The Central Nervous Stimulating Effect of Four Different Halogenated Ether Anesthetics and Halothane in Mice

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Although enflurane is a convulsive anesthetic, its structural isomer, isoflurane, is believed not to be. We reported previously that, unexpectedly, isoflurane more frequently produced opisthotonus in young mice, especially during the induction period, than enflurane. In the present study, we examined the incidences of opisthotonus induced by four halogenated ether anesthetics and halothane to evaluate their CNS stimulating actions. As experimental animals, we used young male mice, with another two aged groups of male mice to clarify the relationship of the incidence of opisthotonus to aging. The percentage incidence of opisthotonus was 93% for sevoflurane, 81% for isoflurane, 64% for enflurane, 17% for methoxyflurane and 2% for halothane. These results suggest that the halogenated ether anesthetic, which is rapidly uptaken by the CNS during induction, is more likely to produce CNS stimulation, subsequently leading to opisthotonus. There was no age related susceptibility difference to anesthetic-induced opisthotonus, except for enflurane, in which the incidence of opisthotonus was higher in the aged group. (Key words: CNS stimulation, volatile anesthetics, aging)

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Enflurane depresses the central nervous system (CNS) as an anesthetic agent, but at the same time it has a CNS stimulating action as a convulsant. On the other hand, isoflurane, a structural isomer of enflurane, is thought to be an intense CNS depressant without CNS stimulating action[1]. Recently, we found that some strains of mice frequently developed opisthotonus during induction of isoflurane anesthesia than with enflurane or halothane anesthesia[2,3]. From these results, we hypothesized that the high incidence of opisthotonus was related to the high rate of cerebral uptake of anesthetic. To confirm this, we examined the incidence of opisthotonus with four halogenated ethers (sevoflurane, isoflurane, enflurane and methoxyflurane) and halothane. In our previous study, we examined only rather young male mice (10 ± 2 weeks old). It is stated that the brain tissue levels of catecholamines and acetylcholine levels, cerebral blood flow, cerebral oxygen consumption and glucose utilization, all decrease in aged animals[4,5]. In the present study, we investigated the incidence of opisthotonus in three different age groups of mice to evaluate the age effect on CNS excitation produced by volatile anesthetics. As anesthetics, we used 2.0% sevoflurane, 1.3% isoflurane, 2.0% enflurane, 0.5% methoxyflurane and 1.0% halothane in air, respectively. As experimental animals, we used male ddN mice in 3 age groups; 10 ± 2 weeks old, 6 ± 1 months old,

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Table 1. Percentage incidence of opisthotonus during induction of anesthesia in three age groups of mice

age group / anesthetics	10±2 weeks old	6±1 months old	13±1 months old	total
sevoflurane 2.0% pc = 0.6	94% (n = 34)	86% (n = 7)	93% (n = 45)	93% (n = 86)
isoflurane 1.3% pc = 1.41	82% (n = 22)	84% (n = 19)	80% (n = 117)	81% (n = 158)
enflurane 2.0% pc = 1.78	42% (n = 45)	45% (n = 11)	78% (n = 98)	64% (n = 154)
methoxyflurane 0.5% pc = 12.0	13% (n = 32)	6% (n = 17)	21% (n = 80)	17% (n = 129)
halothane 1.0% pc = 2.3	0% (n = 34)	0% (n = 18)	3% (n = 88)	2% (n = 140)

*pc: blood/gas partition coefficient at 37°C[11,12]

and 13 ± 1 months old, respectively. The above mentioned concentrations of anesthetic agents, except for sevoflurane and methoxyflurane, were considered to be close to those of MAC[6]. MAC of sevoflurane in mice and methoxyflurane in rats has been reported to be 1.4%[7] and 0.22%[8] respectively, but these reports are likely to underestimate the value for ddN mice; accordingly we used 2.0% sevoflurane and 0.5% methoxyflurane. Each volatile anesthetic in air was administered into a 12 L plastic chamber using a 5 L/min gas flow through the vaporizer. After equilibrating the chamber with anesthetic gas, mice were transferred to the chamber and anesthetized. Room temperature was maintained at 24 ± 2°C throughout the experiment. Observation time was up to 30 min, which we thought to be enough time to determine whether opisthotonus would occur. After observation, application of anesthetic was discontinued and all mice recovered from anesthesia within a few minutes.

The percentage incidence of opisthotonus during induction of anesthesia and blood/gas partition coefficients of anesthetics used in this study are shown in table 1. It appears that in halogenated ethers the higher incidence of opisthotonus was found in anesthetics with lower value of blood/gas partition coefficients. This firmly suggests that CNS excitation by halogenated ethers relates to the rate of cerebral uptake of anesthetics during induction of anesthesia. Halothane hardly ever produced opisthotonus and the incidence was much less than with methoxyflurane. This may relate to the different general characteristics between halogenated hydrocarbons and halogenated ethers. In general, halogenated ethers are more convulsive than halogenated hydrocarbons[9].

With regard to the age effect, we found no difference in the incidence of opisthotonus among the three age groups for each agent except for enflurane which produced a higher incidence of opisthotonus in the advanced age group. Very little is known about the relationship between aging and CNS excitation due to anesthetic agents. Our data seem to show that aging has no relation to CNS excitation due to anesthetics during induction except for enflurane in the advanced age group. In clinical experiences, CNS excitation seems to be more intense in

children than in the aged during induction and on recovery from anesthesia. It is unclear where this discrepancy comes from, and why the incidence of opisthotonus increases with increasing age in the enflurane group. It may be connected with the age-related increase in glutamate receptor concentration (in rats)[10]. The changes with age may be correlated with many different aspects of the aging process. Neuronal density of the brain and cerebral metabolic rate decrease with age[8]. To clarify the mechanism of opisthotonus due to anesthetics and its age effects, further detailed examination will be necessary.

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