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Interleukin-6 is both necessary and sufficient to produce perioperative neurocognitive disorder in mice

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Abstract

Background: Perioperative neurocognitive disorders (PND) result in long-term morbidity and mortality with no effective interventions available. Because interleukin-6 (IL-6), a pro-inflammatory cytokine, is consistently up-regulated by trauma, including after surgery, we determined whether IL-6 is a putative therapeutic target for PND in a mouse model.
Methods: Following institutional approval, adult (12–14 weeks) male C57/Bl6 mice were pretreated with the IL-6 receptor (IL6R) blocking antibody tocilizumab prior to open tibia fracture with internal fixation under isoflurane anaesthesia. Inflammatory and behavioural responses in a trace fear conditioning (TFC) paradigm were assessed postoperatively. Separately, the effects of IL-6 administration or of depletion of bone marrow-derived monocytes (BM-DMs) with clodrolip on the inflammatory and behavioural responses were assessed. Blood brain barrier disruption, hippocampal microglial activation, and infiltration of BM-DMs were each assessed following IL-6 administration.
Results: The surgery-induced decrement in freezing time in the TFC assay, indicative of cognitive decline, was attenuated by tocilizumab ($P<0.01$). The surgery-induced increase in pro-inflammatory mediators was significantly reduced by tocilizumab. Exogenously administered IL-6 significantly impaired freezing behaviour ($P<0.05$) and up-regulated pro-inflammatory cytokines; both responses were prevented by depletion of BM-DMs. IL-6 disrupted the blood brain barrier, and increased hippocampal activation of microglia and infiltration of BM-DMs.
Conclusions: IL-6 is both necessary and sufficient to produce cognitive decline. Following further preclinical testing of its perioperative safety, the IL6R blocker tocilizumab is a candidate for prevention and/or treatment of PND.

Keywords: cognitive dysfunction; cytokines; interleukin-6 (IL-6); surgery; tocilizumab

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Editor's key points

- A mouse model of postoperative surgical trauma (tibial fracture) was used to determine the role of interleukin-6 (IL-6) in postoperative cognitive dysfunction.
- Tocilizumab, an approved IL-6 receptor blocking antibody, prevented surgical trauma–induced behavioural deficits and increases in inflammatory mediators.
- Exogenous IL-6 reproduced the behavioural and inflammatory effects of tibial fracture.
- Therapeutic interruption of the IL-6 pathway provides a potential strategy for prevention and treatment of postoperative cognitive disorders.

Perioperative neurocognitive disorders (PND), encompassing both postoperative delirium and postoperative cognitive dysfunction, complicate postoperative recovery with serious consequences.[1,2] The pathophysiologic processes of PND, and hence possible targets for therapeutic intervention, need to be determined. A growing body of evidence, mainly from animal models of PND, suggests that the innate immune system is engaged through trauma-provoked release of damage associated molecular patterns (DAMPS) that initiate a peripheral inflammatory response.[3] Circulating pro-inflammatory cytokines are sensed by the central nervous system (CNS) through neural mechanisms,[4] resulting in complementary neuroinflammation through a disrupted blood brain barrier,[5] and producing microglial activation[6] with elaboration and release of pro-inflammatory cytokines and chemokines that are capable of disrupting long-term potentiation (LTP),[7] a biologic correlate of learning and memory.[8] Recent clinical studies reveal that neuroinflammation also occurs in the immediate postoperative period following peripheral surgery.[9–11]

The pro-inflammatory cytokine, interleukin-6 (IL-6), is up-regulated in both the periphery and CNS following experimental trauma in preclinical models,[12] and in surgical patients.[9] Circulating IL-6 levels positively correlate with deficits in cognition in humans.[13,14] An observational study suggested that up-regulated postoperative IL-6 levels are associated with subsequent development of short- and medium-term impairment of cognitive function after surgery.[15] Administration of IL-6 diminished LTP in a hippocampal slice preparation[16] and lipopolysaccharide-induced decline in cognitive behaviour was attenuated in IL-6 deficient mice.[17] Interestingly, IL-6 neutralizing antibodies can improve postoperative cognitive impairment in aged mice.[18] These findings suggest that IL-6 might be an important factor that both facilitates immune-to-brain communication and hippocampal inflammatory mechanisms that negatively affect cognitive processing. We investigated whether IL-6 is both necessary and sufficient to produce cognitive decline in a mouse model of PND. If so, IL-6 could be an important target for therapeutic intervention to prevent or attenuate the development of PND.

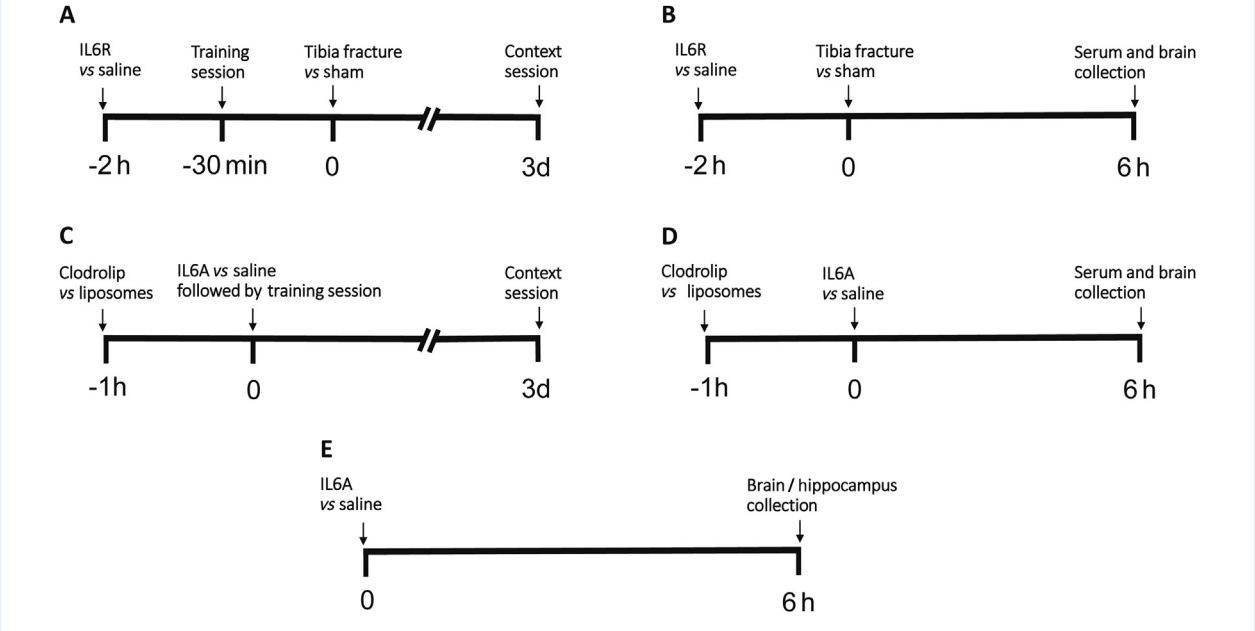

Fig 1. Experimental protocol. (A) Four groups of randomly-assigned mice were treated with either saline or an intraperitoneal (i.p.) injection of tocilizumab, an antibody directed against the interleukin-6 (IL-6) receptor (IL6R) followed by tibial fracture or sham surgery 2 h later. Thirty min prior to tibia fracture/sham, the training session for trace fear conditioning (TFC) was performed and context testing was undertaken 72 h later. (B) Four groups of mice were prepared as for A. Six h after surgery or sham, mice were killed and blood and brain were harvested. (C) Mice were randomly assigned into four groups and treated with i.p. injection of clodrolip in a liposome emulsion or liposome emulsion only 1 h before TFC training session. This was followed by an i.p injection of IL-6 (IL6A) or saline control after training session and thereafter context testing was performed 72 h later. (D) Four groups of mice were prepared as for C. Six h after IL6A, mice were killed and blood and brain were harvested.