Different actions of volatile and intravenous anesthetics on interneurons in organotypic spinal cord slices

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Abstract

Background: Immobility is an important aspect of anesthesia. It is now well accepted that ablation of spontaneous and stimulus-induced movements by general anesthetics is spinally mediated. Comparing the effects of sevoflurane and propofol on spontaneous action potential firing, we have recently shown that the capacity of propofol, but not sevoflurane, in depressing spinal neurons is limited. This finding is explained by the observation that the effects of propofol were almost exclusively mediated by GABA\_A receptors, whereas sevoflurane acted predominantly via glycine and GABA\_B receptors. Two questions are addressed in this study: (1) Do isoflurane and enfurane have a greater capacity in depressing spontaneous action potential firing than diazepam and etomidate? (2) Are the depressant effects of diazepam and etomidate restricted to GABA\_A receptors and thus differ from the effects of isoflurane and enfurane?

Methods: Organotypic spinal cord tissue slices were achieved from pregnant Sprague-Dawley rats (day 13-15) according to the method described by Braschler, and used for experiments after 12 days in vitro. The effects of isoflurane, enfurane, diazepam, and etomidate on spontaneous action potential firing were investigated by extracellular voltage recordings from ventral horn interneurons. All procedures were approved by the animal care committee and were in accordance with the German law on animal experimentation.

Results: Isoflurane, enfurane, diazepam, and etomidate reduced spontaneous action potential firing of neurons. Concentrations causing half-maximal effects (isoflurane: 0.17 mM; enfurane: 0.50 mM; diazepam: 1.41 µM; etomidate: 0.21 µM) were smaller than the EC\_50 of immobility (isoflurane: 0.32 mM; enfurane: 0.62 mM; diazepam: 1.5 µM). At higher concentrations, complete inhibition of action potential firing were investigated by extracellular voltage recordings from ventral horn interneurons. All procedures were approved by the animal care committee and were in accordance with the German law on animal experimentation.

Conclusions: Our results suggest that glycine and GABA\_A receptors are the most important molecular targets mediating depressant effects of isoflurane, like it was reported previously for sevoflurane. For enfurane, GABA\_B and glycine receptors mediated approximately only half of its depressant capacity. The enfurane results are consistent with recent findings obtained from whole spinal cords in mice. Furthermore, our results provide evidence that volatile anesthetics cause immobility by a mechanism distinct from the actions of the interneuronal anesthetics diazepam and etomidate, which exclusively seems to act via GABA\_A receptors. Our results are consistent with the hypothesis that volatile anesthetics produce immobility via multiple molecular targets in the spinal cord, whereas effects of intravenous anesthetics are restricted to GABA\_A receptors.

References:

Methods

Fig. 1: Extracellular recording from an interneuron in a spinal cord-dorsal root ganglion culture after two weeks in vitro. Action potentials appeared in bursts, separated by silent periods. The broken line indicates the threshold for event detection.

Fig. 4: Estimated contributions of molecular targets to the effects of isoflurane (0.75 MAC), enfurane (1 MAC), etomidate (0.5 µM), and diazepam (2.5 µM) on the mean firing rates. These concentrations were considered equipotent since they decreased spontaneous network activity by approximately 60%. Effects of the anesthetics in the absence of bicuculline and strychnine were taken as 100%

Table 1: Half-maximal depression of average spike rates and Upper limits, as calculated from the concentration-response fits in figure 2.