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Differential effects of halothane, enflurane, isoflurane, and sevoflurane on the hemodynamics and metabolism in the perfused rat liver in fasted rats

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Abstract: The effects of volatile anesthetics on hepatic hemodynamics and metabolism were studied using isolated liver perfusion. The liver was isolated from overnight-fasted male Sprague-Dawley rats and placed in a recirculating perfusion-aeration system. The liver was perfused through the portal vein at a constant pressure of 12 cmH_2O. Four volatile anesthetics, halothane, enflurane, isoflurane, and sevoflurane, were administered at concentrations identical to 1 and 2 times the minimal alveolar concentration (MAC). All the anesthetics maintained hepatic flow and decreased hepatic oxygen consumption. Among the anesthetics tested, isoflurane produced the largest decrease in hepatic oxygen consumption. At 2 MAC, the percent decrease in oxygen consumption by isoflurane was significantly greater than that by halothane. The increase in lactate concentration in the recirculating perfusate was significantly enhanced by the volatile anesthetics, and the enhancement was less remarkable in the isoflurane-treated group than in the enflurane- or sevoflurane-treated groups. These results indicate that volatile anesthetics alter hepatic carbohydrate metabolism but maintain hepatic blood flow when the perfusion pressure is kept constant. Isoflurane exerts exceptional influence on hepatic oxygen consumption and lactate production, and may be preferable for operations that limit the oxygen supply to the liver.

Key words: Volatile anesthetics, Isolated liver perfusion, Oxygen consumption, Glucose, Lactate production

Introduction

Not only surgical procedures but also anesthesia alters the hepatic circulation and metabolism. Previous in vivo experiments have shown that volatile anesthetics influence cardiac output, blood flow distribution to the liver, and may modify various metabolic functions of the liver [1–7]. Since some of these *in vivo* metabolic actions are confirmed in the perfused rat liver [7–11] and isolated rat liver mitochondria [12–14], it is suggested that volatile anesthetics directly act on the liver. However, little is known about the difference in direct actions among volatile anesthetics. The present study was conducted to compare the direct effects on hepatic basal hemodynamics and metabolism in the isolated perfused liver among halothane, enflurane, isofiurane, and sevoflurane.

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Materials and methods

Animals and care

The experiments described here were approved by Animal Experimentation Committee in our university and performed in adherence with NIH guidelines. Eight-to 10-week-old, male Sprague-Dawley rats with body weights of 250 to 310 g were obtained from Japan SLC (Shizuoka, Japan). They were acclimated to our animal research facilities for at least 1 week at a room temperature of 24°–26°C. They had free access to standard laboratory chow and water under a 12:12 h light-dark cycle. All animals were fasted overnight before the experiment.

Solution

The perfusion medium was a modified Krebs-Ringer-bicarbonate (mKRB) solution. It contained (in mM) NaCl 117, KCl 4.7, $CaCl_2$ 1.5, KH_2PO_4 1.19, $MgSO_4$ 1.44, and $NaHCO_3$ 24.8. The mKRB solution was saturated with a 95% O_2/5% CO_2 gas mixture, and the pH was adjusted to 7.35 ± 0.05 using 1N NaOH or $NaHCO_3$.

Isolated perfusion of rat liver

The liver was excised and perfused as described previously [15,16]. Briefly, the rats were anesthetized with an intravenous injection of pentobarbital sodium at 35 mg/kg via dorsal pedis vein, and the abdomen was opened. After intravenous injection of heparin sodium at 50 units, the inferior vena cava was ligated above the renal veins. A polyethylene catheter (PE-240 Becton Dickinson and Company, NJ, USA) was inserted into the portal vein and secured in place. The hepatic artery was ligated. A nonrecirculating perfusion with mKRB was immediately initiated and continued during the following surgical procedure to minimize the anoxic period. The thorax was opened and another polyethylene catheter (PE-260 Becton Dickinson and Company, NJ, USA) was inserted through the right atrium and secured in the inferior vena cava. The liver was gently excised and placed in a modified Miller-type recirculating perfusion-aeration chamber. The liver was perfused at a constant pressure of 12 cmH_2O with mKRB containing 0.5% albumin, 10 mM b(+)-glucose. The recirculating volume was 200 ml. The temperature of the perfusate was automatically kept at 37°C, and the pH was maintained in a range of 7.3 ± 0.05 by a continuous infusion of 1 N NaOH.

Determinations

Hepatic flow was monitored continuously by an electromagnetic flow transducer (Nihon Koden, Tokyo, Japan). Two needle-type oxygen electrodes (Intermedical, Nagoya, Japan) were placed in both inflow and outflow chambers to monitor the partial pressure of oxygen (Po_2). Oxygen consumption of the perfused liver was calculated from hepatic flow and the difference in Po_2 between inflow and outflow chambers. Approximately 30 µl of perfusate was sequentially collected, and was analyzed for D-glucose and L-lactate with a YSI 2300 analyzer (YSI, MI, USA).

Experiment protocol

Approximately 30 min after the initiation of perfusion, the hepatic flow and oxygen consumption were stabilized, and then the measurements were commenced in all groups (time 0). Fifteen min after the first basal measurements (time 15), the liver in the anesthetic groups was exposed to volatile anesthetics at a concentration equivalent to 1 times the minimal alveolar concentration (MAC): 1.0% for halothane, 2.2% for enflurane, 1.5% for isoflurane [17], and 2.2% for sevoflurane [18]. Following a 15-min equilibration period, the concentrations of anesthetics were raised to 2 MAC (time 30), and maintained for 15 min.

Acomatec (ACOMA, Tokyo), Abindon (Penlon, London, UK), Forawick (Murako, Tokyo, Japan), and PPVS (Penlon, London, UK) were used for vaporization of halothane, enflurane, isoflurane, and sevoflurane, respectively. The flow rate of the O_2/CO_2 gas mixture into the perfusion system was set at 2 l/min. Accuracy of vaporizers at this gas flow rate was checked with a Capnomac analyzer (Datex, Helsinki, Finland). In preliminary experiments, the concentrations of volatile anesthetics in the medium were determined by gas chromatographic head space analysis [19]. Samples were collected into tightly capped glass tubes from the outflow chamber after the administrations of volatile anesthetics at 1 or 2 MAC. Samples were stored in a refrigerator (4°C) until assay. Standard solutions were prepared in the mKRB solution. A 1-ml volume of sample was transferred to an empty 10-ml headspace tube, and the tube was capped. The tube was vortexed and incubated at 70°C for 60 min. A 1-ml volume of equilibrated headspace vapor was injected into a gas chromatograph (Shimadzu GC-14A or GC-8A, Tokyo, Japan). The concentrations of anesthetics were calculated from the area of the specific peak.

Statistical analysis

Comparisons among the treatment groups were made at each sampling point using one-way analysis of variance (ANOVA) followed by Duncan's multiple range test. Changes in variables from time 0 were analyzed for each treatment group using two-analysis of variance followed by Duncan's multiple range test. Differences and changes were considered to be significant when the P values were less than 0.05. All values are expressed as mean ± SD.

Results

As demonstrated in Table 1, the anesthetic concentrations in the medium quickly rose after the administration of volatile anesthetics. The desired concentration appeared to be obtained within 15 min after commencement of the administration.

Table 2 demonstrates the effects of volatile anesthetics on hepatic flow. There were no significant differences in hepatic flow among the treatment groups from time 0 to time 45. However, hepatic flow decreased slightly but significantly from the basal (time 0) value in the control group at time 45, while it increased slightly but significantly in the enflurane-treated group at times 35, 40, and 45 and in the isoflurane-treated group at times 40 and 45. Thus, the percent change in hepatic flow from the basal value significantly differs between control group and enflurane- or isoflurane-treated groups at times 40 and 45.

Table 1. Sequential determinations of volatile anesthetic concentrations (mg/dl) in the medium

Anesthetics (% concentration)	Time after administration (min)					
	0	5	10	15	30	40
1 MAC						
Halothane (1.0%)	0	4.18	5.38	4.34	5.35	4.51
Enflurane (2.2%)	0	9.77	10.08	9.70	12.78	12.34
Isoflurane (1.5%)	0	4.76	5.37	6.59	6.26	5.66
Sevoflurane (2.2%)	0	5.73	8.36	9.97	11.56	11.85
2 MAC						
Halothane (2.0%)	0	7.71	8.40	9.59	13.02	10.46
Enflurane (4.4%)	0	15.64	21.10	19.40	20.55	18.65
Isoflurane (3.0%)	0	10.16	12.53	12.39	13.35	11.67
Sevoflurane (4.4%)	0	13.61	15.49	19.01	18.82	19.54

Values are mean of duplicated determinations.
MAC: minimum alveolar concentration.

Table 2. Effects of volatile anesthetics on hepatic flow (ml/min)

		Concentration of anesthetics/time (min)									
		0 MAC				1 MAC			2 MAC		
Anesthetics	*n*	0	5	10	15	20	25	30	35	40	45
Control	6	52.0 ± 3.9 (100)	52.0 ± 4.0 (100.0 ± 1.3)	52.2 ± 4.0 (100.3 ± 2.0)	52.2 ± 4.0 (100.3 ± 2.0)	52.0 ± 4.0 (100.0 ± 2.5)	52.2 ± 4.0 (100.0 ± 2.5)	51.5 ± 4.0 (99.0 ± 2.8)	51.5 ± 4.0 (99.0 ± 2.8)	51.3 ± 4.2 (98.7 ± 3.0)	51.2 ± 4.3[¶] (98.3 ± 2.3)
Halothane	6	50.3 ± 2.7 (100)	50.3 ± 2.7 (100.0 ± 0)	50.3 ± 2.7 (100.0 ± 1.3)	50.5 ± 2.6 (100.3 ± 1.5)	50.7 ± 2.9 (100.7 ± 1.6)	50.8 ± 2.9 (101.0 ± 2.1)	51.0 ± 2.7 (101.3 ± 1.6)	51.0 ± 2.7 (101.3 ± 1.6)	50.7 ± 2.5 (100.7 ± 2.1)	50.8 ± 2.3 (101.0 ± 1.7*)
Enflurane	6	54.3 ± 4.8 (100)	54.3 ± 4.8 (100.0 ± 0)	54.3 ± 4.8 (100.0 ± 0)	54.2 ± 4.5 (99.7 ± 0.8)	54.5 ± 4.2 (100.3 ± 1.5)	54.5 ± 4.5 (100.3 ± 1.5)	54.5 ± 4.2 (100.3 ± 1.5)	55.2 ± 4.4[¶§] (101.5 ± 2.3)	55.5 ± 4.6[¶§] (102.2 ± 1.6*)	55.7 ± 4.3[¶§] (102.5 ± 1.8*)
Isoflurane	6	51.3 ± 3.9 (100)	51.5 ± 3.8 (100.3 ± 0.8)	51.5 ± 3.8 (100.7 ± 1.0)	51.7 ± 3.8 (100.7 ± 1.0)	51.8 ± 3.5 (101.0 ± 1.1)	51.7 ± 3.8 (100.7 ± 1.0)	51.8 ± 3.5 (101.0 ± 1.1)	52.0 ± 3.3 (101.3 ± 1.6)	52.2 ± 3.4[§] (101.7 ± 1.5*)	52.2 ± 3.4[§] (101.7 ± 1.5*)
Sevoflurane	6	55.7 ± 3.4 (100)	55.7 ± 3.4 (100.0 ± 0)	55.5 ± 3.6 (99.7 ± 0.8)	55.3 ± 3.7 (99.3 ± 1.0)	55.5 ± 3.6 (99.7 ± 0.8)	55.5 ± 3.8 (99.7 ± 1.5)	55.5 ± 3.8 (99.7 ± 1.5)	55.7 ± 3.6 (100.0 ± 1.3)	55.7 ± 3.6 (100.0 ± 1.3)	55.8 ± 4.0 (100.2 ± 1.6)

Values are mean ± SD. Values in *parentheses* are % changes from time 0.
MAC minimum alveolar concentration.
[¶] Significant change from time 15 (immediately before the administration of anesthetics) within each group
[§] Significant change from time 30 (1 MAC) within each group ($P < 0.05$, two-way ANOVA followed by Duncan's multiple range test).
* Significant difference from control group ($P < 0.05$, one-way-ANOVA followed by Duncan's multiple range test).

Table 3. Effects of volatile anesthetics on hepatic oxygen consumption (μl/min)

		Concentration of anesthetics/time (min)									
		0 MAC				1 MAC			2 MAC		
Anesthetics	*n*	0	5	10	15	20	25	30	35	40	45
Control	6	432.0 ± 59.7 (100)	438.7 ± 64.1 (101.3 ± 3.6)	441.3 ± 60.8 (102.3 ± 5.0)	441.3 ± 65.1 (102.3 ± 6.8)	437.5 ± 65.6 (101.2 ± 5.6)	433.2 ± 65.4 (101.2 ± 5.5)	423.8 ±63.9 (97.8 ± 5.7)	429.7 ± 59.1 (99.5 ± 5.2)	426.5 ± 61.6 (99.0 ± 7.5)	418.0 ± 58.4 (97.2 ± 8.4)
Halothane	6	400.0 ± 36.0 (100)	404.8 ± 37.5 (101.3 ± 2.5)	406.3 ± 39.1 (101.7 ± 4.8)	406.3 ± 46.1 (101.7 ± 5.7)	399.5 ± 46.0 (98.3 ± 4.0)	389.2 ± 45.8 (97.3 ± 6.5)	390.5 ± 44.4 (97.7 ± 5.6)	371.0 ± 46.2[¶§] (92.7 ± 6.3)	361.8 ± 43.4[¶§] (90.3 ± 1.7)	361.2 ± 46.6[¶§] (90.2 ± 6.7)
Enflurane	6	467.0 ± 24.1 (100)	468.7 ± 22.6 (100.2 ± 3.9)	471.7 ± 29.4 (100.7 ± 3.8)	471.5 ± 39.0 (100.8 ± 5.0)	462.8 ± 37.2 (99.2 ± 5.1)	445.8 ± 22.1 (95.5 ± 3.6)	443.5 ± 20.2[§] (94.8 ± 3.8)	411.0 ± 27.1[¶§] (88.3 ± 7.4*)	413.3 ± 37.6[¶§] (88.7 ± 8.8*)	404.0 ± 33.4[¶§] (86.3 ± 4.7*)
Isoflurane	6	433.0 ± 65.4 (100)	430.7 ± 83.3 (99.8 ± 6.0)	437.7 ± 81.8 (100.7 ± 6.0)	437.5 ± 78.8 (100.7 ± 5.7)	413.3 ± 66.3 (95.3 ± 4.2)	401.7 ± 64.6[§] (92.8 ± 7.2)	402.0 ± 61.3[§] (93.0 ± 8.9)	372.3 ± 60.7[¶§] (86.2 ± 8.5*)	362.2 ± 69.3[¶§] (83.7 ± 8.8*)	351.2 ± 69.4[¶§] (80.8 ± 8.6*[#])
Sevoflurane	6	439.7 ± 37.4 (100)	442.2 ± 46.2 (100.7 ± 2.2)	433.0 ± 42.4 (98.7 ± 3.2)	435.7 ± 44.0 (99.0 ± 4.9)	416.5 ± 48.0[¶] (94.8 ± 6.0)	406.7 ± 60.8[¶] (92.3 ± 7.3)	408.5 ±60.4[¶] (92.5 ± 6.4)	391.5 ± 53.7[¶] (88.8 ± 5.6*)	385.7 ± 51.3[¶§] (87.5 ± 5.4*)	384.2 ± 57.6[¶§] (87.2 ± 6.7*)

Values are mean ± SD. Values in parenthesis are % changes from time 0.
MAC, minimum alveolar concentration.
[¶] Significant change from time 15 (immediately before the administration of anesthetics) within each group.
[§] Significant change from time 30 (1 MAC) within each group ($P < 0.05$, two-way ANOVA followed by Duncan's multiple range test).
* Significant difference from control group.
[#] Significant difference from halothane-treated group ($P < 0.05$, one-way-ANOVA followed by Duncan's multiple range test).

As shown in Table 3, hepatic oxygen consumption was stable in the control group throughout the observation period. All anesthetics significantly decreased hepatic oxygen consumption (within-group analysis by two-way ANOVA followed by Duncan's multiple range test). When the concentration of anesthetics was 1 MAC (time 30), the percent decrease from time 0 value was 2.3 ± 5.6% for halothane, 5.2 ± 3.8% for enflurane, 7.0 ± 8.9% for isoflurane, and 7.5 ± 6.4% for sevoflurane. When the concentration was 2 MAC (time 45), the percent decrease increased to 9.8 ± 6.7% for halothane, 13.7 ± 4.7% for enflurane, 19.2 ± 8.6% for isoflurane, and 12.8 ± 6.7% for sevoflurane. There was a significant difference in the percent decrease between the isoflurane- and halothane-treated groups at 2 MAC (time 45). Thus, isoflurane decreased hepatic oxygen consumption more than halothane.

Table 4 summarizes the net glucose consumption in each treatment group. In all treatment groups, glucose consumption was kept around zero throughout the observation period. There were no significant differences in glucose consumption among the treatment groups at any anesthetic concentration. Thus, glucose consumption was not significantly influenced by the administration of anesthetics.

As shown in Table 5, the net lactate production was small and stable in the control group throughout the observation period. Net lactate production was significantly augmented in all anesthetic groups at 1 MAC. However, an increment of anesthetic concentration from 1 to 2 MAC did not further augment net lactate production. When the net lactate production was compared among the treatment groups at each anesthetic concentration, it was significantly less in the control group than in all anesthetic groups. Lactate production was significantly larger in the enflurane- and sevoflurane-treated groups than in the isoflurane-treated group.

Table 4. Effects of volatile anesthetics on net glucose consumption (μmol/min)

		Concentration of anesthetics/time period (min)		
		0 MAC	1 MAC	2 MAC
Anesthetics	*n*	10–15	25–30	40–45
Control	6	−0.6 ± 2.6	0.0 ± 2.5	0.9 ± 1.3
Halothane	6	−1.1 ± 2.9	2.0 ± 2.2	1.1 ± 1.4
Enflurane	6	1.2 ± 3.2	3.1 ± 2.7	0.1 ± 1.4
Isoflurane	6	1.1 ± 2.2	1.0 ± 1.5	1.0 ± 1.7
Sevoflurane	6	1.1 ± 1.5	1.9 ± 2.1	2.0 ± 2.2

Values are mean ± SD.
MAC, minimum alveolar concentration.
There were no significant changes in glucose consumption within any treatment group. There were no significant differences in glucose consumption among the treatment group at any MAC level.

Table 5. Effects of volatile anesthetics on net lactate production (μmol/min)

		Concentration of anesthetics/time period (min)		
		0 MAC	1 MAC	2 MAC
Anesthetics	*n*	10–15	25–30	40–45
Control	6	1.1 ± 1.3	0.4 ± 1.1	1.3 ± 1.2
Halothane	6	0.7 ± 0.7	3.3 ± 0.7¶*	3.8 ± 1.3¶*
Enflurane	6	2.0 ± 1.8	6.4 ± 2.3¶*#†	6.7 ± 2.9¶*#†
Isoflurane	6	0.2 ± 0.5	2.9 ± 1.0¶*	3.1 ± 1.0¶*
Sevoflurane	6	0.9 ± 1.6	4.7 ± 1.4¶*†	5.6 ± 2.0¶*†

Values are mean ± SD.
MAC, minimum alveolar concentration.
¶ Significant change from 0 MAC ($P < 0.05$, two-way ANOVA followed by Duncan's multiple range test).
* Significantly different from control group.
# Significantly different from halothane-treated group.
† Significantly different from isoflurane-treated group ($P < 0.05$, one-way ANOVA followed by Duncan's multiple range test).

Discussion

It has been well documented that in vivo treatment with volatile anesthetics alters hepatic blood flow. Halothane anesthesia seriously decreases both portal and hepatic arterial blood flow [1], while enflurane, sevoflurane, and isoflurane relatively preserve hepatic blood flow [2,3,4,20,21]. In the present study, all anesthetics, including halothane, maintained hepatic blood flow when the rat liver was isolated and perfused via the portal vein at a constant pressure. Therefore, the *in vivo* changes in hepatic and portal blood flow by volatile anesthetics may be attributed to their effects on cardiac output and the blood flow distribution to the gastrointestinal system, but not to their direct actions on the liver.

All volatile anesthetics produced a dose-dependent decrease in hepatic oxygen consumption. The degrees of reduction are quite similar to those described previously in the perfused liver [7,8]. In agreement with previous investigations [7,8], volatile anesthetics enhanced lactate production in the perfused liver. In a mitochondrial suspension, halothane has been shown to impede the mitochondrial energy-converting process due to inhibition of NADH dehydrogenase [8,12,13]. Depression of NAD-linked substrate oxidation has been demonstrated with other volatile anesthetics including diethylether, methoxyflurane, enflurane, isoflurane, and sevoflurane [14,22,23]. Thus, the suppression of oxygen consumption and augmentation of

lactate production by volatile anesthetics may be attributed, at least in part, to the depressed mitochondrial substrate oxidation. If mitochondrial respiration is disturbed by volatile anesthetics, then the administration of volatile anesthetics causes a depletion of hepatic ATP content and a consequent decrease in the energy charge. Supporting this is the finding of Biebuyck et al. [8] that the administration of halothane to the perfused liver interferes with ATP production. However, ATP content in intact lung and isolated lung cells has been reported not to be influenced by halothane [24,25].

There were differences in the effects on hepatic oxygen consumption and lactate production among the volatile anesthetics. Isoflurane decreased the oxygen consumption more than halothane. Isoflurane augmented the lactate production less than enflurane or sevoflurane. Thus, isoflurane produced a large reduction of hepatic oxygen consumption with a slight augmentation of lactate production. This isoflurane-induced discrepancy between oxygen consumption and lactate production suggests that mitochondrial substrate oxidative process is not the sole target of volatile anesthetics, since the depression of oxidative process in mitochondria induces, in a steady state, a decrease in oxygen consumption in parallel with an increase in lactate production. Other underlying mechanisms such as altered membrane transport functions [26] should be taken into consideration.

The liver has multiple functions, including transformation and excretion of endogenous and exogenous substances, synthesis of biologically essential substances, storage of nutrients and phagocytosis of bacteria and foreign materials. The clearance of lidocaine [11], propranolol [11], and verapamil [10], and synthesis of albumin and transferrin [9,27] in the perfused rat liver have been reported to be influenced reversibly by the administration of volatile anesthetics. Interestingly, hepatic lidocaine clearance was reported to be decreased less by isoflurane than by halothane or enflurane [11].

Intraoperatively hepatic blood flow may be reduced by surgical procedures. When the reduction is so large that oxygen supply to the liver decreases below the oxygen demend, the energy status of the liver may deteriorate. Since volatile anesthetics decrease hepatic oxygen consumption, they may protect the liver by lowering oxygen demand in such circumstances. Among the anesthetics tested, isoflurane profoundly decreased hepatic oxygen consumption but slightly augmented lactate production. This property of isoflurane suggests that isoflurane anesthesia may preserve the hepatic energy balance and carbohydrate metabolism in the operations that limit the hepatic blood flow.

In summary, we showed that volatile anesthetics decrease oxygen consumption and augment lactate production in the isolated rat liver perfused at a constant pressure. The remarkable effects of isoflurane, a more pronounced decrease in oxygen consumption and less augmentation of lactate production, suggest that isoflurane anesthesia may be preferable for operations that reduce the hepatic blood flow. Since our experiments were performed in overnight-fasted rats, differences in metabolism between fed and fasted animals should be considered. Apparently, further investigation will be necessary to clarify the underlying mechanisms of direct anesthetic actions on the liver.

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