New findings about mechanisms underlying chronic pain reveal novel therapeutic strategies

May 26 2015

Chronic pain affects hundreds of millions of people worldwide and is a major cause of disability, causing more disability than cancer and heart disease. Canadian researchers, including Michael Salter at SickKids are shedding light on the molecular dynamics of chronic pain. They have uncovered a critical role for a class of cells present in the brain and spinal cord, called microglia, in pain. They have found microglia-to-neuron-signaling to be crucial in the development of pain hypersensitivity after injury, but also for one of the paradoxical effects morphine and other opioids sometimes produce, called hyperalgesia, which is an increase in pain sensitivity. The identification of these key players in the development of chronic pain helps identify important targets for the development of novel therapeutic avenues. Dr. Salter presented his latest results at the 9th Annual Canadian Neuroscience Meeting, on May 26th 2015 in Vancouver, British Columbia.

"We're developing a new understanding of the control of microglia-neuron interactions that may be critical for individualizing pain therapies" said Salter.

Pain is a complex experience. The International Academy for the Study of Pain, IASP defines it as, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." While acute pain can be useful, as a signal that protects us from injury or even death, and inflammatory pain

can protect us during healing, chronic neuropathic pain, which is a disease of the nervous system, is pain that persists after an injury is healed, serves no useful function and is a major cause of disability.

Work done in Dr. Salter's laboratory has helped to gain understanding of the changes in the nervous system, and to uncover the key molecules that form the cascade of events that lead to chronic pain. A class of cells called microglia play a central role in this cascade. Microglia constitute about 10% of the cells of the adult brain and spinal cord (also known as the central nervous system). Initially thought to have simply a role in supporting neurons (the term glia derives from the same root as glue), microglia were later shown to have an important role in the spinal response that follows nerve injury.

"Exciting new discoveries indicate that microglia not only play a critical role in disease states but also in the normal development and functioning of the brain and spinal cord," Salter explained. "We are looking at these cells in an entirely new light."

More recently, microglia have been shown to have a much more active role in the healthy central nervous system, and to be highly active in surveillance and rapid response - microglia monitor and control the activity of neurons in the healthy nervous system. Within the dorsal horn of the spinal cord, the area through which pain signals travel to the brain, microglia block the inhibition of pain transmitting neurons, making transmission of the pain signal more efficient. This can lead to allodynia, which is defined as pain due to a stimulus that does not normally provoke pain.

Nerve injury activates a receptor on microglia, called P2X4, which, in turn causes the release of a molecule called Brain Derived Neurotrophic Factor, or BDNF. BDNF has been shown to have a role in learning in the motor cortex, where its release results in enhanced motor performance.

Dr. Salter proposes that when microglia-derived BDNF facilitates the output of the dorsal horn pain-transmitting network, the result is enhanced pain. When BDNF facilitates this network, it is as if neurons had "learned" pain, and they become more efficient in the transmission of pain signals.

Morphine and other opioids are sometimes prescribed to treat chronic pain when other treatments do not work. While these drugs can be very efficient to relieve pain, some patients develop a paradoxical effect, called hyperalgesia. Paradoxical hyperalgesia is an increase in pain caused by drugs prescribed to alleviate pain. Dr. Salter's research shows that microglia-to-neuron-communication is crucial for the development of this effect.

Research done by Dr. Salter and his colleagues shows how the experience of pain can change the nervous system to make it more sensitive to further painful experiences, to feel pain in response to events that do not cause pain in most people, and how opioids can paradoxically cause more pain. Dr. Salter anticipates that by targeting the signaling pathways identified in these studies new therapeutic strategies for chronic pain will be developed

Provided by Canadian Association for Neuroscience