The Stressed-out Rat

A Model for Anesthetic Prevention of Post-Traumatic Stress Disorder

AWARENESS under general anesthesia is an uncommon, dreaded adverse outcome. Intraoperative awareness can only be studied by accident, inferring from case reports and large clinical cohort trials the causes and consequences of intraoperative awareness. We have learned that most cases of anesthetic awareness consist of neutral auditory memories, with memories of pain and fear occurring less commonly.1,2 A subset of these patients progress to long-lasting psychological trauma and may be diagnosed with posttraumatic stress disorder (PTSD).3 PTSD is a long-lasting psychological syndrome that includes nightmares, flashbacks, general anxiety, fear, and avoidance of triggering situations. PTSD is among the worst possible outcomes of awareness under general anesthesia. Progress in studying anesthetic-related PTSD is limited by the rarity of the intraoperative awareness and the inability to control the setting in which it occurs. An animal model in which to prospectively study risk factors for PTSD and appropriate treatments would be very valuable. In this issue of ANESTHESIOLOGY, Rau et al. present such a model.4

Like other prey animals, rats “freeze” (become motionless) when they are anxious. Rau et al. gave rats PTSD by instilling in them fear of inescapable foot shocks, analogous to the inescapable pain of the awake paralyzed surgical patient. The shocks are delivered in a specially designed cage visually distinct from the cage where the animal is housed. At a later time, the rat is returned to the same cage in which the shocks were received. The amount of time the animal is in a frozen posture is directly related to the number or intensity of shocks given. This behavior, called associative fear conditioning, provides a measure of the intensity of the pairing between the shocks and the context (cage) where they were received. Volatile anesthetics diminish the association, demonstrating direct impairment of memory.5

PTSD differs from simple memory in that it can persist for long periods and is triggered by unconscious reminders of the trauma. It is thought to be mediated by different neural substrates and to involve the amygdala.6 Stress-enhanced fear learning (SEFL) is thought to be an animal model for PTSD.7 In SEFL, the animal that had been stressed with 15 shocks earlier in its life has an exaggerated response to a single shock administered in a different environment. In their study in this issue of ANESTHESIOLOGY, the authors show that SEFL can persist for up to 3 months, a large portion of the animal’s natural life. Treatment with isoflurane at concentrations 0.4% or higher and nitrous oxide 70-80% during the 15-shock stressor prevented SEFL. Unfortunately, treatment with anesthetic after the stressful event had no effect. It is tempting to wonder whether the fact that both anesthetics tested are N-methyl-D-aspartate antagonists provides mechanistic information. No conclusions can be drawn yet, but it will be interesting to see whether anesthetic drugs that have purer γ-aminobutyric acid-A receptor effects will be similarly potent in preventing SEFL.

Balanced anesthetic techniques used in humans typically include drugs to induce hypnosis and amnesia in addition to analgesics. Although 0.6% isoflurane nearly ablated the freezing response after 1-mA shocks, there was a statistically significant increase in freezing behavior after 3-mA shocks, even in the presence of 0.6% isoflurane; 1% isoflurane was able to suppress the response to fifteen 3-mA shocks. This finding would suggest that the intensity of the afferent input is related to the strength of the centrally mediated SEFL response. This finding is not surprising in light of the fact that most patients who develop PTSD after an incident of anesthetic awareness have experienced pain. These findings support the potential value of balanced anesthetic techniques that supplement hypnotics with potent analgesics and regional anesthesia in preventing PTSD.

An animal model of PTSD may facilitate prospective comparison of anesthetic techniques, potential preclinical and clinical adjuvant therapies, and demonstrate the value of monitoring techniques to decrease the incidence of PTSD. The value of processed electroencephalographic monitoring for the prevention of awareness and PTSD has been particularly controversial. Fortunately, electroencephalographic approaches can be applied to rodents,8 and it is likely that the proposed rodent model of perianesthetic PTSD can be expanded to evaluate the electroencephalographic correlates.

Recent studies in slices of the basolateral amygdala have shown that the anesthetic xenon reduces excitatory synaptic transmission in this important nucleus for aversive conditioning through postsynaptic inhibition of N-methyl-D-aspartate receptors.9 The Rau et al. model could provide a behavioral link to such studies. The application of pharmacological inhibitors to brain regions, including the amygdala, receptor knockdown, and other state of the art techniques is currently being used to better understand the mechanism of PTSD. In
the future, these techniques could be used with the Rau model to elucidate the mechanism of action through which anesthetic drugs prevent PTSD. The availability of a rat model allows us a window into the brain from which the anatomy and physiology that underlie this important anesthetic endpoint can be evaluated.

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References

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