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THE EFFECT OF ANAESTHESIA ON THE ADRENALINE CONTENT OF THE SUPRARENAL GLANDS

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Numerous observations have been made on the effect of anaesthetics on intestinal and splenic activity, and it has been customary to attribute these effects to the nervous control of these organs rather than to changes in the concentration of circulating adrenaline. Little attention has been paid to the possibility of a secretion of adrenaline from the suprarenal glands resulting from the central action of the anaesthetic, in spite of the observations made by Elliott in 1912. Elliott showed that the adrenaline content of the suprarenal glands of cats is approximately the same on each side. He found that, during anaesthesia, a considerable amount of adrenaline was lost from the normal gland when compared with the gland which was denervated by cutting the splanchnic nerves. Ether, for instance, produced a loss of 50% of the stored adrenaline during a period of 6 hr.

Elliott, however, carried out relatively few experiments with anaesthetics and did not measure the quantities administered. Failing confirmation by subsequent work, his results have been attributed to the excitement during the induction of anaesthesia. Several authors have repeated his observations with varying results [Keeton & Ross, 1919; Kodama, 1923; Fujii, 1924; Marconi & Marco, 1937; Emerson, 1938; Barman, 1939].

In order to determine whether adrenaline secretion does in fact occur during anaesthesia, we have modified Elliott's method so as to exclude the effect of induction and the accompanying excitement. Observations have been made on the effects of three anaesthetics in common use—ether, cyclopropane and pentobarbitone (nembutal).

Methods

Cats were used because the adrenaline content of the suprarenals of the two sides is approximately equal in the normal animal. In all animals the induction of anaesthesia was carried out with ether; anaesthesia was maintained either

by the administration of ether, or by that of cyclopropane or pentobarbitone. The splanchnic nerves on one side were cut, but not until the animal was fully anaesthetized with the agent under observation, thus excluding the effect of induction. The abdomen was opened by a mid-line incision, the nerves being cut with the least possible disturbance of the viscera, and the wound was sewn up again. It was from this point that the period of anaesthesia was measured.

The mode of administration differed with the three anaesthetics. After a dose of 1·5 mg. morphine hydrochloride, pentobarbitone was injected intravenously as a 2% solution. Sufficient was given to produce complete abdominal relaxation without respiratory or circulatory depression, and this condition was maintained throughout the experimental period by further small doses of pentobarbitone.

In both the cyclopropane and the ether experiments the animals were artificially respired to ensure a control of the anaesthetic concentrations. For the first 10–15 min. of the cyclopropane anaesthesia, 25% cyclopropane in oxygen was delivered to the cat to obtain a partial gas equilibrium before a closed circuit was set up. The closed system was necessary because mixtures of cyclopropane and oxygen are very explosive. A glass T-piece was tied into the trachea and connected to the respiration pump. This drew anaesthetic mixture from a rigid reservoir and delivered it to the cat. The expired mixture passed through the pump, and from there through a soda-lime canister back to the reservoir. A steady flow of oxygen was added to the reservoir to maintain the pressure at atmospheric, and measured quantities of cyclopropane were added so as to maintain the concentration between 20 and 25%. The concentration was determined by taking samples from the system at half-hourly intervals and absorbing the cyclopropane in concentrated sulphuric acid in a simplified Haldane apparatus.

The ether was administered by a respiration pump connected to a valved trachea tube. This ensured that the animal only breathed anaesthetic mixture without the use of a closed system. The mixture delivered to the pump was regulated by the use of an Oxford Vaporiser No. 1 described by Epstein, Macintosh & Mendelssohn [1941]. In this apparatus the ether vapour is diluted with air and the concentration is measured empirically; it varied when the pump stroke was altered.

At the end of the anaesthetic period both suprarenal glands were removed from the cat and extracted by grinding with acidified saline and sand. After heating to coagulate the protein, the extracts were filtered and made up to a standard volume, either 15 or 16 c.c. The adrenaline content of the two extracts from each cat were compared with each other and with a standard adrenaline solution freshly made from powder in the same acidified saline. The assays were done on spinal cats, bracketing the pressor response to doses of one solution between smaller and larger doses of the other. From the adrenaline content

of the extracts the relative depletion of the innervated gland's stored adrenaline was calculated by expressing the estimated content as a percentage of that of the denervated gland.

RESULTS

Ether. At first we determined the effect of varying periods of ether anaesthesia. In Table 1 the denervated suprarenal is taken as the control with which the innervated gland is compared. In cat no. 1 the splanchnic nerves of one

TABLE 1. The effect of periods of ether anaesthesia on the adrenaline content of the innervated suprarenal gland

Cat no.	Side denervated	Period of anaesthesia	Denervated gland Wt. mg.	Denervated gland Content mg./g.	Innervated gland Wt. mg.	Innervated gland Content mg./g.	% control	Rate of loss %/hr.
1	L	Induction	204	0·75	149	0·75	100	—
2	—	—	168	1·06	152	1·05	99	—
3	L	2 hr. 20 min.	157	2·67	159	2·34	88	5·14
4	R	1 „ 55 „	221	0·54	211	0·47	87	6·78
5	R	2 „ 40 „	179	1·29	179	0·83	64	13·5
6	L	4 „ 50 „	338	0·98	342	0·70	72	5·79
7	L	5 „ 0 „	314	0·48	313	0·38	79	4·20
8	R	4 „ 50 „	159	1·08	151	0·83	77	4·76

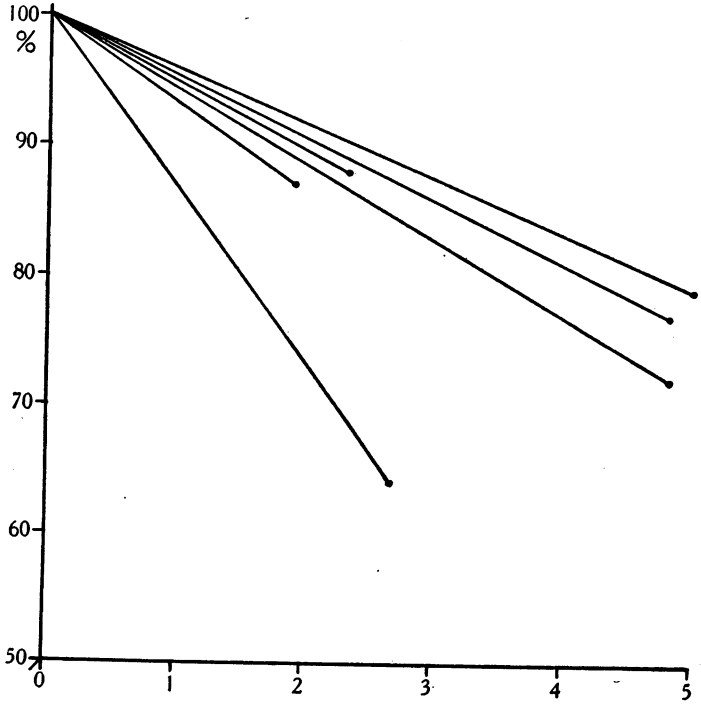

Fig. 1. The loss of adrenaline from the innervated suprarenal glands of six cats during ether anaesthesia. Ordinate: adrenaline content as percentage of that of the denervated glands. Abscissa: duration of anaesthesia in hours.

side were cut by a sterile operation 4 days beforehand. Both the suprarenals were removed immediately after the period of induction which lasted about 15 min.; no difference in adrenaline content was detected. In cat no. 2, both splanchnic nerves were intact, and again there was no significant difference between the two sides. This confirms Elliott's observation that the adrenaline content of the two suprarenal glands in cats is the same, and also shows that the period of induction need not cause more than a negligible secretion. The results obtained in cats nos. 3–8 indicate a progressive loss of adrenaline from the innervated suprarenal gland during anaesthesia. Fig. 1 shows that this loss occurred at approximately the same rate in all except one animal; the average rate of loss for the whole series was 6·7 %/hr. A gradual fall of blood pressure was always noticed during the ether anaesthesia, which was very deep, the ether concentration varying between 4 and 8%. Cat no. 5 had a blood pressure of less than 40 mm. Hg for the last hour of the experimental period, and we believe this to be the reason for the excessive adrenaline loss.

As the rate of adrenaline secretion during ether anaesthesia seemed to be constant throughout the experimental period, we fixed the duration of cyclopropane and pentobarbitone anaesthesia at 5 hr. in order to obtain as great a loss of adrenaline from the innervated gland as possible.

Pentobarbitone. The results obtained with pentobarbitone are shown in Table 2. The total dose necessary to produce surgical anaesthesia for 5 hr. varied between 19·2 and 51·2 mg./kg. We could not discover any relation between this variation and the amount of adrenaline lost from the suprarenal gland. The blood pressure in these experiments remained normal throughout (100–150 mm. Hg).

TABLE 2. The effect of anaesthesia with pentobarbitone and morphine on the adrenaline content of the innervated suprarenal

Cat no.	Period of anaesthesia	Total dose of pentobarbitone mg./kg.	Content as % of control	Rate of loss %/hr.
10	5 hr. 9 min.	51·2	82	3·40
11	5 „ 1 „	25·8	97	0·52
12	5 „ 8 „	29·0	87	2·43
13	5 „ 0 „	19·2	78	4·42
14	5 „ 8 „	26·6	86	2·66

Cyclopropane. The results of the experiments with cyclopropane are shown in Table 3. The rate at which adrenaline was lost from the suprarenal glands varied between 0·65 %/hr. and 10·5 %/hr., a difference which is outside the range of experimental error. We were unable to account for this variation by the factors under observation; the average concentration of cyclopropane given to each cat varied only between 19·9 and 23·7 % and the average blood pressure between 98 and 114 mm. The effect evidently arises from the different reaction of each animal to the anaesthetic.

TABLE 3. The effect of cyclopropane anaesthesia on the adrenaline content of the innervated suprarenal

Cat no.	Period of anaesthesia	Average cyclopropane concentration %	Average blood pressure mm. Hg	Content as % of control	Rate of loss %/hr.
15	5 hr. 10 min.	19·9	114	65	6·76
16	5 „ 1 „	21·1	110	77	4·57
17	5 „ 0 „	20·9	101	47	10·58
18	5 „ 3 „	21·8	114	96	0·65
19	4 „ 55 „	23·7	98	95	1·15

In Fig. 2 the average rates of loss of adrenaline under the three types of anaesthesia are compared. Under ether it is greatest, being $6{\cdot}7 \pm 1{\cdot}4$ %/hr. and it is least under pentobarbitone, being only $2{\cdot}7 \pm 0{\cdot}6$ %/hr. The average

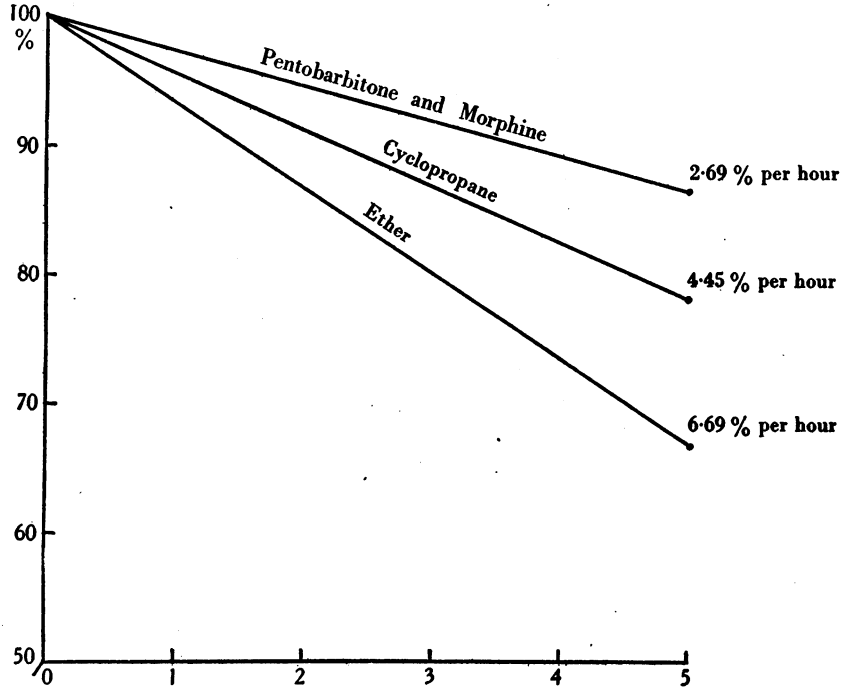

Fig. 2. A comparison of the rate of adrenaline loss from the innervated suprarenal glands of cats under different anaesthetics. Ordinate: adrenaline content as percentage of that of the denervated glands. Abscissa: duration of the anaesthesia in hours.

rate of loss under cyclopropane is $4{\cdot}45 \pm 1{\cdot}8$ %/hr. The highest rate of secretion in any animal was under ether (13·5 %/hr.) and the lowest under pentobarbitone (0·52 %/hr., not significant).

Discussion

The adrenaline content in the suprarenal glands depends both upon the rate of synthesis and the rate of secretion. Thus only if the rate of secretion exceeds the rate of synthesis does a loss of adrenaline from the gland occur. In our experiments we measured this loss, not absolutely, but in relation to the estimated original content of the gland.

The quantities of adrenaline secreted must have been greater than the figures indicate. Nevertheless the blood pressure during anaesthesia was not raised and indeed when ether was given the blood pressure gradually fell. We believe that the action of ether on the medulla causes an increase in the sympathetic outflow. Cattell [1923] and Bhatia & Burn [1933] have shown that this produces a vaso-constriction. At the same time adrenaline is being secreted, and it is well known that small doses of adrenaline can produce vaso-dilatation during ether anaesthesia [Macdonald & Schlapp, 1926]. This may explain the finding of Herrick, Essex & Baldes [1932] that ether increases the blood flow through the hind limb of the dog. The gradual fall of blood pressure we observed during deep ether anaesthesia may, therefore, be due to two factors: first the vaso-dilator action of the adrenaline, and secondly the direct action of ether on the heart.

Under cyclopropane anaesthesia the blood pressure was found to be normal in spite of a wide variation in the adrenaline loss from the suprarenal gland. Meek, Hathaway & Orth [1937] showed that, under cyclopropane anaesthesia, injected adrenaline readily produces ventricular tachycardia and fibrillation in dogs. This has been attributed to an increased excitability of the heart muscle accompanied by an increase in vagal tone. This indicates that the vaso-motor control is increased by cyclopropane and compensates for any adrenaline secretion occurring; the blood pressure remains normal.

Summary

A loss of adrenaline from the suprarenal glands of cats was observed during anaesthesia.

Under ether $6{\cdot}7 \pm 1{\cdot}4\%$ (6) of the original content was lost per hr., under cyclopropane $4{\cdot}45 \pm 1{\cdot}8\%$ (5) and under pentobarbitone-morphine $2{\cdot}7 \pm 0{\cdot}6\%$ (5).

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