Non-adrenergic Vasoconstriction Produced by Halothane and Cyclopropane Anesthesia

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with the assistance of Richard A. Shaffer‡

Vasoconstrictor responses produced by halothane (1.5%) and by cyclopropane (35%) in the perfused dog gracilis muscle persisted in the face of complete blockade of alpha-adrenergic receptors, indicating that the responses were not mediated by systemic or local release of catecholamines. Utilizing extracorporeal perfusion of the muscle, vasoconstriction produced by cyclopropane was found to be the result of a direct stimulant action on vascular smooth muscle, whereas the direct effect of halothane was one of depression. The vasoconstriction with halothane was shown to be mediated indirectly through liberation from the hypophysis of a substance which is probably antidiuretic hormone (vasopressin). It is suggested that the indirect vasoconstrictor effect of halothane, by opposing the direct vascular depressant action, makes an important contribution to the overall hemodynamic consequences of halothane anesthesia.

There are many unanswered questions about effects of anesthetics on the peripheral vasculature and central vasoregulatory mechanisms. While studying the effects of halothane and cyclopropane on baroreceptor reflexes produced in the cross-perfused dog gracilis muscle, we noted that either anesthetic administered to a donor dog supplying blood to the muscle produced a significant increase in muscle perfusion pressure. This increase in vascular resistance had been anticipated with cyclopropane, but was unexpected with halothane, generally considered a vascular smooth muscle depressant. It was the purpose of these experiments to elucidate the mechanism of vasoconstriction observed with both anesthetics.

Methods

Experiments were performed on dogs weighing 12–17 kg. The animals were anesthetized initially with sodium pentobarbital, 30 mg./kg. intravenously. The trachea was intubated to facilitate intermittent positive pressure ventilation. An external jugular vein was cannulated for administration of drugs. Gallamine triethiodide, in doses of 10–20 mg., was administered at intervals to immobilize the animals and to facilitate mechanical ventilation.

The first series of experiments, which involved cross perfusion of a gracilis muscle, was performed on seven pairs of dogs. The details of this preparation are described in a separate communication.

Perfusion pressure of the muscle was adjusted to approximate systemic arterial pressure of the recipient dog by appropriately altering flow rate from the pump. With perfusion pressure stabilized the nerve to the muscle was cut, thus removing any remaining connection of the recipient dog to its muscle. Halothane or cyclopropane was then administered to the donor animal and the effect on the perfusion pressure of the gracilis muscle observed. Norepinephrine, 0.05 µg., was injected intra-arterially into the muscle before and after intra-arterial administration of phentolamine (Regitine), 0.5–1.0 mg. When required, additional doses of 0.25–0.5 mg. of phentolamine...
were administered to maintain alpha-adrenergic receptor blockade.

Following establishment of alpha-adrenergic receptor blockade, halothane and cyclopropane were administered to the donor. The anesthetics were administered on a randomized basis in concentration sufficient to attain an end-expired concentration of 1.5 per cent halothane or 35 per cent cyclopropane. End-expired gas samples were obtained and were analyzed for halothane or cyclopropane as described previously. At intervals throughout the experiment the adequacy of the alpha-adrenergic receptor blockade was tested by intra-arterial injection of 0.05 μg. of norepinephrine. In all experiments, the anesthetics were administered for periods not exceeding 20–25 minutes. Sufficient time was allowed between administrations to allow end-expired concentrations to fall to zero level.

In four experiments, the gracilis muscle was prepared as described and perfused with blood from a modified Lillehei-Dewall bubble oxygenator. After administration of heparin sodium, 5 mg./kg., to the dog the oxygenator was primed with 50–75 ml. of fresh blood. The blood was oxygenated with 95 per cent oxygen–5 per cent carbon dioxide delivered at flow rates of 5–6 liters/minute. The oxygenated blood was defoamed in a chamber filled with stainless steel silicone-coated sponges. Tubing from the oxygenator was passed through a water bath warmed to 33–34° C. and then passed through a constant-flow model T-S Sigmadamotor pump. The artery of the isolated muscle was then cannulated with tubing from the pump. The vein of the muscle was also cannulated and venous effluent discarded. Fresh arterial blood was supplied to the reservoir of the oxygenator. The nerve was then severed. After stabilization of muscle perfusion pressure, anesthetics were introduced into the oxygenator in the same concentrations as given the intact animals, before and after alpha-adrenergic receptor blockade. Gas exhaust from the oxygenator was analyzed for halothane or cyclopropane as described previously.

In two experiments, effects of halothane and cyclopropane on perfusion pressure of the gracilis muscle were determined before and after conversion of the intact animal to a heart-lung-gracilis muscle preparation. In these experiments the muscles were prepared as described above except that perfusion was with blood from the left subclavian artery previously exposed by a midline thoracotomy. The animal was converted to a heart-lung-gracilis muscle preparation by diverting left ventricular outflow through the cannulated brachiocephalic artery into a Starling resistance and finally a reservoir. The reservoir was drained by gravity into the cannulated superior vena cava. All other vascular connections with the heart were ligated. The blood was warmed to 37° C. during passage through a heated condenser located between the reservoir and the vena cava. Alpha-adrenergic receptor blockade was established in these muscles by intra-arterial administration of phentolamine.

Four experiments were performed in which anesthetics were administered to animals before and after exclusion of the entire head from the circulation. Gracilis muscles were prepared in the usual manner for autoperfusion, and alpha-adrenergic receptor blockade of the muscle was instituted by intra-arterial phentolamine. The muscle was perfused with blood from a femoral artery. After administration of anesthetics to the intact animal, the head was completely eliminated from the circulation by means of a blunt clamp placed around the high cervical area. The clamp was tightened sufficiently to crush the cervical vertebrae and completely occlude spinal collateral. After clamping, systemic blood pressure was maintained by transfusion of blood from a donor dog.

Experiments were performed in six dogs utilizing independent autoperfusion of a gracilis muscle on each hind limb. One muscle was perfused with blood from an uninterrupted external jugular vein (catheter inserted through a needle puncture), and the other with blood from a femoral artery. A separate pump was used for each muscle perfusion. In both muscles alpha-adrenergic receptor blockade was produced by phentolamine. Perfusion pressure responses in both muscles were studied during halothane inhalation.

In three animals the gracilis muscle of each hind limb was perfused at constant flow with external jugular venous blood perfusing one muscle and inferior vena caval blood (from
above the level of the renal veins) perfusing the other muscle. In addition to halothane inhalation, bilateral internal carotid artery injections of 0.01 ml. of halothane and 1 ml. of 10 per cent saline solution were performed in one animal.

Water diuresis was produced in nine animals by the following procedure: intravenous infusion of 500 ml. of 6 per cent dextran in saline solution at 1 ml./kg./minute was followed by intravenous infusion of 2.5 per cent dextrose in water at the rate of 0.5 ml./kg./minute. Both ureters were cannulated in each animal. Arterial blood pressure was obtained by cannulation of a femoral artery. Urine volume was measured and urine osmolality was determined with a Fiske osmometer. All animals received halothane anesthesia; in two cyclopropane was also administered. In three dogs bilateral internal carotid artery injections of 0.01 ml. of halothane and 1 ml. of 10 per cent saline were made in addition to halothane administered by inhalation. The dose of intracarotid halothane represents the amount required to achieve an approximate arterial concentration of 9 mg. per cent. This concentration is approximately half that probably achieved during inhalation of 1.5 per cent halothane.\(^3\) Carotid blood flow of 100 ml./minute was assumed for calculation of the dose.

The influence of acute hypophyscetomy upon the peripheral vascular response to halothane was studied in three dogs. The hypophysis was exposed through a transbuccal approach using the techniques described by Markovitz et al.^4\) Responses in the perfused muscle produced by halothane administration were examined before and after the hypophysis was removed by suction.

In all experiments, the animals were ventilated mechanically with 100 per cent oxygen. Whenever an animal was to receive an anesthetic agent, the means of ventilation was a pressure-limited respirator alternately compressing a calibrated bellows. In experiments where a recipient and donor animal were employed, the recipient was ventilated with a volume-limited respirator. Arterial blood samples were obtained from all animals just prior
FIG. 2. Effect of alpha-adrenergic receptor blockade on the perfusion pressure response of the cross-perfused gracilis muscle to administration of halothane. PP: perfusion pressure of the gracilis muscle perfused with blood from a donor dog; BP: systemic blood pressure; NE: norepinephrine; IA: intra-arterial injection. The bottom tracing represents the end-expired halothane concentration of the donor dog.

FIG. 3. Effect of alpha-adrenergic receptor blockade on the perfusion pressure response of the cross-perfused gracilis muscle to administration of cyclopropane to the donor dog. Alpha-adrenergic receptor blockade produced by the intra-arterial administration of phentolamine to the muscle prior to the first intra-arterial norepinephrine injection. PP: perfusion pressure of the gracilis muscle perfused with blood from donor dog; BP: systemic blood pressure; IA: intra-arterial injection.
TABLE 1. The Effect of Alpha-adrenergic Blockade on the Responses of the Cross-perfused Gracilis Muscle to Cyclopropane and to Halothane

<table>
<thead>
<tr>
<th></th>
<th>Perfusion Pressure Changes (mm. Hg)</th>
<th>Control</th>
<th>After Phenolamine†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane, 1.5%</td>
<td>+75±25 (3)</td>
<td>&lt;0.02</td>
<td>-29±5 (6)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+42±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cyclopropane, 35%</td>
<td>+34±7 (3)</td>
<td>&lt;0.05</td>
<td>+44±7 (7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Probability as determined by paired-comparison t-tests.
† Phenolamine (0.5-1.0 mg) given intra-arterially to muscle.
Numbers in parentheses refer to numbers of experiments.
• Initial vasodilation seen after but not before phenolamine treatment.
• Vasocnstriction which followed initial vasodilation.

to discontinuation of the anesthetic and were analyzed for $P_{O_2}$, $P_{CO_2}$, and $pH$ (Instrumentation Laboratories model 113 pH and gas analyzer).

**Results**

The first series of experiments confirmed previous findings that muscle vascular resistance increased when halothane or cyclopropane was administered to a donor animal. With administration of halothane to the donor animal, arterial pressure falls, whereas muscle perfusion pressure increases (fig. 1).

Figure 2 demonstrates the effect of alpha-adrenergic blockade on the vasoconstrictor response. The response to intra-arterial norepinephrine was abolished by intra-arterial administration of phenolamine. Administration of halothane to the donor animal again produced a decrease in arterial pressure. The muscle perfusion pressure initially decreased slightly, then increased significantly. The response to intra-arterial norepinephrine re-

![Figure 4](image_url)
TABLE 2. Effects of Halothane and Cyclopropane on Gracilis Muscle Vessels Perfused with Blood from an Oxygenator

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Perfusion Pressures (mm. Hg)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Phenolamine</td>
<td>After Phenolamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>Peak</td>
<td>Mean Difference ± S.E.</td>
<td>Control</td>
<td>Peak</td>
<td>Mean Difference ± S.E.</td>
<td></td>
</tr>
<tr>
<td>Halothane, 1.5% (4)</td>
<td>119</td>
<td>99</td>
<td>-20 ± 10</td>
<td>184</td>
<td>153</td>
<td>-31 ± 10</td>
<td></td>
</tr>
<tr>
<td>Cyclopropane, 35% (4)</td>
<td>130</td>
<td>162</td>
<td>+32 ± 22</td>
<td>149</td>
<td>210</td>
<td>+61 ± 7</td>
<td></td>
</tr>
</tbody>
</table>

Numbers in parentheses represent numbers of experiments.

Halothane and cyclopropane were administered to the intact animal before and after conversion of the animal to a heart-lung-gracilis preparation were similar to results of the oxygenator experiments. When halothane or cyclopropane was administered to the intact animal, perfusing its own gracilis muscle, the usual increases in perfusion pressure of the muscle (34 mm. Hg increase with cyclopropane and 28 mm. Hg increase with halothane) were observed. After conversion to the heart-lung-gracilis preparation (in vivo oxygenation of blood perfusing the muscle) halothane produced vasodilatation (26 mm. Hg decrease) while cyclopropane still produced vasoconstriction (44 mm. Hg perfusion pressure increase). Table 3 summarizes experiments in which the head was removed from the circulation.

TABLE 3. Effect of Removal of the Entire Head from the Circulation on Vasoconstrictor Responses in the Perfused Gracilis Muscle Treated with Phenolamine

<table>
<thead>
<tr>
<th></th>
<th>Perfusion Pressure Change (mm. Hg)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>After Head</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane, 1.5% (4)</td>
<td>+55±11</td>
<td>-25±13</td>
<td></td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclopropane, 35% (4)</td>
<td>+47±13</td>
<td>+45±19</td>
<td></td>
<td>N.S.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Probability determined by paired-comparison t test.
Numbers in parentheses represent numbers of experiments.
N.S. = non-significant.
TABLE 4. Perfusion Pressure Changes in Separate Gracilis Muscles during Halothane Administration

<table>
<thead>
<tr>
<th>Sources of Blood Perfusing Separate Muscles</th>
<th>Femoral artery</th>
<th>Femoral artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>External jugular vein vs. Femoral artery</td>
<td>37±5</td>
<td>54±4</td>
</tr>
<tr>
<td>External jugular vein vs. Inferior vena cava</td>
<td>93±19</td>
<td>63±17</td>
</tr>
</tbody>
</table>

Numbers in parentheses refer to numbers of experiments.

The vasoconstriction seen in the perfused muscle during halothane administration was reversed to vasodilatation when the head was clamped off. Vasoconstriction produced by administration of cyclopropane was unaffected by the procedure.

Attempts were made to localize a source of blood containing high vasoconstrictor activity. Two muscles in the same dog were perfused with separate sources of blood. A comparison of the effects of external jugular venous versus arterial blood is shown in Table 4. During administration of halothane muscles perfused with jugular venous blood showed greater constrictor responses than those perfused with arterial blood, in four of six experiments. The mean differences, however, were not significantly different. Greater differences were seen when external jugular venous blood was compared with inferior vena caval blood. An example of such an experiment is shown in Figure 5.

With administration of halothane, considerably greater and more immediate vasoconstriction was observed in the muscle perfused with blood from the head. The average changes from the three experiments of this type are summarized in Table 4. The difference between responses produced by blood from jugular vein and inferior vena cava was not statistically significant. In one of these experiments (Fig. 6) halothane and hypertonic sodium chloride were injected into the internal carotid arteries. Both of these procedures resulted in vasoconstriction exclusively in the muscle perfused with jugular

![Graph](image_url)

Fig. 5. Effect of halothane administration on perfusion pressures of two gracilis muscles independently perfused with inferior vena caval and external jugular venous blood. PP: perfusion pressure; P: phenolamine; NE: norepinephrine; IA: intra-arterial injection. The bottom tracing represents the end-expired concentration of halothane.
venous blood. These constrictor responses could not be attributed to halothane or sodium chloride in the blood coming from the head, since intra-arterial injection of these materials into the muscle produced vasodilatation in both cases.

Table 5 summarizes the results of experiments in which effects of halothane on urinary osmolality and urine volume were studied in dogs undergoing water diuresis. Intracarotid injection of hypertonic saline, a known stimulus for the elaboration of antidiuretic hormone, produced an increase in urinary osmolality and a decrease in urine volume. The same effects on urinary osmolality and volume were seen with either inhalation or intracarotid injection of halothane. It should be noted that injection of an extremely small volume of halothane into the carotid artery was capable of producing the same peak effect as inhalation of halothane, without significantly altering systemic blood pressure.

**Table 5. The Effects of Halothane, Hypertonic Saline Solution and Cyclopropane on Urinary Osmolality, Urine Volume and Blood Pressure**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Urine Osmolality (mosm./kg.)</th>
<th>Urine Volume (ml./min.)</th>
<th>Mean Blood Pressure (mm. Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control Max.</td>
<td>MD ± S.E.</td>
<td></td>
</tr>
<tr>
<td>Halothane inhalation (3) 1.5%</td>
<td>229</td>
<td>597</td>
<td>358 ± 91 &lt;0.005</td>
</tr>
<tr>
<td>Halothane intracarotid (3) 0.01 ml. to each artery</td>
<td>212</td>
<td>614</td>
<td>399 ± 69 &lt;0.025</td>
</tr>
<tr>
<td>NaCl-10% intracarotid (3) 1 ml. to each</td>
<td>227</td>
<td>494</td>
<td>237 ± 74 &lt;0.05</td>
</tr>
<tr>
<td>Cyclopropane inhalation (2) 35%</td>
<td>211</td>
<td>269</td>
<td>48 ± 10 N.S.</td>
</tr>
</tbody>
</table>

Numbers in parentheses represent numbers of experiments.

- * Value at maximum effect.
- † Mean difference ± standard error.
- * Probability determined by paired comparison t test (one-tailed).
- N.S. = not statistically significant.
The original observations of vasoconstriction with halothane and cyclopropane could have been explained in each case on the basis of an adrenergic mechanism. Cyclopropane has been reported to activate the sympathetic nervous system. Halothane, by means of its hypotensive action, could result in the liberation of catecholamines by reflex mechanisms. It was obvious at the outset that this explanation was not tenable because vasoconstriction produced by administration of halothane and cyclopropane persisted when the vessels of the perfused muscle were subjected to alpha-adrenergic receptor blockade. Although muscle vasoconstriction produced by cyclopropane was unaffected by alpha-adrenergic receptor blockade, the response to halothane was altered to an initial vasodilatation followed by vasoconstriction. This initial vasodilatation could have been due either to a direct effect of halothane on the vasculature or to a reversal by alpha-adrenergic receptor blockade of the constrictor action of catecholamines liberated during the early phase of hypotension. These experiments provide no support for either mechanism.

The possibility was then open that the vasoconstrictor effect of the anesthetics might have been due either to a direct effect of the anesthetics on the vasculature or to the liberation by these anesthetics of a non-adrenergic vasoconstrictor substance. As a means of distinguishing between these possibilities, the direct effects of the agents on the vasculature were elucidated by means of an extracorporeal circuit. The anesthetics were introduced into a bubble oxygenator which supplied the only source of blood to a completely isolated muscle. Under these conditions halothane exerted a vasodilator effect whereas cyclopropane remained a vasoconstrictor. It should be emphasized that this direct action of cyclopropane was observed in the presence of alpha-adrenergic receptor blockade, thus eliminating the possibility that this agent might produce vasoconstriction by the local release of catecholamines. From these experiments, we concluded that while in intact animals halothane produces muscle vasoconstriction, its direct effect must be to produce vascular smooth muscle relaxation. The vascular effect of
TABLE 6. The Effect of Acute Hypophysectomy on the Vasoconstrictor Response Produced in the Perfused Gracilis Muscle by Halothane Inhalation*

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Pre-hypophysectomy</th>
<th>Post-hypophysectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Halothane</td>
</tr>
<tr>
<td>1</td>
<td>76</td>
<td>112</td>
</tr>
<tr>
<td>2</td>
<td>126</td>
<td>158</td>
</tr>
<tr>
<td>3</td>
<td>120</td>
<td>276</td>
</tr>
</tbody>
</table>

* Gracilis muscle perfused with external jugular vein blood.

cyclopropane in the intact animal appears to be explained in large part by the direct stimulant action of this agent on vascular smooth muscle. These conclusions were supported by in vivo experiments utilizing the heart-lung gracilis muscle preparation. In these experiments, the vasoconstriction observed with halothane anesthesia in intact animals was reversed to vasodilatation after conversion of the animal to a heart-lung-gracilis muscle preparation. Vasoconstriction produced by cyclopropane was unaffected by this conversion. The heart-lung experiments also indicated that halothane was releasing a non-adrenergic substance into the blood whose source was somewhere other than the heart and lungs.

Experiments in which the vasoconstriction observed with halothane in the intact animal was reversed to vasodilatation by complete elimination of the head from the circulation suggested that some area of the brain might be the source of the non-adrenergic vasoconstrictor material. A means of testing this hypothesis would be a comparison of the vasoconstrictor activity of blood coming from the head with that of blood coming from another area. This was done in experiments in which one gracilis muscle was perfused with blood from an external jugular vein and another perfused with either arterial or inferior vena cava blood. The results of these experiments showed that the vasoconstrictor activity of arterial blood was the same as that of external jugular venous blood. This could have been due to the fact that the muscle perfused with arterial blood was more reactive to the vasoconstrictor substance than the muscle perfused with venous blood, perhaps due to a better metabolic state of the "arterialized" muscle. Although the differences noted were not statistically significant, when two muscles were perfused with venous blood more immediate and greater vasoconstriction was observed in the muscle used to test the vasoconstrictor activity of blood from the head. In all instances, the vasoconstriction observed in muscle perfused with inferior vena caval blood was later in onset than that observed in muscle perfused with jugular venous blood, suggesting that some time was required for the concentration of the substance coming from the head to build up in peripheral blood.

A material with known vasoconstrictor properties released from the brain is vasopressin (antidiuretic hormone). This polypeptide is formed in the hypothalamus and elaborated into blood from the posterior portion of the pituitary gland. If halothane causes the release of antidiuretic hormone in quantities sufficient to cause vasoconstriction, it should also exert significant effects on renal function, since the amounts required to produce vasoconstriction are in excess of the amounts necessary for an antidiuretic effect. Experiments were designed in which the effects of halothane on urine volume and urinary osmolality were compared with the effects of hypertonic sodium chloride, a potent stimulus for the elaboration of antidiuretic hormone. In these experiments intracarotid injections of hypertonic saline solution produced effects typical of antidiuretic hormone, i.e., urine volume decreased while urinary osmolality was elevated significantly. Inhalation of halothane produced effects on urinary osmolality and urine volume which were indistinguishable from the effects
of hypertonic sodium chloride. It is not possible from this portion of this study alone to conclude that the renal effects of halothane inhalation were the result of antidiuretic hormone liberation since halothane inhalation produces hypotension and probably decreases renal blood flow, or alternatively, halothane might exert some direct renal tubular effect. It was noted in one experiment (fig. 6) that bilateral intracarotid injection of 0.01 ml of halothane produced the same increase in perfusion pressure of a gracilis muscle as did the bilateral intracarotid injection of 1 ml of 10 per cent sodium chloride. This experiment suggested that halothane, like hypertonic sodium chloride, could exert a local effect on the brain to promote release of antidiuretic hormone, and that the systemic effects of halothane were not required. Intracarotid injection of halothane in diurezing animals produced the same effects on urinary osmolality and urine volume as seen with inhalation of halothane and intracarotid injection of hypertonic sodium chloride. The results obtained with intracarotid injection of halothane strongly suggest that renal actions noted with inhalation of halothane were caused by a direct central action of halothane and did not result from a hypotensive or a direct renal effect. This conclusion is based on the fact that the intracarotid injection of halothane did not alter systemic blood pressure significantly and yet produced the same peak effect on urinary osmolality and urine volume as did the inhalation of halothane. Furthermore, it would seem inconceivable that the intracarotid injection of 0.02 ml of halothane (total dose) could exert any direct renal effect.

The experiments discussed thus far are all consistent with the concept that halothane liberates antidiuretic hormone. The most definitive support for this concept was obtained from experiments in which the effect of acute hypophysectomy on the vascular response to halothane administration was studied. In each of three animals the vasoconstriction obtained with halothane anesthesia was reversed to vasodilatation following removal of the pituitary. Thus, removal of the source of antidiuretic hormone abolished the vasoconstriction associated with halothane anesthesia and unmasked the direct vascular smooth muscle depressant effect of halothane.

Neither the precise mechanism by which halothane stimulates the release of antidiuretic hormone nor the site of such action is evident from these experiments. Halothane might release antidiuretic hormone through reflex means by stimulating the same hypothalamic receptors which are responsive to changes in osmolality of blood. On the other hand, the mechanism of release of antidiuretic hormone by halothane might be a direct effect on the storage site of this hormone in the pituitary gland.

In two experiments, cyclopropane anesthesia was associated with a marked reduction in urine volume and an insignificant increase in urinary osmolality. The failure of cyclopropane in these preliminary experiments to concentrate urine significantly suggests that the antidiuretic effect associated with this anesthetic agent may result from a mechanism other than elaboration of antidiuretic hormone.

The role of the release of antidiuretic hormone during general anesthesia has been investigated previously and has been reviewed by Papper and Papper. Deutsch et al. described, in 11 elderly patients, postoperative hyponatremia which the authors considered secondary to excessive fluid retention related to persistent and inappropriate secretion of antidiuretic hormone. In a recent report by Deutsch et al. it was noted that halothane anesthesia was associated with an antidiuresis which was probably related to both a reduction of glomerular filtration rate and the release of antidiuretic hormone. This antidiuresis was partially reversed in most of their subjects by intravenous administration of ethanol.

The results of the present study clearly indicate that halothane anesthesia in the dog is associated with the release of a substance which appears to be antidiuretic hormone, in concentration sufficient to cause not only antidiuresis but marked vasoconstriction in a skeletal muscle vascular bed. Although it has become well accepted that halothane possesses a vascular depressant effect which contributes to the hypotension produced by halothane anesthesia, this view does not appear to be supported by several hemodynamic observations.
which show that halothane increases total peripheral resistance.\textsuperscript{14, 15, 16} This increase in peripheral resistance might be passive (decrease in vessel caliber secondary to a decrease in distending pressure); reflex in origin; or the result of vasoconstriction promoted by increased blood levels of antidiuretic hormone. If halothane anesthesia in the human causes release of antidiuretic hormone in amounts sufficient to increase total peripheral resistance, this could be a mechanism which helps support arterial pressure during exposure to halothane. The possibility exists, therefore, that more profound hypotension might result from halothane anesthesia in a subject unable to synthesize, store, or release antidiuretic hormone; for example, an individual with diabetes insipidus of hypothalamic or pituitary origin.

The results of these experiments with cyclopropane demonstrate that this agent can produce vasoconstriction by what appears to be a direct drug effect. This vasoconstriction is not mediated by the release of catecholamines, since the vasoconstrictor response was unaffected by complete alpha-adrenergic receptor blockade in the perfused muscle. This same vasoconstrictor response was produced by the introduction of cyclopropane into an extracorporeal oxygenator supplying blood to a completely isolated gracilis muscle. Vasoconstriction elicited by cyclopropane has been noted previously in a variety of experimental situations.\textsuperscript{17, 18, 19, 20, 21} The present study represents the first clear demonstration that this vasoconstriction is a direct effect of this agent rather than an indirect effect mediated by sensitization of vascular smooth muscle to catecholamines or by release of catecholamines.

Summary

Non-adrenergic vasoconstriction in skeletal muscle vessels is produced by inhalation of halothane or cyclopropane. The vasoconstriction seen with cyclopropane is probably a direct drug effect. Halothane, by a mechanism other than hypotension, causes elaboration of a substance which is probably the polypeptide vasopressin (antidiuretic hormone), in amounts sufficient to cause vasoconstriction, increased urinary osmolality, and decreased urine volume.

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References


Drugs

ALCOHOL AND BARBITURATES The concentration of phenobarbital in the liver, kidney, brain, muscle and blood of mice treated with ethyl alcohol is higher and declines more slowly than in control animals. Changes in the concentration of two other barbiturates (barbital and thiopental) are not significantly different in ethanol-treated mice and controls. In particular, the decline in concentration of thiopental in blood and tissue is not affected by alcohol. By impairing the degradation of phenobarbital, alcohol may intensify and prolong phenobarbital anesthesia. (Stöidel, G.: Distribution of Phenobarbital, Barbital and Thiopental under the Influence of Ethanol, Naunyn Schmiedeberg Arch. Exp. Path. 257: 221 (May) 1967.)

STATUS EPILEPTICUS Seven of nine patients in severe status epilepticus were brought under control rapidly with large doses of diazepam (Valium) given continuously intravenously. Drowsiness occurred, but no serious side effect could be attributed to the drug. (Parsonage, M. J., and others: Use of Diazepam in Treatment of Severe Convulsive Status Epilepticus, Brit. Med. J. 2: 85 (July) 1967.)

CORTICOTROPIN TEST The one-hour response of plasma-fluorescent corticoid concentrations to 25 units of corticotropin has allowed complete separation of a group of seven patients with adrenal insufficiency from another group of 31 patients with findings suggestive of adrenal insufficiency but having, in fact, normal adrenal function. The clinical value of the rapid corticotropin test is evident. The rapid diagnosis of adrenal insufficiency is often a matter of urgency, and although clinical suspicion of the disorder may be made on the basis of history or physical findings, the ultimate diagnosis depends upon the laboratory findings. The diagnosis can be established only by demonstrating unresponsiveness of the adrenal gland to corticotropin stimulation. (Musa, B. U., and Doubling, J. T.: Rapid Intravenous Administration of Corticotropin as a Test of Adrenocortical Insufficiency, J.A.M.A. 201: 633 (Aug.) 1967.)