GABA<sub>A</sub> Receptor Theory of Perioperative Neurocognitive Disorders

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Most commonly used intravenous and inhaled general anesthetic drugs have two distinct effects on γ-amino butyric acid type A (GABA<sub>A</sub>) receptors. First, the drugs act as positive allosteric modulators of both synaptic and extrasynaptic GABA<sub>A</sub> receptors. This action enhances the ability of endogenous γ-aminobutyric acid (GABA) to activate the opening of integral ion channels. The resulting increase in chloride (Cl<sup>-</sup>) influx causes neuronal inhibition and the profound neurodepressive state, which allows patients to tolerate surgery. Second, exposure to the anesthetic drugs triggers an overexpression of extrasynaptic GABA<sub>A</sub> receptors on the surface of neurons in the postanesthetic period. These overexpressed GABA<sub>A</sub> receptors are activated by low ambient concentrations of endogenous GABA, which causes a low-grade persistent increase in chloride influx in neurons. This sustained increase in extrasynaptic GABA<sub>A</sub> receptor function causes subtle cognitive deficits in laboratory animals that persist long after the drugs have been eliminated. The excessive cell-surface expression of extrasynaptic GABA<sub>A</sub> receptors is also induced by proinflammatory cytokines that are released during surgery. Both mechanisms may contribute to subtle neurocognitive disorders that occur in patients after surgery, such as postoperative delirium. Dexmedetomidine activates α<sub>2</sub> adrenergic receptors in astrocytes and stimulates the release of brain-derived neurotrophic factor (BDNF), which in turn acts as a paracrine factor to prevent overexpression of extrasynaptic GABA<sub>A</sub> receptors in neurons. Dexmedetomidine thereby mitigates cognitive disorders in animal models. Similar mechanisms may account for the cognition-sparing properties of dexmedetomidine in patients.

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Competing Interests

The authors declare no competing interests.
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References


Dr. C. R. Agnew’s Choice: Cocaine Anesthesia Discoverer Over U.S. President

At a meeting in 1884 in Heidelberg, Germany, a paper was presented—the world’s first on using cocaine as a topical (surface) anesthetic. The author was a surgical intern in Vienna named Carl Koller, M.D. (1857 to 1944). A conference attendee, New Yorker Henry Noyes, M.D., reported Koller’s discovery in the October 11, 1884, issue of the New York Medical Record. One week later, Noyes’s colleague, ophthalmologist Cornelius Rea Agnew, M.D. (1830 to 1888, right) was delighted to publish his own clinical cases confirming the effectiveness of Koller’s cocaine anesthesia. Ironically, Agnew passed away in 1888 in New York, in the same year and city to which Koller would immigrate from Europe. A professional admirer of Koller, Agnew was quoted posthumously in Harper’s Weekly (left) that he (Agnew) would rather have been “the discoverer of cocaine anesthesia than President of the United States.” (Copyright © the American Society of Anesthesiologists’ Wood Library-Museum of Anesthesiology.)

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