Mechanism of emergence agitation induced by sevoflurane anesthesia

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Sevoflurane is an inhalational anesthetic used widely as a pediatric or outpatient anesthesia due to its excellent hemodynamic stability and low blood solubility, which allows rapid induction and emergence from general anesthesia, as well as control of the depth of anesthesia. However, when sevoflurane is used alone it is associated with a higher incidence of emergence agitation in children. The rapid removal of residual anesthetics due to low blood solubility of sevoflurane has been suggested to cause emergence agitation in some patients [1,2]. In addition, a variety of other explanations have been proposed for the etiology of emergence agitation. These include the lack of a young child’s ability to adapt to sudden changes due to an unfamiliar environment after awakening, immature neurological development, anxiety from being separated from their parents, increased pain sensation and sympathetic hyperactivation [2,3].

Emergence agitation is characterized by self-limiting aggressive agitation that develops in the early phase of awakening from anesthesia at the end of surgery. Emergence agitation can be dangerous to patients, particularly to young children. Patients suffering from emergence agitation may harm themselves and dislodge drains or catheters, which affects the results of surgery. They may inflict a bodily injury on their care-givers or cause a paranoiac accident, which makes the management and monitoring of patients at the post anesthesia care unit difficult [4]. There have been many attempts to reduce the incidence of emergence agitation but the etiology and preventive treatments of emergence agitation are still unclear.

Some studies have reported that midazolam which acts on its target effect site GABA\textsubscript{A}, reduces emergence agitation [5,6], and its antagonist, flumazenil reverses this effect [7]. However, the mechanism is still not clear, and it is not known whether sevoflurane and midazolam interact at the GABA\textsubscript{A} receptor level. Most GABA\textsubscript{A} receptors consist of two \(\alpha\) subunits, two \(\beta\) subunits and a \(\gamma\) subunit. The \(\gamma2\) subunits of GABA\textsubscript{A} receptor exist as a long type (\(\gamma2L\)) and a short type (\(\gamma2S\)), generated by alternative splicing of RNA. The most common pattern for GABA\textsubscript{A} receptor is \(\alpha1\beta2\gamma2\) type, which accounts for 43% of all GABA\textsubscript{A} receptors [8]. This implies that the diversity of the subtype variants and the distribution of GABA\textsubscript{A} receptors may affect the anesthetics from subject to subject.

In this edition of the Korean journal of anesthesiology, Eom et al. [9] postulated that alternative splicing of the \(\gamma2\) subunit is related to emergence agitation on the basis of characteristics of midazolam, sevoflurane and \(\gamma2\) subunit. Sevoflurane binds to GABA\textsubscript{A} receptor, benzodiazepine-like midazolam prevents emergence agitation and also binds to \(\alpha\) and \(\gamma\) subunit of GABA\textsubscript{A} receptor, and alternative splicing of \(\gamma2\) subunit is different based on the age of the patient. Whole-cell patch clamp to the \(\alpha1\beta2\gamma2L\) and \(\alpha1\beta2\gamma2S\) GABA\textsubscript{A} receptors expressed in human embryonic kidney 293 cells with midazolam and/or sevoflurane was performed. The concentration-response relationships were recorded for midazolam and sevoflurane. They showed that the concentration-response relationships for midazolam and sevoflurane were dose-dependent with no differences between the \(\alpha1\beta2\gamma2L\) and \(\alpha1\beta2\gamma2S\) subtypes. It was concluded that the difference in the \(\gamma2\) subunit cannot explain the emergence agitation of sevoflurane in children in vitro.

These finding suggests that co-application of sevoflurane and midazolam enhances the GABA current according to the...
alternative splicing of the γ2 subunit and concentration of both drugs. Their effort to reveal the mechanism of emergence agitation induced by sevoflurane anesthesia could be a major step towards studying the basic mechanisms of the anesthetic agent. Further study to reveal the mechanism of emergence agitation is expected.

References

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