

Arthritis drugs could help prevent memory loss after surgery

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Anti-inflammatory drugs currently used to treat diseases such as rheumatoid arthritis may also help prevent cognitive decline after surgery, according to a new study led by researchers at UCSF and colleagues at Imperial College, London.

The research explains for the first time why many patients experience [memory loss](#) or other forms of cognitive dysfunction after surgery or critical illness, a process the researchers traced to a specific inflammatory response in the brain.

The findings could lead directly to human clinical trials in as short as 12 months, the authors said. Their work appears in an upcoming issue of the [Proceedings of the National Academy of Sciences](#) and will be online at <http://www.pnas.org/papbyrecent.shtml>.

For years, anesthesiologists and neurologists have struggled to explain why some patients, especially the elderly, experience confusion, learning disorders and memory loss after surgery.

While typically short-term, this delirium occurs widely in intensive care units, affecting between 28 and 92 percent of hospitalized patients, depending on their age, health status and type of surgery, the authors said. It also has been linked to poorer surgical outcomes, as well as an increased risk of mortality, inability to cope and possible permanent dementia.

Until now, no one has clearly understood what caused the disorder or how to treat it, according to senior author Mervyn Maze, MB ChB, Professor and Chair of the UCSF Department of Anesthesiology and Perioperative Care. The new research not only linked that response to an immune protein called [tumor necrosis factor](#) (TNF- α), a cytokine, but also identified a likely drug therapy to prevent it, he said.

"Antibody therapies already are widely used against cytokines to prevent or treat inflammation, so we know that these are effective in humans," said Maze, who began the research as a member of the Imperial College faculty before joining UCSF. "This study suggests that one day we also might be able to use these therapies as a single, pre-surgical dose to prevent cognitive decline in susceptible patients."

Previous studies have linked post-operative cognitive decline with the rise in blood levels of interleukin-1 beta (IL-1 β), a molecule involved in inflammation. For this study, Maze and his colleagues studied a protein called tumor necrosis factor (TNF- α), which is known to regulate the immune system's [inflammatory response](#) before interleukin-1 is produced.

Working with Sir Marc Feldmann, MB, PhD, FRS – a pioneer in cytokine research in inflammatory disorders and professor at the Kennedy Institute of Rheumatology at Imperial College, London – the team gave a single dose of anti-TNF monoclonal antibody to mice using a model of orthopedic surgery. They found that it successfully acted as a prophylaxis against this disorder, decreasing blood levels of IL-1 β , while limiting inflammation in the brain and eliminating behavioral indications of cognitive decline.

The research suggests that the TNF protein acts "upstream" of IL-1 and triggers a cascade of immune responses during surgery that provokes the production of IL-1 in the brain, Maze said. That in turn contributes to

[cognitive decline](#) after surgery or critical illness.

"This is an important observation, as it demonstrates that cytokines are potential therapeutic targets in a wider range of diseases, not just autoimmune disease and cancer for which they are known targets," Feldmann said. "Moreover, effective therapeutics already are available, with a known safety profile and modest cost if used short term."

More information: N Terrando et al. Tumor necrosis factor- α triggers a cytokine cascade yielding postoperative cognitive decline. Proceedings of the National Academy of Sciences, 1 November 2010.

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