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Halothane is less suppressive than pentobarbital on reflex and neural activation of pancreatic F-cell

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HAVEL, PETER J., THOMAS L. PAQUETTE, AND GERALD J. TABORSKY, JR. *Halothane is less suppressive than pentobarbital on reflex and neural activation of pancreatic F-cell.* Am. J. Physiol. 251 (Endocrinol. Metab. 14): E111-E116, 1986.—To determine the suitability of halothane anesthesia for studies of parasympathetic control of the endocrine pancreas in dogs, we assessed the effect of halothane on reflex, direct neural, and direct chemical activation of the parasympathetic input to the islet. Levels or output of pancreatic polypeptide (PP), an islet hormone under predominant cholinergic influence, were used as an indicator of the degree of parasympathetic activation and its potential suppression by anesthesia. Reflex stimulation of the parasympathetic nervous system by 2-deoxy-D-glucose (2-DG) in dogs anesthetized with halothane (0.8%) caused a fourfold increase in plasma PP levels, equivalent to the response in conscious dogs. In contrast, 2-DG at this dose and at a threefold higher dose did not alter PP levels in dogs anesthetized with pentobarbital (30 mg/kg iv), suggesting that halothane at this dose is not suppressive and that pentobarbital is very suppressive on reflex activation of the parasympathetic nerves to the pancreas. Bilateral electrical stimulation of the cervical vagi in halothane-anesthetized dogs elicited a sixfold increase in the pancreatic output of PP. The same stimulation caused only a twofold increase of PP output in pentobarbital-anesthetized dogs. These data suggests that halothane is also less inhibitory than pentobarbital on either peripheral neurotransmission or pancreatic F-cell responsiveness. The effect of direct activation of the F-cell by bethanechol did not differ between the two anesthetics. Therefore, the attenuated PP response to vagal stimulation in pentobarbital-anesthetized dogs is probably due to an action of pentobarbital on peripheral neurotransmission, perhaps at the intrapancreatic parasympathetic ganglia. Together these data suggest that halothane is a more suitable anesthetic than pentobarbital for use in animal experiments studying reflex or electrical activation of the parasympathetic input to the pancreatic F-cell.

pancreatic polypeptide; 2-deoxy-D-glucose; neuroglucopenia; vagal nerve stimulation; bethanechol; parasympathetic nervous system; dog

WE HAVE RECENTLY SHOWN that pentobarbital anesthesia abolishes reflex activation of the parasympathetic input to the pancreas in dogs (17). This action of pentobarbital could lead to a serious underestimation of the parasympathetic contribution to certain pancreatic endocrine and exocrine responses. In addition, our difficulties in demonstrating a pancreatic response to electrical stimulation of the vagi led us to suspect that pentobar-

bital may also suppress peripheral activation of the parasympathetic input to the pancreas. These documented and potential problems with the inhibition of parasympathetic events by pentobarbital led us to evaluate halothane. Halothane has been demonstrated to be less suppressive than pentobarbital on certain cardiovascular reflexes that have parasympathetic components (5). Our aim was to determine whether halothane at a dose providing surgical anesthesia would be less suppressive than pentobarbital on central and/or peripheral activation of the parasympathetic input to the pancreas.

For the purpose of evaluating the degree of parasympathetic activation we measured pancreatic polypeptide in plasma. Recent studies suggest that the level of pancreatic polypeptide (PP) in plasma may reflect parasympathetic neural input to the pancreas. For example, vagotomy or atropine reduces basal PP levels (17) and the PP response to a meal (9, 16). Vagotomy or atropine also reduce the PP responses to reflex activation of the parasympathetic nervous system produced by insulin-induced hypoglycemia (10, 13) or by 2-deoxy-D-glucose-induced (2-DG) neuroglucopenia (8, 17).

To test whether halothane is less suppressive than pentobarbital on reflex activation of the parasympathetic nervous system, we measured the plasma PP response to 2-DG in dogs anesthetized with halothane and compared it with our previously measured responses in conscious dogs and in dogs anesthetized with pentobarbital.

To determine whether halothane is less suppressive than pentobarbital on peripheral parasympathetic neurotransmission, we compared the PP response to electrical stimulation of the cervical vagi in dogs anesthetized with halothane to that in dogs anesthetized with pentobarbital.

Finally, to determine the effect of halothane directly on the pancreatic F-cell, we compared the plasma PP response to the injection of the acetylcholine analogue bethanechol in halothane-anesthetized dogs to the response we previously observed in pentobarbital-anesthetized dogs.

MATERIALS AND METHODS

Animals and surgical procedures. Thirty-two dogs of mixed breed weighing 19–46 kg were used in the chronic experiments with halothane anesthesia and in the vagal nerve stimulation experiments. Seventeen other dogs

were used in the previously reported chronic experiments in conscious or pentobarbital-anesthetized dogs. Data from these animals are included in Table 1 and in Figs. 1, 2, and 5 for comparison with the halothane experiments. All animals were fasted overnight (~18 h) before the experiments were started.

A total of 22 experiments were performed in the 10 dogs used in the experiments with 2-DG or bethanechol. They were implanted with chronic catheters in the thoracic aorta. For this purpose, dogs were anesthetized with methoxyflurane and a right lateral thoracotomy was performed. The descending thoracic aorta was cannulated with a 16-gauge Teflon catheter, which was then secured to the external aortic wall with 4-0 Teflon-polyester suture. The catheter was then glued to 100 cm of heparin-loaded polyvinyl tubing, which was routed via a subcutaneous tunnel to an incision site dorsal to the thoractomy. The thoractomy incision was closed and the dogs were fitted with a nylon jacket (Alice Chatham, Los Angeles, CA) containing a zippered pocket to hold the coiled external catheter tubing when not in use. The catheters were flushed with heparin solution and checked for patency three times weekly. The dogs were allowed at least 3 days recovery after surgery before the experiments were performed.

A total of 29 experiments were performed in the 22 dogs in which the cervical vagi were electrically stimulated. The dogs were anesthetized either with halothane (0.8% inspired concentration in oxygen) after sodium thiamylal induction or with a bolus of pentobarbital sodium (30 mg/kg, iv) followed by an infusion of 0.05 to 0.2 mg·kg⁻¹·min⁻¹. All dogs were mechanically ventilated. A midline laparotomy was performed, and an extracorporeal blood flow circuit was established. The superior pancreaticoduodenal vein (SPDV) was isolated and cannulated with a Silastic catheter that routed blood through an electromagnetic flowmeter past a sampling port and into the portal vein (18). Anticoagulation was maintained by an infusion of heparin (30 U/min) into the SPDV end of the circuit. The femoral artery and vein were also cannulated. Blood was sampled from the artery and the mean arterial blood pressure and heart rate were monitored by means of a pressure transducer. Normal saline (0.9%) was infused slowly into the femoral vein during the surgery and the experiment.

After the abdominal procedures, the right and left branches of the cervical vagi were isolated from the fascia adjacent to the common carotid arteries. The vagal trunks were cut between two ligatures, and the distal part of each was connected to an electrode (Harvard Apparatus, South Natick, MA). The experiments were performed 1 h after these procedures.

Protocols. To determine the effect of halothane anesthesia on reflex activation of the parasympathetic input to the pancreas, dogs bearing chronic catheters were administered 2-deoxy-D-glucose (2-DG). Anesthesia was first induced with 18 mg/kg intravenous (iv) thiamylal sodium (Surital, Parke Davis, Morris Plains, NJ), an ultra short-acting barbiturate. The trachea was intubated and the animal was ventilated with an air-driven respirator connected to a vaporizer (Draeger, West Ger-

many) supplying 0.8% halothane (inspired concentration) in oxygen. At least 45 min was allowed for the barbiturate to be redistributed and for thorough halothane induction before a base-line sample was drawn. The 2-DG was administered as a bolus of 100 or 300 mg/kg and flushed in rapidly with saline. Blood samples were drawn from the chronically implanted catheter at 5, 15, 30, 45, 50, and 60 min after the 2-DG injection.

To evaluate the effects of halothane or pentobarbital anesthesia on peripheral neurotransmission in the operated dogs, we measured the PP response to bilateral electrical stimulation of the cervical vagi. The vagal nerves were stimulated for 10 min with square-wave pulses of 5 ms duration and 13.5 mA current at a frequency of 10 Hz. The stimulations were performed with a Grass model S-44 stimulator with a Grass PSIU6 constant current stimulus isolation unit (Grass Instruments, Quincy, MA). Blood samples from both the femoral artery (FA) and from SPDV were drawn at -5 and 0 min before, at 5 and 10 min during, and 5 and 10 min after the stimulation. Blood flow in the SPDV was measured with an electromagnetic square-wave flowmeter (Zepeda Instruments, Seattle, WA, model SWF-4RD). Hematocrit was determined at regular intervals throughout the experiments.

To assess the effect of halothane anesthesia on direct chemical activation of the pancreatic F-cell, halothane-anesthetized dogs bearing chronic catheters were injected with the acetylcholine analogue bethanechol (Urecholine, Merck Sharp & Dohme, West Point, PA) at a dose of 100 µg/kg iv. Blood samples were drawn at -5 and 0 min before and at 2, 3, 4, 5, 10, 15, and 30 min after the bethanechol injection.

Assays and data analysis. Blood samples for pancreatic polypeptide (PP) were drawn and put into tubes containing EDTA and placed on ice; immediately after the experiments the blood samples were centrifuged at 4°C for 20 min. Plasma was separated and frozen at -20°C until assayed. Plasma PP was measured by a radioimmunoassay using an antibody similar to that developed by Chance (4) and a tracer of ¹²⁵I-porcine PP.

The changes of systemic plasma concentrations of PP in response to 2-DG were calculated by subtracting the 0-min value from the 15-min value after the injection of 2-DG. The 0- to 60-min integrated response is expressed as an incremental area under the PP-time curve (in pg·min⁻¹·ml⁻¹).

The changes of FA and SPDV plasma PP concentrations during vagal nerve stimulation were calculated by subtracting the mean of the two base-line samples from the mean of the 5- and 10-min values. The output of PP from the right lobe of the pancreas in picograms per minute was calculated as follows: [(PP)SPDV - (PP)FA] × blood flow × (1 - hematocrit).

The changes of systemic plasma PP concentration in response to bethanechol were calculated by subtracting the mean of the -5- and 0-min values from the 5-min value following bethanechol injection. The integrated PP response to bethanechol was calculated as the incremental area under the PP-time curve (in pg·min⁻¹·ml⁻¹), for the 10 min following the injection of bethanechol.

The data are reported in the RESULTS as means $\pm$ SE. Statistical comparisons of means within a group were made with a paired *t* test; statistical comparisons of means of different groups were made with a two-sample *t* test.

RESULTS

PP response to 2-DG (100 mg/kg) in halothane-anesthetized dogs. In dogs anesthetized with halothane (0.8%), base-line PP averaged 192 ± 35 pg/ml in systemic plasma. PP increased to 760 ± 218 pg/ml by 15 min after the injection of 100 mg/kg of 2-DG ($\Delta = 568 \pm 208$ pg/ml; $P < 0.025$). PP remained at this level for the 1-h observation period after the 2-DG injection (Fig. 1). The incremental area under the PP-time curve (0–60 min) was $24,072 \pm 9,417$ pg $\cdot$ min $\cdot$ ml $^{-1}$ ($P < 0.025$). These data are compared with the previously reported data (17) obtained from pentobarbital-anesthetized or conscious dogs given in Table 1. The PP response to 2-DG (100 mg/kg) was significantly greater in halothane-anesthetized dogs than in pentobarbital-anesthetized dogs ($P < 0.025$; Fig. 1). Neither the basal nor 2-DG stimulated PP levels in conscious dogs were significantly different from those of the halothane-anesthetized dogs (Fig. 1).

PP response to 2-DG (300 mg/kg) in halothane-anesthetized dogs. In a second set of experiments dogs were anesthetized with halothane (0.8%). Basal concentrations of PP were 367 ± 160 pg/ml. PP increased to $1,180 \pm 297$ pg/ml by 15 min after the injection of 300 mg/kg of 2-DG, an increase of 813 ± 195 pg/ml ($P < 0.005$). The 0- to 60-min incremental area under the PP-time curve was $29,383 \pm 5,732$ pg $\cdot$ min $\cdot$ ml $^{-1}$ ($P < 0.0025$). These data are compared with the previously reported data (17) obtained from pentobarbital-anesthetized dogs given in Table 1. The PP response to this increased dose of 2-DG in halothane-anesthetized dogs was significantly larger than that in pentobarbital-anesthetized dogs whether expressed as the peak response 15 min after the

2-DG ($P < 0.0005$) or as an incremental area ($P < 0.0005$; Fig. 2).

In conscious dogs, a dose of 300 mg/kg of 2-DG caused convulsions that were quickly terminated by pentobarbital injection. Therefore the comparable PP data from conscious dogs are not available.

Comparison of the PP responses to bilateral cervical vagal nerve stimulation in halothane-anesthetized and pentobarbital-anesthetized dogs. Arterial concentrations of PP in operated dogs anesthetized with halothane (0.8%) were 282 ± 103 pg/ml. Arterial PP increased to 749 ± 135 pg/ml (the mean of 5- and 10-min points) during electrical stimulation of the cervical vagi ($\Delta = 467 \pm 108$ pg/ml; $P < 0.0025$).

In dogs anesthetized with pentobarbital (30 mg/kg + $0.05 - 0.2$ mg $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$), the basal arterial PP concentration was 527 ± 50 pg/ml. In response to vagal nerve stimulation, arterial PP increased to 731 ± 82 pg/ml ($\Delta = 204 \pm 44$ pg/ml; $P < 0.00025$). The increase of arterial PP in response to electrical stimulation of the vagus nerves was greater in halothane-anesthetized dogs than in pentobarbital-anesthetized dogs ($P < 0.025$; Fig. 3).

In dogs anesthetized with halothane, basal PP output (see MATERIALS AND METHODS) from the right lobe of the pancreas was $4,186 \pm 2,157$ pg/min. PP output increased to a mean of $29,634 \pm 5,520$ pg/min at the 5- and 10-min time points during nerve stimulation, an increment of $25,448 \pm 5,243$ pg/min ($P < 0.0025$).

In pentobarbital-anesthetized dogs basal PP output was $7,301 \pm 1,392$ pg/min. During vagal nerve stimulation PP output increased to $15,972 \pm 4,166$ pg/min, an increase of $8,671 \pm 3,398$ pg/min ($P < 0.025$).

The increase of PP output during electrical stimulation of the cervical vagi was significantly larger in the dogs anesthetized with halothane than in the dogs anesthetized with pentobarbital ($P < 0.005$; Fig. 4).

PP response to bethanechol injection in halothane-anesthetized dogs. Basal concentrations of PP in the arterial plasma of halothane-anesthetized dogs averaged 247 ± 29 pg/ml. PP increased to a concentration of 583 ± 49 pg/ml 5 min after the intravenous injection of 100 μ g/kg of bethanechol, an increase of 336 ± 52 pg/ml ($P < 0.0005$). The incremental PP response expressed an area under the PP-time curve from 0 to 10 min was $2,550 \pm 415$ pg $\cdot$ min $\cdot$ ml $^{-1}$ ($P < 0.0005$). These data are compared with the previously reported data (17) obtained from pentobarbital-anesthetized dogs given in Table 1. The PP response to bethanechol in the halothane-anesthetized dogs was not significantly different from that in the pentobarbital-anesthetized dogs, whether expressed as a peak 5-min response or as an integrated total 0- to 10-min area response (Fig. 5).

DISCUSSION

In the present studies we sought to determine whether a dose of halothane producing surgical anesthesia suppresses parasympathetic outflow to the pancreas. To this end we compared the effects of reflex activation, preganglionic electrical activation, and direct chemical activation of the cholinergic input to the pancreas in dogs

FIG. 1. Change of plasma pancreatic polypeptide (PP) in response to 2-deoxyglucose (2-DG; 100 mg/kg iv) in 8 dogs anesthetized with halothane (0.8%), in 7 dogs anesthetized with pentobarbital (30 mg/kg), and in 7 unanesthetized dogs.

TABLE 1. *Effects of halothane and pentobarbital on PP responses to 2-DG and bethanechol*

Stimulus	2-DG (100)			2-DG (300)		Bethanechol	
	Halo (8)	Pento* (7)	Cons* (7)	Halo (6)	Pento* (7)	Halo (8)	Pento* (6)
Basal [PP], pg/ml	192±35	145±15	233±55	367±160	186±13	247±29	183±29
Δ[PP], pg/ml	568±208	-2±13†	676±249	813±195	13±13‡	336±52	524±187
PP Area, pg·min·ml ⁻¹	24,072±9,147	-267±588†	23,991±8,787	29,383±5,732	-9±399‡	2,550±415	3,670±1,261

Values are means ± SE. Halo, halothane anesthesia (0.8%); Pento, pentobarbital anesthesia (30 mg/kg iv); Cons, conscious, no anesthesia. * Previously published data included for the purpose of comparison with halothane data. † $P < 0.025$ vs. halothane. ‡ $P < 0.0005$ vs. halothane.

FIG. 2. Change of plasma pancreatic polypeptide (PP) in response to 2-deoxyglucose (2-DG; 300 mg/kg iv) in 6 dogs anesthetized with halothane (0.8%) and in 7 dogs anesthetized with pentobarbital (30 mg/kg).

FIG. 3. Change of plasma pancreatic polypeptide (PP) in response to bilateral cervical vagal nerve stimulation (10 Hz, 5 ms, 13.5 mA) in 13 dogs anesthetized with halothane (0.8%) and 16 dogs anesthetized with pentobarbital (30 mg/kg).

FIG. 4. Change of pancreatic polypeptide (PP) output (see MATERIALS AND METHODS) in response to bilateral cervical vagal nerve stimulation (10 Hz, 5 ms, 13.5 mA) in 13 dogs anesthetized with halothane (0.8%) and in 16 dogs anesthetized with pentobarbital (30 mg/kg).

anesthetized with halothane with those in dogs anesthetized with pentobarbital. When appropriate, we compared the effects with those observed in conscious dogs. However, to determine the magnitude of the activation, it is necessary to have a reliable measurement of the parasympathetic input to the pancreas. Because the parasympathetic neurotransmitter, acetylcholine, is rapidly eliminated from plasma by acetylcholinesterase, its use as an indicator of parasympathetic neural activity is precluded. One alternative, the measurement of plasma pancreatic polypeptide levels, is useful for two reasons. First, pancreatic polypeptide is specific to the pancreas and therefore its levels will reflect parasympathetic input to the pancreas even when this differs from general parasympathetic outflow. Second, PP secretion appears to be predominantly under cholinergic control. For example, atropine or vagotomy blocks the PP response to a meal (9, 16), to insulin-induced hypoglycemia (10, 13), and to 2-DG-induced central neuroglucopenia (3, 8, 17),

FIG. 5. Change of plasma pancreatic polypeptide (PP) in response to bethanechol (100 mg/kg iv) in 8 dogs anesthetized with halothane (0.8%) and in 6 dogs anesthetized with pentobarbital (30 mg/kg).

all presumably reflexively mediated events. In addition, combined adrenergic blockade does not influence the PP response to insulin-induced hypoglycemia (12). Atropine also blocks the PP response to either electrical stimulation of the vagi (3, 13) or to chemical muscarinic stimulation with bethanechol (16). Further, reports that graded doses of acetylcholine and graded electrical stimulations of the vagus nerves produce proportional increases of plasma PP (13) suggest that the level of PP in plasma might be used as an index of the degree of parasympathetic cholinergic input to the pancreas. Therefore, in the present study we have assessed the effect of halothane anesthesia on parasympathetic input to the pancreas by measuring the PP response to reflex, electrical, and chemical activation of the pancreatic F-cell.

A dose of 0.8% (inspired concentration) was chosen because this was the highest level that has been shown to allow cardiovascular responses of conscious magnitude in dogs (1). Other doses of halothane were not studied because our goal was consistent surgical anesthesia without parasympatholytic effects.

The PP response to reflex activation of the parasympathetic nervous system by 2-DG in halothane-anesthetized dogs was not significantly different from the response observed in unanesthetized dogs and clearly larger than that in pentobarbital-anesthetized dogs who had no measurable PP response to this dose of 2-DG (17). A threefold higher dose of 2-DG exaggerated the difference between anesthetics because it produced a larger PP response in the halothane-anesthetized dogs and still no measurable PP response in pentobarbital-anesthetized dogs. Taken together, these data suggest that halothane anesthesia does not suppress the reflex activation of the parasympathetic input to the pancreas and is therefore superior to pentobarbital anesthesia for this type of study.

Next we investigated the possibility that halothane might also be superior to pentobarbital for studies of the

effects of electrical stimulation of the vagal nerves to the pancreas. This possibility was suggested by our own difficulties in producing a PP response to vagal nerve stimulation in dogs anesthetized with pentobarbital and by the known effects of barbiturates to inhibit synaptic transmission (7). We measured the PP response to electrical stimulation of the cervical vagi in dogs anesthetized with halothane and compared the response with that measured in dogs anesthetized with pentobarbital. The increment of arterial PP was significantly larger in dogs anesthetized with halothane. The increment of PP output was also significantly larger. This demonstrates that the larger charge of peripheral PP reflects a true increase in the rate of PP secretion and not a differential effect of the anesthetics on PP clearance. These results indicate that, while pentobarbital anesthesia does not abolish the PP response to electrical stimulation of the vagus nerves, it nonetheless is suppressive when compared with halothane anesthesia.

The suppressive effect of pentobarbital on the PP response to vagal nerve stimulation could be due to an action either on the vagal nerves and associated ganglia or on the pancreatic F-cell directly. To determine whether the attenuated PP response to vagal stimulation is due to an effect of pentobarbital on the F-cell, we measured the PP response to the intravenous injection of bethanechol in halothane-anesthetized dogs and compared it with the responses observed in pentobarbital-anesthetized dogs. The PP response to bethanechol in pentobarbital-anesthetized dogs was equivalent to that in halothane-anesthetized dogs. Thus the smaller PP response to vagal stimulation seen in pentobarbital-anesthetized dogs does not appear to be due to an inhibitory effect directly on the F-cell but rather to an inhibitory effect of pentobarbital on peripheral parasympathetic neurotransmission. One likely site of this inhibitory action is the intrapancreatic parasympathetic ganglia. Barbiturates are known to suppress neurotransmission across sympathetic ganglia (7) and there are reports of the same effect on parasympathetic ganglia (15).

Although the data presented here suggest that halothane is superior to pentobarbital for the preservation of parasympathetic responses, other studies of the effect of halothane show progressive suppression of cardiovascular reflexes in proportion to the concentration of halothane administered (1). It is important to recognize that the difference between halothane and pentobarbital may be less marked at a higher concentration of halothane. The level of halothane (0.8% inspired concentration) used in the present study is less than that established to produce surgical anesthesia in dogs. An expired concentration of 0.87% is reported to be the minimum alveolar concentration necessary to prevent movement in 50% of dogs in response to noxious stimuli (11). Yet in our experience, 0.8% inspired halothane has produced surgical anesthesia in over 90% of the cases. We believe that this reduced halothane requirement is due to our use of thiamylal induction. Indeed, induction with thiopental, a very similar short-acting barbiturate, does reduce minimum alveolar concentration in dogs (6). It is possible that 0.8% inspired halothane would not produce

surgical anesthesia in dogs induced with halothane alone.

In summary, halothane does not suppress the PP response to 2-DG, suggesting little, if any, suppression of the reflex activation of parasympathetic outflow to the pancreas. This reflex is markedly suppressed by pentobarbital (17). Halothane is also less suppressive than pentobarbital on the PP response to electrical stimulation of the cervical vagi, suggesting that pentobarbital inhibits parasympathetic neurotransmission, perhaps by inhibiting synaptic transmission in the intrapancreatic parasympathetic ganglia. Thus, for experiments studying the effects of either reflex or electrical parasympathetic activation of the pancreatic F-cell, halothane anesthesia appears to be superior to pentobarbital. Although these interpretations of the data are confined to the pancreatic polypeptide response, they may well be applicable to the parasympathetic components of other physiological responses.

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None of the data from the experiments with halothane anesthesia or the nerve stimulation experiments with pentobarbital anesthesia have been presented before, even in abstract form. Some data from experiments in pentobarbital-anesthetized or conscious dogs in Table 1 and in Figs. 1, 2, and 5, which are included for purposes of comparison with the halothane data, are from Ref. 17.

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