Prehabilitation for Prevention of Postoperative Cognitive Dysfunction?

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SURGERY sets the old brain on fire and prehabilitation is a fire retardant. That is conclusion of an interesting study by Kawano *et al.*[1] in this issue of ANESTHESIOLOGY. Specifically, they hypothesized that the old brain is more vulnerable than a young one to surgery-induced neuroinflammation because its innate immune cells, principally microglia, develop an exaggerated inflammatory response to a peripheral surgical procedure. Furthermore, in a novel twist, Kawano *et al.*[1] theorized that preoperative environmental enrichment (PEE) consisting of both physical and cognitive activity would attenuate the neuroinflammation and prevent postoperative cognitive impairment. They tested these hypotheses by exposing young adult and old rats to brief abdominal surgery under isoflurane anesthesia with or without a 2-week period of PEE, while age-matched controls were housed under standard laboratory conditions. They discovered that reference memory was impaired, and hippocampal concentrations of the cytokines tumor necrosis factor-α and interleukin-1β were increased 7 days after surgery in old sedentary but not young adult rats and that PEE negated both the neuroinflammation and memory impairment in the old animals. Moreover, they found that microglia from the hippocampus of PEE-exposed rats had markedly lower lipopolysaccharide-stimulated cytokine release *in vitro* compared with those from sedentary cage controls. Hence, Kawano *et al.*[1] provide evidence that prehabilitation might prevent surgery-induced cognitive impairment in old subjects and identify a cellular mechanism by which it could occur.

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Neuroinflammation is a credible candidate mechanism for postoperative cognitive dysfunction (POCD). Surgery causes tissue injury, release into the circulation of damage-associated and proinflammatory molecules which, by stimulating vagal cholinergic afferents or directly entering the central nervous system (CNS), activate astrocytes and microglia to release a host of proinflammatory mediators.[2–6] Many of these mediators disturb neuronal function and, if concentrations become high enough and last long enough, can kill neurons. It is no surprise then that an inflamed, smoldering brain does not work well. In fact, neuroinflammation is implicated in the pathogenesis of a wide array of acute (*e.g.*, delirium) and chronic cognitive impairments (*e.g.*, dementia).[7,8] Thus, it is an attractive theory for POCD—the brain fog of which patients complain after surgery.

This cascade of surgery, neuroinflammation, and cognitive impairment has been studied previously but often using young animals and short-term outcomes.[3,4] What makes the study by Kawano *et al.*[1] relevant is that they used an aged animal model, looked at cognitive and biochemical outcomes a week postoperatively, and investigated a natural nonpharmacologic potential remedy. These are not trivial considerations because long-lasting postoperative cognitive debility is mainly an affliction of the old. Furthermore, the immune system becomes dysregulated with age; CNS responses are either hypoactive or hyperactive (*i.e.*, primed) and resolution of inflammation is impaired.[9,10] Inasmuch as a coordinated neuroimmune, response is thought to be beneficial and promote recovery, whereas an exaggerated, uncoordinated response is deleterious, and it is easy to see how older age might predispose to greater vulnerability to and slower recovery from surgery-induced cognitive impairment. Like others,[5,6] Kawano *et al.*[1] found this to be the case. In fact, they identified no change in hippocampal cytokines or behavioral performance in the

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young adult rats after surgery. This could be explained by the relatively minor nature of the surgical procedure (*i.e.*, 10-min bowel manipulation) but is at odds with previous animal studies[3,4] and undermines the premise that neuroinflammation is a unifying mechanism of POCD because young and middle-aged patients also develop it but recover quickly.[11] Still, Kawano *et al.*[1] provide important support for age as a vulnerability factor for surgery-induced neuroinflammation and cognitive impairment.

It is nevertheless premature to conclude that neuroinflammation causes POCD or that microglia are responsible. POCD is typically defined by a battery of neuropsychological tests and is characterized by deficits in executive function and working memory.[12,13] These cognitive domains were not tested by Kawano *et al.*[1] nor most other animal studies on the subject. The microglia story is similarly nuanced. There is controversy about how best to identify microglia, the resident phagocytes, and immune competent cells of the brain. This is typically done by morphology or, as in Kawano *et al.*,[1] by immunostaining for expression of certain purportedly microglia-specific surface protein markers. The problem, however, is that morphology is unreliable and mononuclear cells from the blood express many of the same markers as microglia, making it difficult—some would say impossible—to distinguish resident microglia from infiltrating blood bourn immune competent cells with these methods.[14,15] The phenotype of cells in culture can also change with time, so cells harvested from old hippocampus may develop an older or younger phenotype in the dish. Therefore, although it does not detract from the primary observations of Kawano *et al.*,[1] it is too early to say whether inflammatory microglial mechanisms underlie clinical POCD.

The most exciting and potentially translatable part of the study by Kawano *et al.*[1] is the observation that PEE can mitigate both the cognitive deficit and hippocampal cytokine response of surgery. Such prehabilitation has great appeal for improving cognitive outcomes of geriatric surgery. Older patients have a high rate of postoperative cognitive disability and often are deconditioned to start. Moreover, the prehabilitation concept rests on a fairly strong and growing body of information that demonstrates enduring structural and cognitive benefits of even modest physical activity in seniors.[16–18] Data for a benefit of cognitive training, such as with puzzles and games, are less consistent. Some studies find no advantage of generic brain training with commercial products, but others report positive neuroplasticity and improvement in both trained and untrained aspects of cognition, especially with action video games.[19–22] There are already some data that preoperative physical status forecasts surgical morbidity[23,24] and that conditioning improves physical outcomes,[25] but the cognitive advantages, if any, of physical or cognitive prehabilitation are not well studied in the surgical setting. On this score, Kawano *et al.*[1] contribute important insight by showing that PEE modifies the surgically induced neuroinflammatory response, an effect demonstrated for exercise in other models.[26] However, that is probably not the whole story; upregulation of neurotrophic factors, stimulation of neurogenesis, and enhanced synaptic plasticity are also strongly implicated in the cognitive benefits of exercise. In addition, exercise has potent systemic anti-inflammatory effects, so some of the CNS benefits of exercise may be an indirect result of improvement in the function of other organs or the circulating anti-inflammatory milieu.[27]

Whatever the mechanism, there are reasons to be cautious until more data are available. The sedentary cage controls might have biased the study in favor of finding an effect of PEE and probably do not mirror the activity state of most seniors. Clinical evidence that physical activity is cognitively beneficial is compelling, but the duration of exposure is typically far longer (months or years) than the 2-week prehabilitation interval used by Kawano *et al.*[1] Prehabilitation is not feasible prior to urgent or emergency surgery, which are common in seniors and associated with a high risk of cognitive morbidity. Although the weekly amount of physical activity required for a cognitive benefit is modest, it may be impractical for surgical candidates with limited mobility due to cardiopulmonary, orthopedic, or neurologic disease. A prescription for preoperative exercise might also predispose older patients to falls, which are a major source of morbidity in seniors already. Finally, cognitive training might be unrealistic preoperatively because seniors are typically not facile with technology, and it is difficult to imagine those who are taking to World of Warcraft (Blizzard Entertainment Inc., USA) anytime soon.

Nonetheless, the overarching message of Kawano *et al.*[1] is clear: lifestyle-based cognitive protection is possible and might have a positive impact on geriatric surgical outcomes. A preemptive, nonpharmacologic approach to POCD prevention—and better perioperative brain health—is an exciting prospect for geriatric surgical patients. Exercise is medicine that does not require a prescription.

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Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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References

1. Kawano T, Eguchi S, Iwata H, Tamura T, Kumagai N, Yokoyama M: Impact of preoperative environmental enrichment on prevention of development of cognitive impairment following abdominal surgery in a rat model. Anesthesiology 2015; 123:160–70
2. Rosas-Ballina M, Tracey KJ: The neurology of the immune system: Neural reflexes regulate immunity. Neuron 2009; 64:28–32
3. Cibelli M, Fidalgo AR, Terrando N, Ma D, Monaco C, Feldmann M, Takata M, Lever IJ, Nanchahal J, Fanselow MS, Maze M: Role of interleukin-1beta in postoperative cognitive dysfunction. Ann Neurol 2010; 68:360–8
4. Terrando N, Monaco C, Ma D, Foxwell BM, Feldmann M, Maze M: Tumor necrosis factor-alpha triggers a cytokine cascade yielding postoperative cognitive decline. Proc Natl Acad Sci U S A 2010; 107:20518–22
5. Hovens IB, Schoemaker RG, van der Zee EA, Heineman E, Nyakas C, van Leeuwen BL: Surgery-induced behavioral changes in aged rats. Exp Gerontol 2013; 48:1204–11
6. Xu Z, Dong Y, Wang H, Culley DJ, Marcantonio ER, Crosby G, Tanzi RE, Zhang Y, Xie Z: Peripheral surgical wounding and age-dependent neuroinflammation in mice. PLoS One 2014; 9:e96752
7. Cunningham C, Maclullich AM: At the extreme end of the psychoneuroimmunological spectrum: Delirium as a maladaptive sickness behaviour response. Brain Behav Immun 2013; 28:1–13
8. Perry VH, Nicoll JA, Holmes C: Microglia in neurodegenerative disease. Nat Rev Neurol 2010; 6:193–201
9. Corona AW, Fenn AM, Godbout JP: Cognitive and behavioral consequences of impaired immunoregulation in aging. J Neuroimmune Pharmacol 2012; 7:7–23
10. Arnardottir HH, Dalli J, Colas RA, Shinohara M, Serhan CN: Aging delays resolution of acute inflammation in mice: Reprogramming the host response with novel nano-proresolving medicines. J Immunol 2014; 193:4235–44
11. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, Gravenstein JS: Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008; 108:18–30
12. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE, Gravenstein JS: Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet 1998; 351:857–61
13. Price CC, Garvan CW, Monk TG: Type and severity of cognitive decline in older adults after noncardiac surgery. Anesthesiology 2008; 108:8–17
14. Butovsky O, Jedrychowski MP, Moore CS, Cialic R, Lanser AJ, Gabriely G, Koeglsperger T, Dake B, Wu PM, Doykan CE, Fanek Z, Liu L, Chen Z, Rothstein JD, Ransohoff RM, Gygi SP, Antel JP, Weiner HL: Identification of a unique TGF-β-dependent molecular and functional signature in microglia. Nat Neurosci 2014; 17:131–43
15. Martinez FO, Gordon S: The M1 and M2 paradigm of macrophage activation: Time for reassessment. F1000Prime Rep 2014; 6:13
16. Hillman CH, Erickson KI, Kramer AF: Be smart, exercise your heart: Exercise effects on brain and cognition. Nat Rev Neurosci 2008; 9:58–65
17. Brinke Ten LF, Bolandzadeh N, Nagamatsu LS, Hsu CL, Davis JC, Miran-Khan K, Liu-Ambrose T: Aerobic exercise increases hippocampal volume in older women with probable mild cognitive impairment: A 6-month randomised controlled trial. Br J Sports Med 2015; 49:248–54
18. Middleton LE, Mitnitski A, Fallah N, Kirkland SA, Rockwood K: Changes in cognition and mortality in relation to exercise in late life: A population based study. PLoS One 2008; 3:e3124
19. Owen AM, Hampshire A, Grahn JA, Stenton R, Dajani S, Burns AS, Howard RJ, Ballard CG: Putting brain training to the test. Nature 2010; 465:775–8
20. Bavelier D, Green CS, Pouget A, Schrater P: Brain plasticity through the life span: Learning to learn and action video games. Annu Rev Neurosci 2012; 35:391–416
21. Anguera JA, Boccanfuso J, Rintoul JL, Al-Hashimi O, Faraji F, Janowich J, Kong E, Larraburo Y, Rolle C, Johnston E, Gazzaley A: Video game training enhances cognitive control in older adults. Nature 2013; 501:97–101
22. Bejjanki VR, Zhang R, Li R, Pouget A, Green CS, Lu ZL, Bavelier D: Action video game play facilitates the development of better perceptual templates. Proc Natl Acad Sci U S A 2014; 111:16961–6
23. Robinson TN, Wu DS, Pointer L, Dunn CL, Cleveland JC Jr, Moss M: Simple frailty score predicts postoperative complications across surgical specialties. Am J Surg 2013; 206:544–50
24. Robinson TN, Wu DS, Sauaia A, Dunn CL, Stevens-Lapsley JE, Moss M, Stiegmann GV, Gajdos C, Cleveland JC Jr, Inouye SK: Slower walking speed forecasts increased postoperative morbidity and 1-year mortality across surgical specialties. Ann Surg 2013; 258:582–8; discussion 588–90
25. Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, Liberman AS, Stein B, Charlebois P, Feldman LS, Carli F: Prehabilitation versus rehabilitation: A randomized control trial in patients undergoing colorectal resection for cancer. Anesthesiology 2014; 121:937–47
26. Barrientos RM, Frank MG, Crysdale NY, Chapman TR, Ahrendsen JT, Day HE, Campeau S, Watkins LR, Patterson SL, Maier SF: Little exercise, big effects: Reversing aging and infection-induced memory deficits, and underlying processes. J Neurosci 2011; 31:11578–86
27. Lancaster GI, Febbraio MA: The immunomodulating role of exercise in metabolic disease. Trends Immunol 2014; 35:262–9