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Editorial

Volatile anesthetic antagonism by long-chain free fatty acids

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If there were a specific anesthetic antagonist available without side effects, clinical management of general anesthesia would benefit greatly. However, such an anesthetic antagonist is not available, partly because the mechanisms of general anesthesia in the central nervous system have yet to be fully elucidated. In this issue of the *Journal of Anesthesia*, Hanada et al. [1] expand their earlier interesting finding that myristate, a saturated free fatty acid with 14 carbons, antagonizes volatile anesthetics in goldfish [2]; they show that the antagonizing effects of long-chain free fatty acids are determined not only by their hydrophobicity but also by the ability of their molecular configuration to perturb lipid membrane structures [1]. Thus, they suggest that free fatty acids alter the function of membrane protein by both a direct action on membrane protein, and an indirect action through lipid bilayers.

As a result of recent research into anesthetic mechanisms, membrane proteins, especially ligand-gated and other ion channels, have been considered as plausible target molecules of general anesthetics [3]. Although free fatty acids are shown to regulate the activity of ion channels, the reported effects do not seem very consistent. For example, in respect of the effects of unsaturated free fatty acids on the agonist binding or function of $GABA_A$ (γ-aminobutyric acid type A) receptors, both potentiation [4,5] and inhibition/no effect [6,7] have been reported, although the experimental conditions were different. Thus, to understand the mechanism of volatile anesthetic antagonism by free fatty acids, more evidence concerning interactions between volatile anesthetics and free fatty acids may be required for each ion channel. Because the enhancement of the agonist binding of $GABA_A$ receptors by pentobarbital is decreased by unsaturated fatty acids, which themselves enhance the agonist binding [4], it may not be necessary for free fatty acids to have opposite effects on ion channels to those of anesthetics to antagonize the anesthetic effects.

Recently, a target molecule for in vivo anesthesia by propofol has been identified, using the elegant knock-in mouse technique. With this technique, in mice, a mutation was introduced into a $GABA_A$ receptor β3 subunit that eliminated the propofol potentiation of $GABA_A$ receptors but did not alter other physiological functions [8]. The elimination of or profound reduction in anesthetic behaviors by propofol in these mice strongly suggests that the $GABA_A$ receptor is a major determinant of propofol anesthesia in vivo. Thus, the antagonism of propofol anesthesia in rats by the $GABA_A$ receptor antagonists picrotoxin and gabazine [9] may be an example of anesthetic antagonism at a target molecule level. However, propofol anesthesia can also be reversed by an anticholinesterase agent, physostigmine [10,11]. Because physostigmine does not affect $GABA_A$ receptors [12], the antagonism of propofol anesthesia by physostigmine may be an example of anesthetic antagonism induced by an action on a molecule other than the anesthetic target. Thus, it may not be necessary for anesthetic antagonists to act on the anesthetic target itself. In this context, free fatty acids may not directly affect an anesthetic target protein to antagonize the action of volatile anesthetics.

Although it is difficult to clarify whether anesthetics bind to a specific site on the membrane protein, evidence using the techniques of photoaffinity labeling [13] and sulfhydryl-specific agents [14] suggests that anesthetic actions on ion channels are due to binding at a specific site. Thus, the ideal selective anesthetic antagonist would be a competitive antagonist at such an anesthetic binding site. However, as discussed by Hanada et al. [1], free fatty acids may not compete at a specific anesthetic binding site on the ion channel, because free fatty acids are negatively charged and isoflurane is un-

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charged. Nevertheless, free fatty acids may be attractive as antagonists, because no remarkable adverse effects from free fatty acids were observed in goldfish [1], and free fatty acids are essential human nutrients. Further studies in mammals will be needed to more fully examine the abilities and safety of free fatty acids as volatile anesthetic antagonists.

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