Modulation of postoperative cognitive decline via blockade of inflammatory cytokines outside the brain

Lawrence Steinman[1]
Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA 94305

Postoperative cognitive decline (POCD) following surgery and its acute counterpart, known as postoperative delirium, are a major cause of morbidity associated with surgery. POCD occurs in 7–26% of patients undergoing surgery (1). In a study published in PNAS, Terrando et al. (2) show that brain inflammation with postoperative cognitive dysfunction follows experimental orthopedic surgery on the tibia and anesthesia with isoflurane and analgesia with buprenorphine. Serum levels of inflammatory cytokines, including TNF-α, are elevated following this experimental surgical protocol with accompanying anesthesia in this mouse model. Remarkably, treatment of mice with prophylactic administration of a monoclonal antibody to TNF-α prevented this postsurgical cognitive decline. One of the intriguing issues raised in this study is how blockade of TNF-α in the serum can modulate brain inflammation and cognitive impairment. The possibility of treating surgical patients at risk for POCD with anti-TNF, already used by more than 2 million patients worldwide for rheumatoid arthritis, inflammatory bowel disease, and psoriasis (3), is a legitimate possibility, given these encouraging results in a preclinical model of surgery and anesthesia in the mouse.

TNF is induced in the periphery following surgery and general anesthesia. It appears in blood at 30 min after surgery and precedes the appearance of IL-1b and IL-6, which do not appear until 6 h after surgery (2). Surgery and anesthesia lead to POCD in this model. Cognitive impairment is measured in a model of fear, which serves as a surrogate for hippocampal dysfunction (2). Some hallmarks of an inflammatory response in the brain are present, including activation of microglia. Prophylaxis with anti-TNF antibody attenuates behavioral abnormalities and microgliosis.

How do changes in the periphery following surgery lead to changes within the central nervous system? How is the periphery in communication with the brain? There are two well-known phenomena that help us to understand this. The first is the febrile response (4, 5). The second is a remarkable vagal nerve pathway with afferent nerve fibers that signal the brain about conditions in the periphery ranging from inflammation to sepsis, and even to changes in blood pressure (6). Efferent nerve connections from the vagal nerve to the spleen can be modulated to block experimental septic shock and autoimmune immune models of rheumatoid arthritis. These intricate interactions between the periphery and brain have been well characterized and represent fertile ground for understanding how an effect of surgery and anesthesia on the brain can be modulated via anti-TNF antibody given i.v.

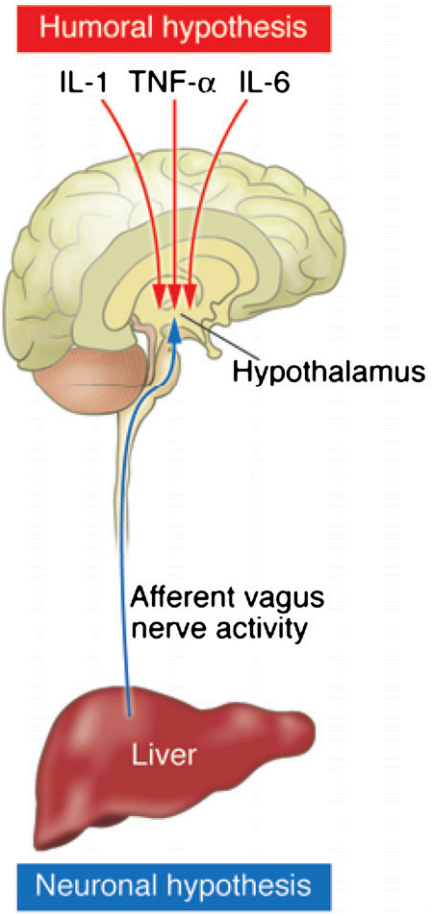

Fig. 1. Comparison of the humoral and neuronal hypotheses for fever induction. According to the humoral hypothesis of fever induction, the pyrogenic cytokines IL-1, IL-6, and TNF-α gain access to the hypothalamus via fenestrations in the blood–brain barrier in the circumventricular organs or via active transport mechanisms mediated by the cells surrounding the hypothalamus. A key feature of the humoral hypothesis is that the pyrogenic cytokines activate the febrile response indirectly by inducing local endothelial cells or microglial cells to secrete prostaglandin E_2 (PGE_2). The PGE_2 then acts via PGE receptor 3 to initiate a neuronal response that regulates the body temperature. According to the neuronal hypothesis, C5a stimulates PGE_2 production in the liver and signaling to the hypothalamus occurs via a neural pathway mediated by the vagus nerve and the nucleus tractus solitarius." [Reproduced with permission from ref. 4 (Copyright 2008, *J Clin Invest*).]

One might first inquire if there is any possibility that anti-TNF antibody reaches the brain in this mouse model of surgery and anesthesia, and thereby modulates the elevations in TNF seen with surgery. Although there is no formal answer to this from the current set of experiments (2), we do know that anti-TNF does not reach the brain when administered i.v. to treat multiple sclerosis (7). In fact, monoclonal antibodies are too large to penetrate the blood–brain barrier even in inflammatory conditions like multiple sclerosis. Moreover, for reasons that are still poorly understood, anti-TNF antibody worsens the quintessential inflammatory disease of the brain, multiple sclerosis. The US Food and Drug Administration warns against administration of anti-TNF to patients with multiple sclerosis (8). So, one ought to explore other pathways whereby anti-TNF may modulate postoperative decline by neutralizing TNF in the serum or tissues in the periphery, outside the brain.

Fever is perhaps the best understood pathway whereby mediators like TNF induce changes in the brain. In fact, in fever, elevation of IL-1 in the periphery induces profound changes in the brain, with the well-known elevation of temperature and associated behavioral abnormalities that include sleepiness, loss of appetite, and, in some cases, delirium (4, 5). Although IL-1 is the primary pyrogen, there are rare cases of severe fever that can be modulated with anti-TNF. In the Jarisch–Herxheimer reaction seen following antibiotic treatment of diseases like brucellosis, leptospirosis, Lyme disease, louse-borne relapsing fever, and secondary syphilis, administration of anti-TNF antibodies can block the associated fever, rigor, and hypotension that could be deadly accompaniments of therapy (4, 9, 10). How do elevations of TNF in the

Author contributions: L.S. wrote the paper.

The author declares no conflict of interest.

See companion article on page 20518 in issue 47 of volume 107.

[1]E-mail: steinman@stanford.edu.

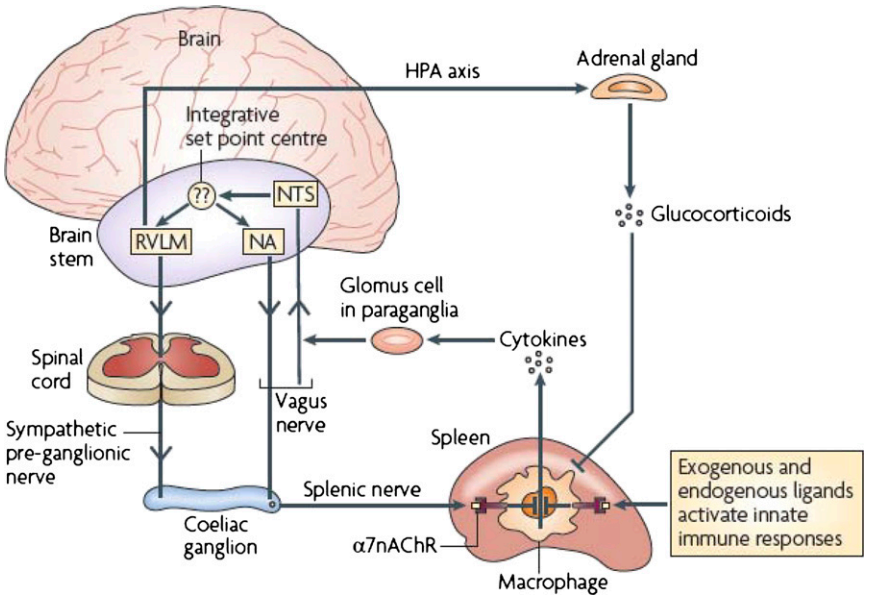

Fig. 2. Tracey (6) has described a functional inflammatory reflex involving both afferent and efferent arms of the vagus nerve. The afferent arm projects via the nucleus tractus solitarius (NTS) to the brainstem. Efferent fibers project along the vagal motor nerve via the nucleus ambiguous (NA) and the dorsal motor vagal nucleus. These efferents connect to the celiac ganglia. The vagus nerve suppresses innate immunity and proinflammatory cytokine production in the spleen via a synapse involving the nicotinic acetylcholine receptor subunit α7. There is an additional reflex circuit that is stimulated after afferent vagal stimulation of the brainstem. The hypothalamic pituitary axis (HPA) is activated, increasing glucocorticoid release from the adrenal gland. The efferent vagal outflow also is interconnected to the excitatory autonomic nervous system via synapses with rostral ventrolateral medullary (RVLM) sympathetic neurons. [Reproduced with permission from ref. 6 (Copyright 2009, *Nat Rev Immunol*).]

periphery induce fever and the associated behavioral changes?

There are two mechanistic explanations, which are not mutually exclusive, as shown in Fig. 1. In the humoral hypothesis, cytokines like TNF, IL-1, and IL-6 gain access to the hypothalamus via fenestrations of the blood–brain barrier in the circumventricular organs surrounding the hypothalamus. Within the hypothalamus, microglial cells have receptors for these cytokines. So, in the humoral theory, administration of anti-TNF would neutralize TNF before it passed the windows in the blood–brain barrier and activated microglial cells in the hypothalamus. The second theory involves activation of the hypothalamus via a vagal nerve afferent pathway from the liver to the nucleus tractus solitarius in the brainstem (4, 11). The neural mediator is prostaglandin E2, but the vagus nerve itself can be activated via peripheral inflammatory signals like TNF (4, 11, 6).

The mechanism whereby TNF induces fever is a good precedent to begin to understand how peripheral cytokines can induce postoperative changes in cognition. After all, there are cognitive changes in fever that, fortunately, are usually only transient, unlike postoperative cognitive changes that become chronic (1). A second explanation for how TNF in the blood might influence long-term changes in the brain comes from the exciting work of Tracey (6) on the neural immune reflex, again involving the vagus nerve, this time with important afferents to the brain emanating not only from liver but also from splenic lymphoid tissue.

In a series of brilliant experiments, Tracey (6) has provided evidence that there are afferent pathways of the vagal nerve from the abdomen and spleen that can sense inflammation and signal the brain (Fig. 2). These afferent vagal pathways have been studied most intensively in relation to fever, but there is every reason to expect that vagal projections would influence other regions of the brain in addition to the hypothalamus, including the hippocampus and limbic system, thus leading to cognitive decline. The efferent arc of this reflex has been shown to modulate animal models of sepsis and autoimmunity, and it is mediated by cholinergic neurotransmission (6).

It is noteworthy that anesthesiologists often give anticholinergics to decrease secretions and reduce the risk for aspiration. Indeed, this logical maneuver may actually be counterproductive, given the importance of cholinergic signals in the pathology of TNF-mediated autoimmune disease (6). Vagotomy and cholinergic blockade may actually worsen autoimmune conditions (6). Such practices involving routine administration of anticholinergics, such as atropine, bear scrutiny and further assessment of risk vs. benefit. Clinical trials to stimulate the vagus nerve are about to commence, and such a strategy runs counter to the common practice of using anticholinergics in anesthesia.

Given the high incidence of POCD, the costs and benefits of short-term prophylactic blockade prior to TNF for routine surgery need careful consideration, as do all medical expenditures, which should be cost-effective. We need to learn more about who is at risk for POCD. Will there be biomarkers, perhaps baseline or intraoperative levels of TNF, that might instruct us about who is most at risk? Such studies should be performed as translation of this concept proceeds from preclinical models to clinical trials. The notion that elevations of TNF in the periphery lead to cognitive decline after surgery is intriguing and worthy of significant allocation of resources for further research.

1. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS; ISPOCD Group (2009) Long-term consequences of postoperative cognitive dysfunction. *Anesthesiology* 110:548–555.
2. Terrando N, et al. (2010) Tumor necrosis factor-α triggers a cytokine cascade yielding postoperative cognitive decline. *Proc Natl Acad Sci USA* 107: 20518–20522.
3. Feldmann M, Maini RN (2003) Lasker Clinical Medical Research Award. TNF defined as a therapeutic target for rheumatoid arthritis and other autoimmune diseases. *Nat Med* 9:1245–1250.
4. Steinman L (2008) Nuanced roles of cytokines in three major human brain disorders. *J Clin Invest* 118: 3557–3563.
5. Dinarello CA, Wolff SM (1982) Molecular basis of fever in humans. *Am J Med* 72:799–819.
6. Tracey KJ (2009) Reflex control of immunity. *Nat Rev Immunol* 9:418–428.
7. Steinman L (2004) Immune therapy for autoimmune diseases. *Science* 305:212–216.
8. US Food and Drug Administration (2001). Safety update on TNF-α antagonists: Infliximab and etanercept. Available at http://www.fda.gov/OHRMS/DOCKETS/ac/01/briefing/3779b2_01_cber_safety%20_revision2.pdf. Accessed November 2, 2010.
9. Negussie Y, et al. (1992) Detection of plasma tumor necrosis factor, interleukins 6, and 8 during the Jarisch-Herxheimer Reaction of relapsing fever. *J Exp Med* 175:1207–1212.
10. Fekade D, et al. (1996) Prevention of Jarisch-Herxheimer reactions by treatment with antibodies against tumor necrosis factor alpha. *N Engl J Med* 335: 311–315.
11. Blatteis CM (2007) The onset of fever: New insights into its mechanism. *Prog Brain Res* 162:3–14.