Dexmedetomidine prevents post-anesthetic delirium by neutralizing excessive $\alpha 5$ GABAA receptor activity in mice

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Video Abstract

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Abstract

An international team of researchers is looking at ways to prevent cognitive impairment following the use of general anesthetics. Their work could lead to better outcomes for the over 312 million surgical patients who undergo anesthesia each year. General anesthetics are associated with the occurrence of postoperative delirium. This complication – often marked by inattention, memory disturbances and confusion – makes it hard for surgical patients to resume daily living activities, and has even been linked to an increased risk of death. The drug dexmedetomidine helps prevent postoperative delirium, but the biological basis for this protection isn't clear. The researchers previously reported that a single exposure to the common anesthetic etomidate can trigger long-lasting changes to an inhibitory receptor in the brains of mice. Specifically, etomidate increased the number of $\alpha 5$ GABAA receptors expressed on the surface of neurons. Similar overexpression and hyperactivity of these receptors has been associated with several neurological disorders, including stroke and Alzheimer disease. The team postulated that dexmedetomidine could neutralize excessive $\alpha 5$ GABAA receptor activity to prevent altered postanesthetic function. To test this hypothesis, the researchers examined how the drug affects brain cells in mice. In mice, etomidate caused an upsurge in the surface expression and activity of $\alpha 5$ GABAA receptors. This effect was counteracted by the use of dexmedetomidine. Exposing human brain cells to the combination caused similar changes in receptor expression and activity. The team also subjected etomidate-exposed mice to several behavioral tests. Their results showed that etomidate impaired the animals' problem-solving abilities in part by reducing short-term memory, and cotreatment with dexmedetomidine prevented this dysfunction. Additional mechanistic insights were uncovered by exposing laboratory cultures of mouse neurons and astrocytes to the drug. In these experiments, dexmedetomidine stimulated astrocytes to release brain-derived neurotrophic factor, a protein with neuroprotective properties. This release, in turn, prevented increases in $\alpha 5$ GABAA receptor surface expression and activity in etomidate-exposed neurons. Overall, the study provides a model to account for the cognition-sparing properties of dexmedetomidine. The work also identifies several potential therapeutic targets that may be tied to postoperative delirium.