Inhibition of Adrenal Medullary Catecholamine Secretion by Enflurane:

1. Investigations in Vivo

Manfred Göthert, M.D.,* Johannes Wendt†

The effects of enflurane anesthesia on adrenal medullary catecholamine secretion and on the pressor effect of splanchnic-nerve stimulation were studied in cats given pentobarbital for basal anesthesia. Inhalation of enflurane, 1.2 and 2.2 per cent, caused dose-related inhibition of both spontaneous catecholamine release and secretion evoked by splanchnic-nerve stimulation. During inhalation of 2.2 per cent enflurane spontaneous release of epinephrine and norepinephrine was decreased to 19 and 25 per cent, respectively, of the initial values, and the stimulated release was decreased to 30 and 15 per cent, respectively. Enflurane also inhibited the pressor effect of splanchnic-nerve stimulation, whereas that of norepinephrine was not changed significantly. These results are similar to those previously obtained with halothane and methoxyflurane. It is concluded that the decrease in catecholamine secretion caused by enflurane is in part due to a direct effect on the chromaffin cell, namely to an inhibition of the secretion-stimulating effect of acetylcholine released from splanchnic nerves. (Key words: Anesthetics, volatile, enflurane; Sympathetic nervous system, enflurane.)

It has been shown in cats and dogs that halothane¹ and methoxyflurane²—a decrease both spontaneous adrenal medullary catecholamine release and the secretion evoked by splanchnic-nerve stimulation. In contrast, spontaneous release was not affected by chloroform and was even increased by diethyl ether, although these anesthetics decreased secretion in response to splanchnic-nerve stimulation.⁴ Therefore, it was not possible to predict the effects of enflurane on adrenal medullary function.

Consequently, it was the purpose of the present study to investigate the effects of enflurane on spontaneous and stimulated catecholamine output from the adrenal medulla in cats, using the same experimental procedures as in our previous investigations.¹ ² ⁴ Thus, a comparison of the effects of enflurane with those of the other compounds was made possible.

* Professor of Pharmacology.
† Graduate student.

Received from the Institute of Pharmacology, University of Hamburg, Martinstr. 52, D-2000 Hamburg 20, Federal Republic of Germany. Accepted for publication February 8, 1977. Reported in part at the Fourth European Congress of Anesthesiology, Madrid, Spain, September 1974, and at the Sixth World Congress of Anesthesiology, Mexico City, April 1976. Address reprint requests to Dr. Göthert.

Methods

All methods used have been described in detail.¹ ³ ⁴

Briefly, the experiments were performed on cats of either sex (weights 1.6–4.0 kg) that received injections of pentobarbital, 30 mg/kg, intraperitoneally. After tracheotomy, mechanical ventilation was initiated with a tidal volume of 35–65 ml and

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Fig. 1. Effects of enflurane anesthesia on the spontaneous release of epinephrine (solid line) and norepinephrine (broken line) from the adrenal medullas of cats given pentobarbital (30 mg/kg) for basal anesthesia. Controls: inhalation of air, n = 5. Enflurane, 1.2 per cent: n = 6. Enflurane, 2.2 per cent: n = 6. Means ± SEM. *P < 0.05.
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a respiratory frequency of 19/min to maintain arterial blood carbon dioxide tensions of 23 to 28 torr; arterial blood pH values remained constant throughout the experiments (range of mean values 7.43 to 7.46). The femoral arteries were cannulated for drawing blood samples and recording blood pressure and a femoral vein was cannulated for drug injection. Heart rate was determined from the pulse trace by increasing the chart speed. After midline laparotomy, the left adrenolumbar vein was cannulated and the tip of the catheter was placed 1 to 2 mm from the adrenal gland for drawing samples of adrenal venous blood. Spontaneous catecholamine secretion, secretion evoked by splanchnic-nerve stimulation, and the pressor effect of splanchnic-nerve stimulation were investigated in different groups of cats using techniques identical to those reported previously.1,3 The analytical methods and statistical analyses used were also identical.

Results

SPONTANEOUS CATECHOLAMINE RELEASE

The spontaneous epinephrine and norepinephrine output from the adrenal medullass of cats not exposed to enflurane tended to increase with time (fig. 1). However, this increase was not statistically significant. Enflurane caused a dose-dependent inhibition of catecholamine release. Inhalation of 1.2 per cent enflurane decreased epinephrine and norepinephrine release to 70 and 47 per cent of the values before enflurane anesthesia, respectively; inhalation of 2.2 per cent enflurane decreased them to 19 and 25 per cent, respectively. The inhibition of catecholamine output proved to be completely reversible.

In addition, enflurane produced dose-dependent decreases in heart rate and blood pressure (table 1).

STIMULATED CATECHOLAMINE SECRETION

In control cats not exposed to enflurane the epinephrine and norepinephrine release evoked by splanchnic-nerve stimulation administered four times at intervals of 35 min did not change significantly (fig. 2). During inhalation of enflurane the output of epinephrine and norepinephrine was inhibited in a dose-dependent manner.

Inhalation of 3.5 per cent enflurane decreased the pressor effect of splanchnic-nerve stimulation to 47 per cent of the control level, whereas that of norepinephrine injection was not significantly altered (table 2). Similar results were obtained when supramaximal stimuli of 20 V were delivered to the splanchnic nerve.

Discussion

Enflurane causes marked inhibition of spontaneous catecholamine secretion from the adrenal
medulla. Since enflurane also markedly inhibits stimulated catecholamine secretion and the pressor effect of splanchnic-nerve stimulation, it may be concluded that it possesses a peripheral site of action on the synapses between splanchnic nerve endings and the chromaffin cells. To determine the site and mechanism of action underlying the inhibition of catecholamine release, we measured the effect of enflurane on catecholamine secretion evoked by acetylcholine in isolated bovine adrenals perfused with Locke's solution. These experiments revealed that the stimulating effect of acetylcholine on chromaffin cells is decreased by enflurane. Hence, the decrease in catecholamine secretion determined in vivo is probably due to an inhibition of the secretion-stimulating effect of acetylcholine released from splanchnic nerve endings.

Central nervous inhibition of the sympathetic-adrenal system may be an additional mechanism contributing to the decrease in spontaneous catecholamine secretion. Preganglionic sympathetic activity has been shown to be depressed by enflurane in cats anesthetized with chloralose or nitrous oxide. However, it is difficult to evaluate to what extent this mechanism contributes to the inhibition of spontaneous catecholamine secretion in our cats anesthetized with pentobarbital. The effects of pentobarbital on the sympathoadrenal system (discussed in our previous papers) are at least quantitatively different from those of chloralose and nitrous oxide.

Our finding that enflurane decreases adrenal medullary catecholamine secretion is in agreement with the results of catecholamine determinations in peripheral blood plasma. Norepinephrine and epinephrine concentrations in the plasmas of rats have been shown to decrease during enflurane anesthesia, particularly when deep anesthetic levels are attained.

It is well known that the total amount of catecholamines and the relative amount of epinephrine in the adrenal gland vary from species to species, e.g., the relative content of epinephrine is lower in cats (59 per cent of total catecholamines) than in dogs (73 per cent), rats (91 per cent), and man (83 per cent). The percentage of epinephrine in adrenal venous blood is also higher in dogs than in cats (present paper). However, it has been shown with methoxyflurane that the effects of inhalation anesthesia on catecholamine secretion in dogs and cats are not different from each other.

Inhalation of high concentrations of enflurane produces a negative inotropic effect and decreases heart rate and blood pressure. It appears probable that the considerable inhibition of adrenal medullary catecholamine release contributes to these cardiovascular side effects.

Comparison of the effects of inhalation of 1.7 to 1.9 MAC of various anesthetics using MAC values determined by Brown and Crout indicates that enflurane, halothane, and methoxyflurane act qualitatively in the same manner on spontaneous catecholamine release and on the secretion in response to splanchnic-nerve stimulation (table 3).

### Table 2. Pressor Effects of Splanchnic-nerve Stimulation and Norepinephrine

<table>
<thead>
<tr>
<th></th>
<th>Increase in Blood Pressure</th>
<th>Norepinephrine (1 μg/kg)</th>
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<tbody>
<tr>
<td></td>
<td>Splanchnic-nerve Stimulation</td>
<td>Norepinephrine</td>
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<tr>
<td></td>
<td>Torr*</td>
<td>Per Cent</td>
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<td>Stimulation of splanchnic-nerve with 4 V (5 cats)</td>
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<td></td>
</tr>
<tr>
<td>Before enflurane</td>
<td>55 ± 7</td>
<td>100</td>
</tr>
<tr>
<td>Enflurane, 3.5 per cent</td>
<td>26 ± 8</td>
<td>-11</td>
</tr>
<tr>
<td>50 min after enflurane</td>
<td>53 ± 10</td>
<td>96</td>
</tr>
<tr>
<td>Stimulation of splanchnic-nerve with 20 V (5 cats)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before enflurane</td>
<td>65 ± 10</td>
<td>100</td>
</tr>
<tr>
<td>Enflurane, 3.5 per cent</td>
<td>27 ± 9</td>
<td>-23</td>
</tr>
<tr>
<td>50 min after enflurane</td>
<td>64 ± 16</td>
<td>98</td>
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</tbody>
</table>

* Values are means ± SEM.
† P < 0.05.
‡ P < 0.01.

### Table 3. Inhibitory Effects Induced by Inhalation of 1.7–1.9 MAC of Various Anesthetics on Catecholamine Secretion from the Cat Adrenal Medulla

|                        | Spontaneous Secretion | Secretion Evoked by Splanchnic-nerve Stimulation |
|------------------------|                       |                                               |
|                        | Epinephrine           | Norepinephrine                               |
| Enflurane, 2.2 per cent| 19                    | 25                                            |
| Halothane*, 1.5 per cent| 26                    | 12                                            |
| Methoxyflurane*, 0.4 per cent | 17                    | 6                                             |
| Diethyl ether*, 4.0 per cent | 171                   | 201                                           |

* Values are mean percentages of preanesthetic levels.
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Quantitatively, the slight differences between these agents are not significant. In contrast to the other anesthetics, diethyl ether, which also depresses the stimulated catecholamine discharge, causes an increase in spontaneous catecholamine secretion. This increase is probably due to the central nervous stimulation of the sympathoadrenal system by diethyl ether, whereas the other compounds induce central sympathetic depression.

We conclude that the effects of enflurane on adrenal medullary catecholamine secretion are similar to those previously found for halothane and methoxyflurane. Enflurane decreases the release of both epinephrine and norepinephrine from the adrenal medulla. This decrease is in part due to a direct effect on the chromaffin cell, in particular to inhibition of the secretion-stimulating effect of acetylcholine released from the splanchnic nerve endings.

The authors are indebted to Mrs. G. Thielecke for technical assistance and to Deutsche Abbott (Ingelheim/Rhein) for the gift of enflurane.

References