J Anesth (2010) 24:325–327
DOI 10.1007/s00540-010-0918-1

JA SYMPOSIUM

Neuropathic pain and neuron–glia interactions in the spinal cord

Tatsuro Kohno

Received: 14 December 2009 / Published online: 18 March 2010

T. Kohno

Normally, physiological pain is essential to warn us of danger; however, it becomes harmful when it occurs without any evident stimulus. If this pain persists, it can cripple a person's life. Pain is sensed by nociceptive neurons in the periphery of the body, and these send signals to the spinal cord. There, the nociceptive neurons form synaptic contacts with spinal neurons [1]. Some of these spinal neurons project to higher brain structures, while others form local circuits within the spinal cord. Melzack and Wall [2] first emphasized the critical role of the spinal cord, especially the spinal dorsal horn, for "gating" pain, because this is the first set of synapses in the pain pathway and regulates the flow of afferent information to the central nervous system (CNS).

A common kind of chronic pain, called neuropathic pain, often develops when nerves are damaged by surgery, cancer, diabetes, or infection. Unlike acute or physiological pain, these pathological pain syndromes far outlast the initial insult and seem to result from maladaptive changes in both the peripheral and CNS. Unfortunately, neuropathic pain is a debilitating chronic pain and often resistant to currently available treatment such as morphine. Therefore, unraveling the mechanisms of neuropathic pain is essential for the development of new therapeutic drugs, but this remains an unmet clinical need. Neuropathic pain encompasses a wide range of symptoms, including spontaneous (ongoing and paroxysmal) and stimulus-evoked pain. Patients typically experience intense pain in response to mechanical and thermal stimuli that are not normally painful (allodynia) and noxious stimuli evoke exaggerated pain (hyperalgesia). Such a diversity of symptoms suggests that multiple mechanisms underlie the onset and persistence of chronic neuropathic pain hypersensitivity [3].

Increasing evidence from diverse animal models of neuropathic pain suggests that neuropathic pain may involve aberrant excitability of the nervous system, notably in nociceptive and spinal dorsal horn neurons, resulting from multiple functional and anatomical alterations following peripheral nerve injury [3]. Multiple mechanisms seem to be responsible for this injury-induced pain, including aberrant primary afferent activity and heightened dorsal horn neuronal excitability due to central sensitization, structural reorganization of synaptic contacts in the spinal cord (for example, A β fiber sprouting), and loss of tonic and/or phasic inhibition (i.e., spinal disinhibition).

T. Kohno (✉)
Division of Anesthesiology,
Niigata University Graduate School of Medical
and Dental Sciences, 1-757 Asahimachi,
Niigata 951-8510, Japan
e-mail: kohno-t@umin.net

T. Kohno
Pain Mechanism Research Group,
1-757 Asahimachi, Chuo ku, Niigata 951-8510, Japan

Spinal disinhibition after peripheral nerve injury

Excitability in the dorsal horn of the spinal cord is normally checked by endogenous inhibitory control systems. Reduction or elimination of spinal cord inhibition could therefore be expected to augment sensory and motor responses to certain signals from the periphery, and could play a role in generating pathological excitability. We studied synaptic transmission in lamina II neurons of an isolated adult rat spinal cord slice preparation after three types of peripheral nerve injury, complete sciatic nerve transection (SNT), CCI [4], and spared nerve injury (SNI) [5]. Although excitatory transmission remained intact in all three models [6], presynaptic GABA release was markedly reduced in the two partial peripheral nerve injury models, CCI and SNI, but not in the SNT model [7]. Furthermore, we found that partial nerve injury also decreases dorsal horn levels of the 65-kDa GABA-synthesizing enzyme glutamic acid decarboxylase (GAD) ipsilateral to the injury site, and induces neuronal apoptosis. Both of these mechanisms could reduce presynaptic GABA levels and promote a functional loss of GABAergic transmission in the superficial dorsal horn, resulting in expected amplification of the excitatory responses of lamina II neurons to afferent inputs.

Microglial–neuronal signaling in neuropathic pain

To date, basic research on neuropathic pain has tended to focus on injury-induced changes in nociceptive and spinal cord neurons that receive sensory information before it is relayed to the brain. This is the reason why it was believed that neuropathic pain was purely a matter of miscommunication between neurons. However, recent work shows that nerve injury-induced changes also occur in spinal glial cells, the immune cells of the CNS [8–10], and the importance of glial biology in neuropathic pain now seems undeniable.

Glial cells make up over 70% of the total cell population in the CNS and are classified into astrocytes, oligodendrocytes, and microglia. Although glial cells were originally regarded as supporting cells in the CNS, mounting evidence suggests that glial cells actively communicate with neurons and contribute importantly to the development of different types of neurodegenerative diseases. Among the three types of glial cells in the CNS, although oligodendrocytes and astrocytes are found in close apposition to neurons, microglia have attracted more attention, in part because nerve injury-induced microglial changes are much more robust than these changes to oligodendrocytes and astrocytes. Microglia are known as resident macrophages in the CNS, and account for 5–10% of the total population of glial cells. After peripheral nerve injury, microglia in the normal state (traditionally called "resting" microglia) in the spinal dorsal horn are converted to an activated state through a series of cellular and molecular changes [9, 10]. The activated microglia can evoke various cellular responses.

A study by Tsuda and colleagues [11] provided strong evidence that nerve injury activates microglia in the spinal cord and implicates these cells in the resulting neuropathic pain. Since reporting the results of their study, that view now has substantial support. They showed that pharmacological blockade of spinal $P2X_4$ ATP receptors, a molecule with no previously known connection to the field, reversed tactile allodynia caused by peripheral nerve injury without affecting acute pain behaviors in naive animals. After nerve injury, $P2X_4$ receptor expression increased strikingly in the ipsilateral spinal cord, and these receptors were induced in hyperactive microglia, not in neurons. The resulting neuropathic pain was suppressed by inhibiting $P2X_4$ receptors, and was mimicked by infusing microglia bearing activated $P2X_4$ receptors into the spinal cords of normal rats.

Moreover, Coull and colleagues [12] identified a critical link between microglia activated via $P2X_4$ receptors and the altered sensory-neuronal processing that underlies neuropathic pain. They showed that activated microglia disrupt the inhibitory control of dorsal horn lamina I neurons and, crucially, they found that a small neuronal modulating protein called BDNF (brain-derived neurotrophic factor), which is secreted by microglia, mediates this microglial–neuronal signaling [13].

Using a rat model, Coull et al. [14] showed that nerve injury somehow reduces the levels of the potassium chloride co-transporter KCC2 in the membranes of spinal cord neurons, so that the intracellular chloride concentration increases. This shifts the anion reversal potential (E_{anion}) so that it is positive relative to the resting membrane potential. $GABA_A$ receptor activation then results in anions flooding out of the neuron, making the neuron's membrane potential more positive, or depolarized, relative to the resting membrane potential. As a result, the normally inhibitory transmitters GABA and glycine are no longer able to suppress signaling in the lamina I pain pathway.

This group's recent study [12], mentioned above, suggests that $P2X_4$-mediated activation of microglia after nerve injury triggers a mechanism of disinhibition. Because ATP-stimulated microglia are required for the development of allodynia following nerve injury [11], they performed electrophysiological recordings in spinal cord slices taken from rats that had developed allodynia after intrathecal administration of ATP-stimulated microglia. They found that ATP-stimulated microglia positively shifted the E_{anion} in lamina I neurons and caused GABA-induced

depolarization, rather than hyperpolarization, in these neurons. Furthermore, they demonstrated that ATP-evoked activation of $P2X_4$ receptors induces release of BDNF from microglia. They also found that spinally administered BDNF produced allodynia and induced the predicted change in the anion gradient, enabling GABA to depolarize the lamina I neurons rather than inhibit them. These results imply that spinal microglia stimulated via $P2X_4$ receptors after nerve injury secrete BDNF and alter the E_{anion} in spinal lamina I neurons, resulting in neuropathic pain.

In addition to microglia, accumulating evidence has also identified a role for astrocyte-specific molecules in neuropathic pain, and demonstrated a critical role of spinal astrocytes in this type of pain, in particular in the maintenance phase [15, 16]. How these two distinct groups of glial cells interact with each other is now open for investigation. It is expected that increased understanding of the functions of glial molecules will provide us with exciting insights into pain mechanisms and clues to developing new therapeutic agents for the management of neuropathic pain.

References

1. McCleskey EW. New player in pain. Nature. 2003;424:729–30.
2. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150:971–9.
3. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science. 2000;288:1765–9.
4. Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain. 1988;33:87–107.
5. Decosterd I, Woolf CJ. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. Pain. 2000;87:149–58.
6. Kohno T, Moore KA, Baba H, Woolf CJ. Peripheral nerve injury alters excitatory synaptic transmission in lamina II of the rat dorsal horn. J Physiol. 2003;548:131–8.
7. Moore KA, Kohno T, Karchewski LA, Scholz J, Baba H, Woolf CJ. Partial peripheral nerve injury promotes a selective loss of GABAergic inhibition in the superficial dorsal horn of the spinal cord. J Neurosci. 2002;22:6724–31.
8. Watkins LR, Milligan ED, Maier SF. Glial activation: a driving force for pathological pain. Trends Neurosci. 2001;24:450–5.
9. Tsuda M, Inoue K, Salter MW. Neuropathic pain and spinal microglia: a big problem from molecules in "small" glia. Trends Neurosci. 2005;28:101–7.
10. Inoue K, Tsuda M. Microglia and neuropathic pain. Glia. 2009;57:1469–79.
11. Tsuda M, Shigemoto-Mogami Y, Koizumi S, Mizokoshi A, Kohsaka S, Salter MW, Inoue K. P2X4 receptors induced in spinal microglia gate tactile allodynia after nerve injury. Nature. 2003;424:778–83.
12. Coull JA, Beggs S, Boudreau D, Boivin D, Tsuda M, Inoue K, Gravel C, Salter MW, De Koninck Y. BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. Nature. 2005;438:1017–21.
13. Torsney C, MacDermott AB. Neuroscience: a painful factor. Nature. 2005;438:923–5.
14. Coull JA, Boudreau D, Bachand K, Prescott SA, Nault F, Sik A, De Koninck P, De Koninck Y. Trans-synaptic shift in anion gradient in spinal lamina I neurons as a mechanism of neuropathic pain. Nature. 2003;424:938–42.
15. Ji RR, Kawasaki Y, Zhuang ZY, Wen YR, Decosterd I. Possible role of spinal astrocytes in maintaining chronic pain sensitization: review of current evidence with focus on bFGF/JNK pathway. Neuron Glia Biol. 2006;2:259–69.
16. Kawasaki Y, Xu ZZ, Wang X, Park JY, Zhuang ZY, Tan PH, Gao YJ, Roy K, Corfas G, Lo EH, Ji RR. Distinct roles of matrix metalloproteases in the early- and late-phase development of neuropathic pain. Nat Med. 2008;14:331–6.