Different actions of sevoflurane and propofol on central nicotinic receptors may explain differences in hypnotic antagonism by cholinesterase inhibitors

Editor—We read with interest the study by Plourde and colleagues[1] measuring the action of physostigmine, a centrally acting anticholinesterase, on the hypnotic effect of inhaled volatile anaesthetics, using sevoflurane as an example. The authors conclude that physostigmine can at least partially antagonize the hypnotic effect of sevoflurane, and that the resulting arousal is reflected by an increase in the amplitude of the auditory steady-state response (ASSR) and, to a lesser extent, of the bispectral index score (BIS). Nevertheless, the effect of sevoflurane was not as clear or reliable as that seen with propofol,[2] and Plourde and colleagues[1] were unable to speculate about its cause.

The inhibition of acetylcholinesterase enhances cholinergic synaptic transmission.[3] Previous studies showed that intrathecal neostigmine probably inhibits the metabolism of spinally released acetylcholine (Ach) in cerebrospinal fluid,[4] and co-administration of intrathecal physostigmine with Ach potentiates the action of Ach.[5] Furthermore, intrathecal neostigmine inhibits the activity of cholinesterase present in the spinal cord, thereby increasing the cerebrospinal fluid level of Ach.[6] It is conceivable that intrathecal administration of cholinesterase inhibitors may increase the concentration of cerebrospinal Ach, which in turn may act on spinal nicotinic receptors.[7]

Although there is considerable uncertainty about the physiological roles that nicotinic acetylcholine receptors (nAChRs) play in the central nervous system, their extraordinary sensitivity to general anaesthetics, particularly inhalational agents, suggests they may mediate some of the effects of general anaesthetics at surgical, or even subanaesthetic, concentrations.[8] Volatile anaesthetics are potent inhibitors of nAchRs receptors with clinically relevant IC_{50} values.[9 10] Moreover, subanaesthetic concentrations of volatile anaesthetics inhibit activation of nAChRs. Sevoflurane reduces the binding of nicotinic receptor agonists, at concentrations at and above those required for anaesthesia.[11] The mechanism by which volatile anaesthetics reduce the activation of nicotinic acetylcholine receptors is unknown.[11] At the nicotinic acetylcholine receptor and in concentrations equal to and less than those encountered clinically, sevoflurane affects the open and the closed state of the channels; the current elicited by acetylcholine is reduced reversibly and in a concentration-dependent manner.[12] Moreover, even with concentrations equal to or less than those encountered clinically, isoflurane and sevoflurane act primarily through the same mechanisms affecting the open and closed state of the channels. The time courses of current decay can be fitted by single exponentials for isoflurane, whereas for sevoflurane the current decay becomes biexponential. The kinetics of desensitization are also altered in a different manner. Thus, there may be several different sites of interaction between volatile anaesthetics and the nicotinic receptor.[12]

Propofol also exerts an inhibitory effect on these nicotinic receptors, but only at high concentrations.[9,10] The inhibition of the $\alpha 4\beta 2$-receptor by both volatile anaesthetics and propofol appears to be competitive with respect to acetylcholine.[13] Nevertheless, volatile anaesthetics induce a 'flickery' pattern in which openings occur in brief bursts, whereas propofol causes the channels to appear as isolated brief openings.[14]

These findings, taken together, support not only the hypothesis that volatile anaesthetics and propofol act differently on the nicotinic receptors, accounting for the different response to physostigmine administration, but also demonstrate that the results obtained by Plourde and colleagues[1] should be applied with caution to other volatile anaesthetics in terms of modification of the hypnotic effect. Sevoflurane may not be representative of all volatile anaesthetics, which act differently at nicotinic receptors. This possibility is also consistent with the study by Hill and colleagues,[15] reporting that physostigmine decreased the time for return of consciousness after halothane anaesthesia, suggesting that antagonism does occur. In the study by Plourde and colleagues,[1] physostigmine partially antagonized the hypnotic effect of subanaesthetic concentration of sevoflurane, but in the study by Paraskeva and colleagues[16] the antagonism did not occur during sevoflurane anaesthesia at clinical concentrations.

Finally, reading the interesting study by Plourde and colleagues,[1] some questions arise regarding the clinical relevance of these findings. If reversal of neuromuscular block occurs during anaesthesia using physostigmine, could patients be at risk of intraoperative awakening? Could it have legal implications? Should the monitoring of the level of anaesthesia, using the auditory steady-state response and/or the BIS, be essential when a centrally acting anticholinesterase is administered?

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Editor—We appreciate the interest expressed by Drs Fodale and Santamaria in our article.[1] We did not speculate about the subtype(s) of cholinergic processes involved because this was beyond the scope of our study. In our article concerned with propofol,[2] we presented evidence implicating muscarinic receptors. Drs Fodale and Santamaria present interesting arguments to suggest that propofol and sevoflurane interfere with nicotinic transmission and attempt to explain why antagonism of anaesthesia by physostigmine is more reliably achieved for propofol[2] than sevoflurane.[1]

Enthusiasm for the role of decreased central nicotinic transmission as a common mechanism mediating the hypnotic effect of anaesthetics should be tempered with the observations that nicotinic antagonists do not produce hypnosis nor do they decrease the dose of isoflurane required for loss of the righting reflex in mice.[17] In addition, there is a lack of stereoselective inhibitory effect of ketamine[18 19] and thiopental[20 21] on nicotinic receptors, although these drugs demonstrate stereoselective hypnotic effects. Moreover, the inhibitory effect of propofol and etomidate on nicotinic receptors occurs with doses higher that those that are clinically relevant.[22 23] Furthermore, the extensive clinical and experimental literature implicating anaesthetic action on muscarinic processes[2 24–28] should not be ignored. Finally, anaesthetic drugs may interfere with cholinergic transmission indirectly, by altering activity in non-cholinergic neuronal systems projecting to cholinergic neurones.

We agree that our observations with sevoflurane should be applied cautiously to other volatile drugs. Current practice is to employ a peripherally-acting anticholinesterase drug to antagonize neuromuscular block. Administration of a centrally acting agent for this purpose could potentially increase the risk of intraoperative awareness. We are unclear as to why Drs Fodale and Santamaria should consider embarking on this venture.

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