

Protein Found That May Provide Relief from Neuropathic Pain

December 05, 2007 |

Neuropathic pain is caused by injury to the peripheral nerves in diseases such as HIV/AIDS, shingles, and cancer or in repetitive motion disorders and trauma, and does not respond well to conventional pain-relieving drugs.

Research in rodents by scientists from the University of California, San Diego (UCSD) School of Medicine has provided evidence that a protein called LRP1 may help to ease neuropathic pain by blocking the response of glial cells that support and protect sensory neurons in the peripheral nervous system. Their findings, which could represent a novel target for neuropathic pain therapy, are published in the December 3 issue of the *Journal of Clinical Investigation*.

“Neuropathic pain differs from ordinary pain in that it is usually perceived as ongoing burning or as ‘pins and needles’ electric-shock type of sensation,” said Wendy Campana, Ph.D., associate professor in UCSD’s Department of Anesthesiology, who led the study. “It is caused by nerve damage that can be associated with chronic inflammation or direct nerve injury.”

The UCSD studies show that a form of LRP1 that is present in body fluids such as blood counteracts the activity of inflammatory cytokines, proteins which are involved in developing and sustaining chronic pain states. Cytokines act as messengers to either stimulate or inhibit the immune response, are produced by many cell types including white blood cells present during infection and inflammation

“We think that the anti-inflammatory activity of LRP1 can be harnessed to decrease chronic pain,” said Campana. “By decreasing the presence of cytokines in the area of nerve damage, LRP1 calms the pain signals that are sent to the spinal cord.”

In-vitro analysis confirmed that LRP1 works to modify the response of glial cells that results in neuropathic pain, according to Campana, who added that interactions of neurons and glial cells are very important in determining pain.

Campana worked with post-doctoral scholar Alban Gaultier, Ph.D., and Steven L. Gonias, M.D., chair of UCSD’s Department of Pathology, who are exploring other aspects of LRP1 function. The

UCSD scientists observed that injured peripheral nerves in both mice and rats release LRP1 into the surrounding tissue. Administration of LRP1 into the rodents' sciatic nerves prior to injury provided a protective effect, decreasing the level and activity of injury-induced proinflammatory cytokines, such as TNF-alpha, in the local environment and inhibiting spontaneous pain.

In addition to decreasing inflammatory cytokines locally, treatment with LRP1 also decreased inflammatory cytokines in a region called the spinal dorsal horn, where central pain processing occurs.

"TNF-alpha has some positive properties in infection, so you may not want to block its activity entirely," said Campana. "It appears that LRP1 limits, but doesn't completely block, the increase in proinflammatory cytokines produced by glial cells after nerve injury. We think this research opens up a number of new research directions for understanding and treating chronic neuropathic pain."

Additional contributors to this study include Sanja Arandjelovic and Nikola Dragojovic, UCSD Department of Pathology; Robert R. Myers, UCSD Departments of Pathology and Anesthesiology; and Xiaoqing Li, Julie Janes, George P. Zhou and Jenny Dolkas, UCSD Department of Anesthesiology. The research was supported in part by grants from the National Institutes of Health.

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