Study reveals previously unknown site of anesthetic action

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Anesthetics have been used in surgical procedures for more than 150 years, but the mechanisms by which inhaled anesthesia actually work are poorly understood. Now, researchers at Johns Hopkins Medicine have discovered that anesthetics bind to and interfere with certain proteins in excitatory neurons, which are necessary for these neurons to transmit signals involved in anesthesia and the perception of pain.

"Our discovery may be an important component of the mechanism of anesthesia and—because this particular protein is also involved in neuronal development—could be involved in the mechanism of recent reports of neurotoxicity and long-term cognitive dysfunction in infants and neonates undergoing anesthesia for surgical procedures," says Roger Johns, M.D., M.H.S., senior author of the study, which will be published in the March 17 issue of *Anesthesiology*. "It could help to design new and more specific anesthetics or allow us to lower the anesthetic concentration needed for anesthesia, as anesthetics at higher concentrations can have dangerous side effects."

For more than a decade, Johns and his colleagues have been studying postsynaptic density protein-95 (PSD95), a scaffolding protein that helps assemble the proteins needed for neurons to communicate with each other. Their previous work revealed that blocking PSD95 prevents the development of certain kinds of chronic pain and reduces the amount of anesthesia required to induce its effects.

In their latest work, the investigators show that inhalational anesthetics

bind to certain sites on PSD95 and prevent the ability of excitatory neurons to transmit signals. These protein sites appear to be important for the effectiveness of general anesthesia.

Johns notes that there has been a great deal of concern in recent years that anesthesia in infants and newborns may cause neurotoxicity leading to long-term cognitive problems and impaired learning. "The data in rodents, primates and humans all point in this direction, and the Food and Drug Administration has just elevated its level of concern about this issue," he says. His research team is currently studying whether anesthetic interactions with PSD95 and other scaffolding proteins play a role. "We hypothesized that because PSD95 is also involved in neuronal synapse formation—or making the proper connections between neurons as the brain is forming—during fetal and infant brain development, the ability of anesthetics to block the action of PSD scaffolding proteins, as shown in our new study, could also be preventing correct neuronal synapse development, leading to the long-term learning and memory deficits observed."

Strategies for Mitigating Anesthesia-Related neuroToxicity in Tots (SmartTots), a program created by the FDA and the International Anesthesia Research Society, is working to coordinate and fund research intended to make surgery, anesthesia and sedation safer for infants and young children. In June, SmartTots met to review the most recent data from animal and human studies on the effects of anesthesia in children. The participants released a statement recommending that surgeries and procedures requiring anesthesia and sedatives be postponed if possible due to the potential risk to the developing brains of infants, toddlers and preschool-age children.

When surgeries and procedures are required using current standard of care anesthetics, caregivers should consider having their children participate in clinical studies to help identify better practices and/or

drugs that have the least effect on the developing brain.

Johns notes that mutations and dysfunction of neuronal scaffolding proteins have recently been implicated in several forms of human autism spectrum disorders and certain types of mental illness. "Might early anesthesia play a role in these complex mental health issues?" he wonders.

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