On the Influence of Ether Anaesthesia on the Epinephrine Content of the Suprarenals of the Dog.

By

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While Elliott was able to observe in the cat that the exhaustion of residual epinephrine in the suprarenal gland by ether anaesthesia could be prevented on either side by the section of the splanchnic nerves of that side,¹⁾ Keeton and Ross were unable to establish such a relationship in the case of the dog.²⁾ At the end of 3 hours of ether insufflation, the epinephrine content of the gland on the previously splanchnectomized side was sometimes greater or nearly equal, but sometimes smaller in comparison with that of the gland on the other side. These inconclusive results led them to the view that the ether causes more probably increased production as well as increased partition.

The second of the above mentioned papers having been published while I was engaged on study on the ether hyperglycaemia in the rabbit, experiments of an exactly similar nature with those essays were tried on the rabbit, and the chromaffine substance content was judged by the method of Negrin and Brücke. The results in the case of rabbits agreed with those of Elliott in the case of cats.³⁾

So, investigation of the same kind has been further performed on the dog. The results will be presented in the following pages.

According to Kodama, who made use of the "cava pocket" method, the ether anaesthesia reduces the residual epinephrine content in the suprarenals, whereas it decreases

1) T. R. Elliott, *J. Physiol.*, 1912, **44**, 388 ff.

2) R. W. Keeton and E. L. Ross, *Am. J. Physiol.*, 1919, **48**, 156 f.

3) Iju. Fujii, *Tôhoku J. Exp. Med.*, 1921, **2**, 202.

the epinephrine output from the gland.⁴⁾ So, his view is exactly contrary to that of Keeton and Ross.

METHODS.

Since the present research was made in succession to our study on the ether hyperglycaemia in the dog, the results of which will be reported elsewhere, the blood sugar content was also determined in the unilateral splanchnectomized dog mentioned in this paper, for the sake of comparing its intensity with that in the normal as well as in the bilateral splanchnectomized one.

The methods employed for the present investigation were essentially the same as those applied in the former researches⁵⁾; in the studies on the ether hyperglycaemia special care was taken in the feeding of the animals, so that two weeks before the experiment a mixed diet of roughly the same composition was given daily: It consisted of rice (potatoes, radishes and other vegetables), fish, and soup in the ratio of about 3 : 2 : 1 in volume.

The mask used for etherization of the dog was constructed nearly in the same way as that used for the rabbit, described in the previous paper, only on a larger scale. The broad end of the muzzle was fitted over the dog's face by means of an oilcloth cushion. The closed, narrow end of the mask had a wide soldered inlet tube in the centre and two somewhat narrower tubes on the edge. Through one of the narrow tubes, fixed just under the centre tube, saliva was removed from time to time. The other narrow tube was used to send fresh air to the animal, when asphyxia was accidentally induced. The central tube, through which the dog breathed, was connected to the glass tube of Y form, to each of the limbs of which a valvular arrangement was attached, so that inspiration could be performed only through the one limb and expiration only through the other. The limb for inspiration was connected to the ether bottle with a regulator, which enabled us to alter the concentration of ether vapour at will. The respiratory movement of the etherized dog under the mask was so powerful, that there was no need of artificial respiration, contrary to the case of ether experiments on rabbits.

For the determination of the epinephrine content of suprarenal glands Kodama's modification of Folin, Cannon and Denis' method came

4) Sakuji Kodama, *Tohoku J. Exp. Med.* 1924, 4, 631.

5) Iju. Fujii, *ibid.*, 1922, 3, 84 f.; *ibid.*, 1921, 2, 173.

into application.⁶⁾ In two dogs the content of chromaffine substance was judged by the method of Negrin and Brücke.⁷⁾

The major and minor splanchnic nerves were exposed through the lumbar route under morphine and ether plus chloroform, and cut just under the diaphragma. The ether experiment was carried out at least ten days later.

EXPERIMENTAL RESULTS.

The dog was muzzled at the start, brought on the table, caught by the head and legs, gently placed on its side, and then the central tube of the muzzle cone was connected with the ether bottle by means of the Y formed glas tube in the above mentioned manner. The animal then struggled somewhat for a while; when the limbs became limp, the animal was allowed to lie down, without being restricted. Etherization continued. At the end of some hours etherization the suprarenals were excised by the abdominal route. The section of the nerves was verified by autopsy.

In the unilateral splanchnectomized dogs, fed on a mixed diet rich in carbohydrates, as is seen in Table I, ether administration caused rather remarkable hyperglycaemia. The intensity of hyperglycaemia, fall of body temperature, and fluctuation of frequency of pulse as well as of respiration did not materially differ from those in the ether experiments on the normal dogs, which we hope to report on an other occasion, as above mentioned.

In 5 dogs out of 11, the left splanchnic nerves were divided, and in the remaining 6 the right. The influence of ether anaesthesia upon the epinephrine quantity in the gland on the side not denervated was practically equal to that of the control gland in 4 dogs (Nos. 1, 3, 5 & 6), and smaller in 5 dogs (Nos. 2, 4, 7, 9 & 10), whereas in the remaining 2 (Nos. 8 & 11) the reverse was the case i.e. the control gland had a smaller storage than its sister gland. In the comparison of the percentage content of epinephrine these two dogs were also an exception.

Whether the splanchnic nerves were cut on either side had no bearing on these results.

The total epinephrine quantity in the gland in the splanchnectomized side was 0.49–1.33 mgrms. (on an average 0.76 mgrm.) in the right (6 dogs) and 0.57–0.87 mgrm. (on an average 0.69 mgrm.) in the left (3 dogs). The content in the gland in the intact side was 0.47–1.10 mgrms. (on an average 0.68 mgrm.) in the left and 0.60–0.74 mgrm. (mean 0.67 mgrm.) in the right. In the paper of Ross and Keeton who made use of Folin, Cannon and Denis'

6) Sakuji Kodama, J. Biochem., 1922, 1, 281.

7) Iju. Fujii, Tōhoku J. Exp. Med., 1920, 1, 44 f.

method for the determination of epinephrine the content was: The denervated glands—right 0.35–1.34 mgrms. (0.81 mgrm.), left 0.14–1.20 mgrms. (0.73 mgrm.); The glands not denervated—right 0.33–1.08 mgrms. (0.71 mgrm.), left 0.39–1.46 mgrms. (0.78 mgrm.). The figures in both papers closely agree with each other.

Out of the 13 dogs experimented on by American investigators, there were 5 cases where the epinephrine store in the gland on the splanchnectomized side was smaller than that in the gland on the opposite side. In the present investigation the cases of the same kind were 2 out of 11 dogs. Indeed these results agree well with those of Keeton and Ross.

Then should we also consider these results as finally inconclusive, as they did? To make sure, however, control experiments were performed. The previously unilateral splanchnectomized dogs were killed by a blow on the neck, without etherization or any

TABLE I.

Exp.-Number	Date	Sex	Body weight (kilos)	Splanchnectomized side	Days after operation	Duration of narcosis (hours)	Quantity of ether (c.c.)	Blood sugar (%)			Body temperature (°C)		Frequency of heart beat (per min.)	Frequency of respiration (per min.)	Weight (g)		Quantity of Epinephrine		Room temperature (°C)
								Before narcosis	Maximum during narcosis	Hours to maximum	Before narcosis	During narcosis					right	left	
123.	XII. 20	♂	7.5	left	26	6 ¹ / ₂	360	0.10	0.14	6	38.6	38.3–37.5	132–210	18–56		0.977	0.836	strong stained	16.7–23.0
210.	V. 21	♀	8.3	"	163	6 ¹ / ₂	360	0.07	0.12	4 ¹ / ₂	39.1	38.8–37.4	92–194	28–104		0.977	0.836	strong stained	17.0–20.0
326.	IX. 22	♀	15.5	"	248	2 ¹ / ₂	250	0.08	0.33	2	38.6	38.9–39.1	74–186	24–18		0.977	0.836	strong stained	23.5–25.2
428.	IX. "	♂	21.5	"	133	3	250	0.08	0.19	1	39.1	39.5–40.2	108–132	18–42		0.654	0.850	0.64	0.08
512.	X. "	♂	10.0	right	15	7	400	0.07	0.16	3	38.9	37.3–30.8	128–196	30–36		0.654	0.850	0.87	0.10
619.	X. "	♂	15.2	"	23	6	500	0.07	0.25	5	38.8	37.1–32.7	126–190	20–36		0.603	0.547	0.08	0.08
7	2.	XI.	10.0	"	28	3 ¹ / ₂	260	0.10	0.27	3	39.2	38.3–36.2	111–210	20–42		0.580	0.592	0.11	0.15
8	6.	XI.	6.1	left	27	7	300	0.10	0.12	4	38.2	38.5–36.9	120–210	16–48		0.755	0.654	0.78	0.10
917.	XI.	♂	14.0	right	43	5	460	0.06	0.19	1	38.4	37.2–34.6	98–218	20–54		0.763	0.608	0.74	0.10
1027.	XI.	♀	15.0	"	19	1 ¹ / ₂	230	0.08	0.17	3	38.4	37.3–32.3	148–226	28–40		0.802	0.688	1.33	0.16
1130.	XI.	♀	13.0	"	22	5	450	0.08	0.14	3	38.7	38.1–35.3	128–228	24–40		0.710	0.618	0.51	0.07

In Nos. 3, 4, 7 & 10 the glands were excised immediately after death. No female cat in this paper (Tables I & II) was pregnant.

harmful manipulation other than the blood drawing from the previously de-afferented ear vein, measuring the anal temperature and laying the stethoscope on the chest. The suprarenal glands were immediately excised.

The approximate equality of the total epinephrine quantity in the sister glands, the well-established fact in the cat⁸⁾ as well as in the rabbit,¹⁰⁾ seems exists also in the dog.⁹⁾

This approximate equality of the total epinephrine quantity in the sister glands exists even in the previously unilaterally splachnectomized cat¹¹⁾¹²⁾ and rabbit.¹³⁾

The same fact in the dog was shown by Stewart and Rogoff,¹²⁾¹⁴⁾ with the following data.¹⁴⁾

TABLE II.

No. of animals	Days after operation	Weight of glands (gram.)		Epinephrine (mgrm.)	
		Left	Right	Left	Right
12	9	0.400	0.408	0.72	0.72
13	4	0.640	0.550	0.83	0.83

(Left ? major and minor splachnics were cut)

Concerning the dog, however, the number of experiments up to date is small, too small for the purpose of control in the present investigation, the results of which are apparently so inconclusive.

8) T. R. Elliott, *J. Physiol.*, 1912, **44**, 379.

9) Matsu. Morita (Fukuoka-Ikwadaigaku Zasshi, 1923, **16**, 10.) estimated the epinephrine content of the suprarenals in 4 normal dogs. In 2 of these the load in the sister glands was quite equal, while in the remaining 2 the right gland had a little greater epinephrine store than the left (ca. 10%). The total quantity in his dogs was far smaller than the values in Stewart and Rogoff, in Keeton and Ross and those in the present paper. The difference may probably be due to the difference of the methods for the epinephrine assay used by him (Comesatti's method, modified by Suto and Inoue) and those used by us. See Iju. Fujii, *Tôhoku J. Exp. Med.*, 1924, **5**, 414.

10) For example: Iju. Fujii, *Tôhoku J. Exp. Med.*, 1924, **5**, 416. ("This smallness of inequality etc." on p. 416 is an erroneous statement. It must be deleted.)

11) T. R. Elliott, *J. Physiol.*, 1912, **44**, 381 f.

12) G. N. Stewart and J. M. Rogoff, *J. Exp. Med.*, 1916, **24**, 711.

13) G. N. Stewart and J. M. Rogoff, *J. Exp. Med.*, 1916, **24**, 719. Iju. Fujii, *Tôhoku J. Exp. Med.*, 1920, **1**, 66 & 68 f. (chromaffine substance)

14) G. N. Stewart and J. M. Rogoff, *J. Exp. Med.*, 1916, **24**, 716.

Six dogs were sacrificed for the control experiment. 12-29 days after the unilateral splanchnectomy the control experiment was, as above described, carried out in the morning, just at the time when ether experiments were usually started.

Table III illustrates the results obtained in these dogs. In 3 dogs the sister glands stored practically the same quantity of epinephrine, in agreement with Stewart and Rogoff. But in the remaining 3 dogs the store in the gland in the side not splanchnectomized was far greater than that in the sister gland on the side denervated. The surplus was 0.16-0.25 mgrm.; two examples in the left side (right nerves were interfered with), and one in the right (left nerves were severed).

The number of experiments was small and this inequality was not found in every case, but only in half of the cases. Additional examples are to be desired.

It may be strange, yet it is not unreasonable, to expect to discover such a fact. That the epinephrine output from the suprarenal gland is depressed to the minimum by the interference of the splanchnics on the side is a definitely established fact. We have also been able to see abundant confirmation of the fact in the course of studying the epinephrine output in our Laboratory, which shall be reported on another occasion. Agents augmenting the output by direct influence upon the gland itself are seldom discovered. The action of mechanical press or nicotine can be seen only in experimental

TABLE III.

Exp-Number	Date	Sex	Body weight (kilos)	Splanchnectomized side	Days after operation	Blood sugar (%)	Body temperature (°C)	Frequency of heart beat (per min.)	Frequency of respiration (per min.)	Suprarenal glands				Room temperature (°C)
										Weight (g)	Quantity of epinephrine		%	
											right	left		
											mgrs.	mgrs.		
1	16. III. 23	♂	4.2	left	13	0.07	38.9			0.372	0.293	0.41	0.14	16.0
2	16. III. "	♂	12.65	right	21	0.08	38.9	26		0.733	0.716	1.18	0.16	16.0
3	12. IV. "	♂	4.75	"	20	0.08	39.0	120		0.365	0.345	0.62	0.18	18.0
4	12. IV. "	♂	6.2	left	12	0.08	38.9	126		0.405	0.362	0.93	0.21	18.0
5	9. V. "	♂	6.0	"	18	0.09	39.2	114		0.307	0.305	0.74	0.23	20.0
6	9. V. "	♂	19.5	right	39	0.08	39.3	120		0.865	0.805	1.42	0.18	20.0

research, and not in the natural life of the animals. It seems not to be unreasonable, therefore, to expect that the epinephrine producing tissue undergoes atrophy in the gland not working in consequence of denervation. Or, on the other hand, it may be suggested that the gland not denervated is compelled to overwork as a compensation for the denervated fellow, so that the epinephrine store becomes increased.

As a matter of fact, numerous experiments along this line must be done in the normal as well as the unilaterally splanchnectomized dogs previous to speculate so far.

Now, the apparent exceptional cases in the ether experiments being illustrated by the light of the new finding, there is no more opposition to the conclusion that the epinephrine content of the gland in the side not splanchnectomized reduces or remains unchanged by ether anaesthesia in comparison with the denervated sister gland.

The surplus of the load in the intact gland over the denervated in the ether experiments was 0.18 and 0.21 mgrm. in the present paper, and 0.10, 0.13, 0.19 and 0.19 mgrm. in Keeton and Ross. So, they never exceeded the surplus in the control experiments.

SUMMARY.

So, the statement, that the exhaustion of residual epinephrine in the suprarenal gland by ether anaesthesia can be prevented on either side by the section of the splanchnic nerves on that side, also holds true in the case of the dog.