clinical information with specific treatment options. The international mix of authors reflects the "casting of a broad net" to recruit authors on the cutting edge of their area of interest. Pain Management - Current Issues and Opinions is a must read for the up-to-date pain clinician.

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