## MIND

## Chronic Pain Associated with Activation of Brain's Glial Cells

Patients with chronic pain show signs of glial activation in brain centers that modulate pain, according to results from a PET-MRI study

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By Will Boggs MD

NEW YORK (Reuters Health) - Patients with chronic pain show signs of glial activation in brain centers that modulate pain, according to results from a PET-MRI study.

"Glia appears to be involved in the pathophysiology of chronic pain, and therefore we should consider developing therapeutic approaches targeting glia," Dr. Marco L. Loggia from Massachusetts General Hospital, Harvard Medical School, Charlestown, Massachusetts, told Reuters Health by email.

"Glial activation is accompanied by many cellular responses, which include the production and release of substances (such as so-called 'pro-inflammatory cytokines') that can sensitize the pain pathways in the central nervous system," he explained. "Thus, glial activation is not a mere reaction to a pain state but actively contributes to the establishment and/or maintenance of persistent pain."

To test their hypothesis that patients with chronic pain demonstrate in vivo activation of brain glia, Dr. Loggia's team imaged the brains of 19 individuals diagnosed with chronic low back pain as well as 25 pain-free healthy volunteers using 11C-PBR28, a PET radioligand that binds to the translocator protein (TSPO), a protein upregulated in activated microglia and reactive astrocytes in animal models of pain. In the thalamic region of interest, 11C-PBR28 uptake was significantly higher in patients with chronic low back pain than in healthy controls (p<0.01 left thalamus, p<0.05 right thalamus), according to the January 12 *Brain* online report.

Each patient exhibited higher 11C-PBR28 uptakes than his/her age-, sex-, and TSPO genotype-matched control in the thalamus, and there were no brain regions for which the healthy controls showed statistically higher uptakes than the patients with chronic low back pain.

11C-PBR28 uptakes, and presumably TSPO levels, were negatively associated with pain measures and with circulating levels of proinflammatory cytokines in the chronic pain patients.

"It's important to stress that although TSPO upregulation is a marker of glial activation and therefore of a pro-inflammatory state, animal studies suggest that its role is actually to limit the magnitude of glial responses after their initiation, thereby promoting the return to pre-injury pain-free status and recovery from pain," Dr. Loggia explained. "This means that what we are imaging may be the process of glial cells trying to 'calm down' after being activated by the pain. Thus, subjects with low levels of pain-related TSPO upregulation on activated glia may be less able to adequately inhibit neuroinflammatory responses, and have a more exaggerated response that ultimately leads to more inflammation and pain."

"In the thalamus (which is the 'sensory gateway' from the pain and other sensory stimuli to the brain) the increase in PET signal relative to the controls was so consistent across patients, that just by looking at the subjects' thalamus we could tell who was a patient from who was a control," he said. "No objective biomarkers exist to determine if somebody is in pain (e.g., there isn't a 'blood test' or any other laboratory test that can confirm or disprove whether you are in pain or not). Thus, this study - aside from suggesting glia as a therapeutic target for pain - is important as it may provide an important step toward the identification of objective biomarkers for pain conditions."

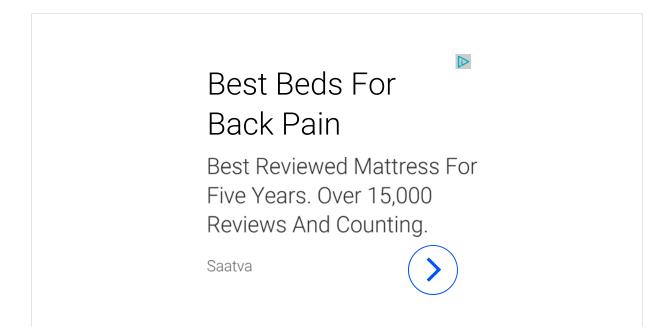
"In animal studies we know that glial modulators, which limit glial activation, can potently inhibit or reverse pain," Dr. Loggia said. "However, evidence of glial involvement in human pain has been very limited until now. Observing glial activation in humans has important potential implications for the development of new therapies based on glial modulation."

"Of note, in humans there have been some attempts to test the efficacy of some glial modulators in some pain conditions," Dr. Loggia added. "Unfortunately these attempts so far have been quite limited in scope, and with mixed results. Seeing that glial activation really happens in patients will provide the rationale to justify a more aggressive exploration of this therapeutic route, and identify which patients are more likely to benefit from these types of therapies."

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