Postoperative pain may increase risk of temporary problems with learning, memory

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The pain caused by a surgical incision may contribute to the risk of postoperative cognitive dysfunction, a sometimes transient impairment in learning and memory that affects a small but significant number of patients in the days following a surgical procedure. An animal study from Massachusetts General Hospital (MGH) researchers, appearing in the November 6 *Journal of Neuroscience*, also identifies a probable mechanism for pain-induced cognitive impairment, suggesting pathways that may be targeted by potential preventive measures.

"These findings suggest, for the first time, that pain is one of the perioperative factors that contribute to the risk of cognitive dysfunction in surgical patients – in addition to the surgery itself, anesthetics, sleep disturbance and other factors," says Zhongcong Xie, MD, PhD, director of the Geriatric Anesthesia Research Unit in the MGH Department of Anesthesia, Critical Care and Pain Medicine. "While postoperative cognitive dysfunction may be temporary, it still can have a major impact on the quality of life of patients and their caregivers at a time when patients' ability to participate in their own care is very important."

Up to 80 percent of surgical patients in the U.S. have some level of postoperative pain, and several studies have suggested that pain could contribute to the development of postoperative cognitive dysfunction. To investigate the potential connection, Xie's team conducted a number of experiments with a group of mice that had small incisions made on one of their paws under general anesthesia. At 1, 3 and 7 days after the procedure, the animals were tested to see how sensitive the affected foot

was to discomfort. The animals showed increased sensitivity to pressure with a nylon filament in the area of the incision on days 1 and 3 but not day 7.

Several standard tests of learning and memory revealed that, compared with a group of mice that underwent a sham procedure involving no incision, the animals that received an incision had impaired performance on particular tasks at day 3 and 7 but not on day 30. The animals' ability to remember tasks learned before the incision was not affected, but their performance on certain new tasks was diminished.

While pain-associated cognitive impairment was seen in animals that could be considered middle-aged, young adult animals exhibited little cognitive dysfunction despite showing postoperative discomfort. A group of mice with incisions that were subsequently treated with local anesthetic did not show either the increased level of discomfort or the extent of cognitive impairment that was seen in the other incision-treated mice, implying that the postoperative pain and not the incision itself contributed to the dysfunction.

Previous research has indicated that a molecule called the NMDA receptor 2B (NR2B), present on several types of brain cells, is involved with pain perception as well as learning and memory. The team's analysis of brain tissues of animals in this study revealed that those with incision-related pain also had decreased NR2B expression in neuronal synapses within particular brain structures involved in learning and memory. Further investigation suggested that reduced synaptic NR2B expression was a consequence of increased levels of the inflammatory cytokine TNF-alpha and the neuronal enzyme CDK5, which is known to regulate NR2B expression.

"Our findings suggest that inadequate pain treatment may lead to postoperative cognitive dysfunction through a synapse-associated

mechanism," Xie says. "Along with improved pain control, treatments that target inflammation and CDK5 activity could also mitigate the problem. We hope this research will promote more studies into the underlying mechanism of postoperative cognitive dysfunction – specifically whether aged animals have greater pain-associated postoperative impairment – findings of which should ultimately improve outcomes for surgical patients." Xie is an associate professor of Anesthesia at Harvard Medical School.

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