Protection by Halothane of the Vagal Baroreflex System from Transient Global Cerebral Ischemia in Dogs

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ABSTRACT — A possible cerebroprotective effect of halothane was investigated in a canine model of 5-min global cerebral ischemia. In pentobarbital-anesthetized dogs, additional inhalation of 0.5 to 1% halothane prior to ischemia prevented the post-ischemic dysfunction of the vagal component of reflex bradycardia. In contrast, pretreatment with thiopental at 10 mg/kg, i.v. failed to prevent it. The influence of ischemia in the absence of anesthetics was similar to that under barbiturate anesthesia. The results suggest that halothane, but not barbiturate, may actively protect the vagal baroreflex system from ischemia.

Keywords: Cerebral ischemia, Halothane, Vagal baroreflex

Halothane has been generally considered to be less cerebroprotective than barbiturates against ischemic neuronal injury (1–3). On the contrary, in the previous study (4), we found that the central vagal baroreflex system was more resistant to transient global cerebral ischemia under halothane anesthesia than barbiturates anesthesia. However, it remains to be elucidated whether halothane is actively more protective than barbiturates against the ischemic dysfunction of the baroreflex system or only less harmful for it. Thus, the present study compared the influence of the pretreatment with halothane and thiopental on the post-ischemic dysfunction of the vagal component of reflex bradycardia in pentobarbital-anesthetized dogs. Additionally, the influence of the withdrawal of anesthesia prior to ischemia was investigated in halothane anesthetized dogs.

Mongrel dogs of either sex, weighing about 6 to 17 kg, were anesthetized with sodium pentobarbital (32 mg/kg, i.v., followed by an infusion of 3.2 mg/kg/hr, i.v.) or halothane (2% in room air for induction and 0.75 to 1.0% in room air for maintenance). The animals were artificially ventilated (a tidal volume of 20 ml/kg at a rate of 20 breaths/min) and immobilized with suxamethonium chloride (2 mg/kg, i.v., followed by an infusion of 1 mg/kg/hr, i.v.). Arterial P O2 and P CO2 were maintained at about 100 and 35 mmHg, respectively, providing an appropriate volume of O2 and CO2 gasses via a respirator. The rectal temperature was maintained at about 38°C using a heating pad and lamp.

Arterial blood pressure was measured from the left femoral artery by means of a pressure transducer (Nihon Kohden, TP-200T), and heart rate was measured by a heart rate counter (Nihon Kohden, AT-600G) triggered by the lead II ECG. The cortical EEG was continuously monitored from the parietal skull using a frequency analyzer (Nihon Kohden, OEE-7102). Reflex increase in pulse interval by L-phenylephrine hydrochloride (0.3 to 10 μg/kg injected into the left cephalic vein) was correlated with the increase in mean blood pressure by the method of least squares. The slope of the regression line (msec/mmHg) was used as a measure of baroreflex sensitivity (BRS). Incomplete global cerebral ischemia was produced by a 5-min occlusion with clamps of the brachiocephalic artery and the left subclavian artery following ligations of about 14 intercostal arteries. Regional cerebral blood flow in the dorsal medulla oblongata was continuously measured by a tissue flow monitor (Unique Medical, UMW-101) using a plate-type thermocouple electrode, and the mean residual blood flow during ischemia was calculated as an index of the severity of ischemia (5).

In 8 animals under pentobarbital anesthesia (Fig. 1A), halothane (2% in room air) was given for 5 min just after the measurement of BRS. Then, the concentration of halothane was reduced to 0.5 to 1% (0.88 ± 0.07% in average) 10 min prior to ischemia. Halothane
was withdrawn at the end of ischemia. In another 6 animals under pentobarbital anesthesia (Fig. 1B), sodium thiopental (10 mg/kg, i.v.) was administered for over 3 min just after the measurement of BRS, and the animals were subjected to ischemia 10 min later. Administration of halothane or thiopental increased the depth of anesthesia, producing an intermittent burst suppression of the cortical EEG in 5 out of 8 or 4 out of 6 animals, respectively, and reducing α (8 to 12.5 Hz) and β (13 to 32 Hz) components of the EEG in the rest of the animals. Since our previous study (4) indicated that a period of 60 to 120 min was necessary for the recovery from anesthesia with thiopental (10 mg/kg, i.v.), BRS was measured during the period later than 120 min of reperfusion in animals pretreated with thiopental to avoid any direct effect of the additional anesthesia on BRS measurement. In the third group of 6 animals under halothane anesthesia (Fig. 1C), halothane was withdrawn just after the measurement of BRS, and the animals were subjected to ischemia 15 min later. Judging from the change in the cortical EEG, halothane seemed to be well-eliminated until the ischemic insult. The animals were re-anesthetized with halothane 5 to 10 min after reperfusion and kept under halothane anesthesia thereafter.

As shown in Fig. 1A, addition of halothane to background anesthesia with pentobarbital prevented the post-ischemic decrease in BRS. Bilateral section of the cervical vagosympathetic trunk (vagotomy) decreased BRS by 50.9 ± 2.6% (n = 8), indicating that the vagal component of BRS was well-preserved. On the other hand, thiopental failed to prevent the post-ischemic decrease in BRS (Fig. 1B), and no significant influence of vagotomy on BRS was observed. In halothane-anesthetized animals, ischemic insult following withdrawal of halothane produced a significant post-ischemic decrease in BRS (Fig. 1C). In these animals, vagotomy failed to affect BRS.

Figure 2 shows the correlation between the severity of ischemia and the extent of damage of the vagal component of BRS. The correlation in the animals that were treated with halothane (open circles) was similar to that in the animals subjected to ischemia under halothane anesthesia in the previous study (4), where the correlation curve (dotted line H in Fig. 2) indicated that the vagal component of BRS survived an ischemic insult, if the mean residual blood flow during ischemia was greater than approximately 30%. On the other hand, the data from animals subjected to ischemia under combined anesthesia with pentobarbital and thiopental (closed circles) or in the absence of anesthesia (open triangles) fitted the regression curve (dotted line P in Fig. 2) obtained previously under pentobarbital anesthesia (6). In these cases, the vagal component of the baroreflex was completely abolished when the residual blood flow during ischemia was lower than approximately 50%. Thus, the present study demonstrated that halothane, but not thiopental, may actively protect the vagal component of the baroreflex from 5-min global cerebral ischemia. Additionally, barbiturate
seemed to possess no deleterious effect on ischemic damage of the vagal baroreflex.

Since both halothane and thiopental increased the depth of background anesthesia with pentobarbital in a similar manner, the change in the depth of anesthesia itself may be independent of the cerebral protection by halothane. Recently, we found that a2-adrenoceptor blocking agents, yohimbine and idazoxan, had a cerebroprotective effect in the same canine model of cerebral ischemia as used in the present study, suggesting that the a2-adrenoceptor system may be involved in the pathogenesis of the ischemic damage of the vagal baroreflex (7). In this context, it is interesting that halothane has been shown to inhibit a2-adrenoceptor-mediated vasoconstriction in rats (8) and dogs (8, 9), and a2-adrenergic modulation of adenylate cyclase activity in rat cerebral cortex (10). Halothane also inhibits signal transduction through M2-cholinergic receptors (11). Nevertheless, it seems that the ability of halothane to inhibit receptor-mediated signal transduction in the brain is receptor-specific, because halothane is devoid of influence on other receptors coupled to G protein, adenosine A1 and 5-HT1A receptors (12). In contrast with these observations, Armstrong et al. (13) showed that pentobarbital failed to affect the cardiovascular responses mediated by peripheral and central a2-adrenoceptors in rats. Therefore, it is likely that the cerebroprotective effect of halothane in the present study may be due to the blockade of central a2-adrenoceptor system, although the mechanism of the blockade is still controversial. Baumgartner et al. (10) showed in rat cerebral cortical membranes that halothane disturbed the a2-adrenoceptor–G protein interactions. On the other hand, Wikberg et al. (14) suggested that halothane induces a direct conformational change in the ligand binding subunit of the a2-adrenoceptor in mouse cerebral cortical membranes.

![Fig. 2. Correlation between the severity of ischemia and the extent of the influence of vagotomy on the baroreflex sensitivity during the reperfusion period. Abscissa scale: severity of ischemia is indicated as the mean residual blood flow in the dorsal medulla oblongata during ischemia. Ordinate scale: the extent of the influence of vagotomy is indicated as the ratio of the baroreflex sensitivity after vagotomy to that before vagotomy. • and △ represent the individual data from the animals included in groups A, B and C in Fig. 1, respectively. The broken lines H and P are the superimpositions of the logistic regression curve obtained in the previous studies where anesthesia was maintained solely with halothane (reference 4) and pentobarbital (reference 6), respectively, throughout the experiments.]

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