SECRETION OF ADRENALINE, PARTICULAR

REFERENCES

4) Stewart and Rogoff, *J. Exp. Med.*, 1917, 26, 613; *Am. J. Physiol.*, 1920, 51, 484.

B. Particular


This section of the chapter is chiefly composed of data from the experiments in which a given stimulation is applied to the dog, which has been prepared for collecting the adrenal venous blood in quiet, almost normal, or physiological conditions, as in the manner described in Chapter V. The adrenaline was estimated by means of the rabbit intestine segment method. In some instances the cat paradoxical pupil method was used in addition.

Remark 1. The rate of secretion of adrenaline given in this monography, i.e. in texts and figures as well, is generally the value from both adrenals, while the gland on one side is commonly experimented on in "the lumbar method."

Figures in this book which show curves of the adrenaline secretion, blood sugar fluctuation, etc. are plotted against the time indicated on the abscissa. Of estimates given on the ordinate, zero in the adrenaline secretion, 0.1% in the blood sugar concentration, 39°C. in the anal temperature, the value at the start of measurement in the arterial blood pressure and that in the pulse rate are plotted on the origin. The former three values expressed are actual ones, and the latter two are in the percentage of actual value against that at the start, this being taken as 100. The agency was commonly given or started at the origin (e.g. injected).

In general the scales of the values and time are the same throughout all the figures; only in a few cases where the secretion of adrenaline takes place at an extraordinarily enormous rate or when it fluctuates very rapidly, are their scales suitably adjusted. Such are cases with nicotine, carbon monoxide, cooling, etc., and the adjustment is especially annotated in the legend under the figure.

By way of precaution it should be pointed out that the rate of secretion, blood sugar, pulse rate, etc. here commonly reproduced in the figures with constant scales might erroneously lead the reader to conclude that there is some relationship in respect to the greatness of variations of the factors. The reason for such an arrangement, however, is that it has the merit of making it easy to compare the variations of all factors in several figures.
In most of the cases the blood sugar, arterial blood pressure, heart rate and anal temperature were simultaneously determined. In certain cases the denervated heart reaction or the paradoxical pupil reaction was also determined at the same time with the collection of adrenal venous blood. The outcome re the blood sugar, denervated heart, and paradoxical pupil will be particularly dealt with in Chapter VIII with those of the adrenaline secretion, and discussed there in advance of their interrelationship.

**General remarks on the figures given in Chapters VII and VIII.**

In all figures each subject is indicated respectively with a special form of line, as given below.

- **Solid line** — adrenaline, rate of secretion in γ per kg.-min.; pupil width in Figs. 26 & 27.
- **Dash line** — blood sugar, in per cent.
- **Dotted line** — blood pressure, in mm. Hg.
- **Chain line** — heart rate, in beats per min.
- **Double line** — body temperature, in °C.

On the original are marked: 0 of adrenaline secretion rate, 0.1% of the blood sugar content, 100 mm. Hg. of the arterial blood pressure, 100 beats per min. of the pulse and 39°C. of the anal temperature. The scale of each subject and the time is quite the same throughout all the figures, but there are a few exceptional cases. This makes the data in almost all the figures readily comparable with each other. The exceptions are of such cases where the adrenaline secretion reaches an extraordinarily great rate or varies quickly; they are Figs. 9, 32, 35 A & B in part, 36, 37, special remarks are noted there. Time scale is modified there accordingly.

Experiments were carried out on dogs under various conditions, i.e. on the normal dog, the dog with bilateral medulli-adrenalectomy, or with double splanchnicotomy, or the dog with the completely denervated heart or pupil or further with their combined operations. In some cases an intravenous infusion of adrenaline solution in imitating the augmented secretion in the control dog or the like was simultaneously run.

The figures obtained under these various conditions are indicated with the following symbols:

- **Remark 2.** The pulse rate given in the figures in this book are not the actual rates, but those recalculated on the basis of the body temperature. The rate of the excised heart varies according to the temperature of the heart itself. The heart rate, recalculated in this manner, when compared with the rate at the start of experimentation, enables one to quantitatively estimate the influence of a certain factor or factors other than the temperature, such as adrenaline, sympathin, etc. (Cf. Chapter VIII)

- **Remark 3.** Literature which is directly or indirectly related to the problems presented in this chapter, has been already as exhaustively as possible referred to in our previous papers. In this chapter, however, those which have direct or indirect but intimate bearings on our quantitative data, or the ideas deduced therefrom, are as a matter of course, quoted here again, and evaluated and discussed anew.

- **Remark 4.** Of the pulse rate, blood pressure, and anal temperature the original protocols have been consulted, because they were not fully reproduced in the previous papers. The pulse rate has been recalculated on the above given principle; the method is given in Chapter VIII.
ASPHYXIA HYPERADRENALINEMIA

Light circle ○ The normal dog, given with a stimulus
Solid circle ● The dog with double medulli-adrenalectomy, given with a stimulus; the rabbits or dogs (in Figs. 12 & 22) with double adrenalectomy, given with a stimulus
Light circle with point ◆ The same, with the adrenaline infusion
Cross × The same, with a stimulus given and the adrenaline infusion; the adrenalectomized dogs treated similarly to the former (Fig. 12)
Double quadrate □ The same, with a stimulus given and the saline solution infusion; the adrenalectomized dogs, similarly treated (Fig. 12)
Light triangle △ The dog with double splanchnicotomy with a stimulus given
Solid triangle ▲ The same, with the adrenaline infusion
Double triangle △ The same, with a stimulus given and the adrenaline infusion
Light quadrate ◊ The dog with the denervated heart, with a stimulus given
Solid quadrate ● The dog with the denervated heart and double medulli-adrenalectomy, with a stimulus given

These measures together facilitate the comparison of the figures with each other.

The data given in this following paragraphs are roughly in the order of agents producing anoxemia, blood pressure fall, hypoglycemia, some effects on the central nervous system or the body temperature, narcotics, autonomic hormones and poisons, inorganic salts, bacterial toxins, and so on.

**Asphyxia**

For asphyxiating the normal dog, certain manipulations other than the asphyxiation itself are necessary.

For example: the dog is first muzzled, though not tightly, lifted by the head and legs, and gently placed on its side; the mouth and nose are then wrapped around with a folded wet towel, having a thin rubber plate between the folds. The dog is asphyxiated in this manner. When the respiration becomes laboured and slow or wholly stopped, a matter of from 1.5 to 9 minutes, the wet towel is taken off and the animal set free; the animal then usually begins to breath spontaneously: if it does not, artificial respiration has to be conducted.¹

Asphyxiation produces in the normal dog an oversecretion of adrenaline (7 experiments). The peak of oversecretion appears in a few minutes, schematically 1–2 minutes following the asphyxiating period; then the rate goes back rather rapidly to the initial. The longest duration of oversecretion was a half hour. The mean of the greatest rate was 0.8 γ, per kg.-min.; the highest 3 γ. Ten minutes after having reached the peak the initial rate was almost recovered; 20–30 minutes after discontinuation of asphyxiation the rate was completely normal. The course of oversecretion of adrenaline might thus be assumed as of Type A₂.

The total oversecretion of adrenaline due to the asphyxiating in such an amount as to stop the respiration and render the dog unconscious, is
computed at 2–4 ρ usually, or on an average 3 ρ per kg., the greatest being 10 ρ per kg.

The oversecretion is due chiefly at least to an increase of adrenaline concentration in the blood. It depends wholly upon the integrity of the splanchnic nerves (3 experiments).

The maximum rate of adrenaline secretion on asphyxiating the dog under ether or chloralose is 7 ρ per kg.-min., as reported by Kodama,2 and 2 ρ by Houssay.3 Such experimental conditions as those are sufficient to cause an oversecretion of adrenaline per se, as discussed elsewhere in this book.

In the experiments on the foregoing normal dogs, the secretion was not estimated during the asphyxiation. The cava pocket experiment on anesthetized dogs will therefore now be quoted to supplement the lacunae there.2 The oversecretion already starts within twenty seconds of asphyxiation and advances as the asphyxiation is maintained for a further thirty seconds. The secretion taking place immediately after the end of asphyxiation of sixty seconds might be of a still greater rate.

A few words may be added here in conclusion: it has been well established that the asphyxia, especially if deep, is capable of eliciting glycemic, pressoric, and paradoxical pupil reaction, though less, even after excluding the adrenal secretion from the circulation or cutting the splanchnic nerves.2,4 According to Stewart and Rogoff the denervated heart may be accelerated in cats in the amount, not less than normal.5

REFERENCES

2) Kodama, Ibid., 1923, 4, 166.

CARBONMONOXIDE

The method applied for letting the normal dog, provided with the "lumbar route" preparation, inhale CO-air mixture was as follows: a cannula with inspiratory and expiratory valves was inserted into the trachea under local anesthesia. Then 3% CO-air mixture was released for inhalation there-through, e.g. 20 litres1 in 2 minutes. About twenty to thirty minutes later 5%–3% CO-air mixture was further given in an amount of 10–16 litres.1

In the first test the blood pressure and pulse rate mostly increased, while

* When one and the same investigation was published in two or more periodicals, only the paper more common and readily available is given in this book, provided it does not interfere with the priority, so far as the references here are concerned.
on the second inhalation the reverse invariably resulted. In both the tests the pulmonary ventilation increased largely and the breathing rate increased. While the blood pressure rose, the animal struggled strongly.

Carbonmonoxide inhalation induces an enormously rapid but transitory increase in the rate of secretion of adrenaline, of Type $A_2$, as indicated in Fig. 9. Simultaneously the arterial pressure either ascends or falls as explained above.

Taking all the cases together, the mean maximum rate is $3 \gamma$ per kg.-min., the greatest one being $10 \gamma$. That is: CO inhalation can induce usually some hundred times acceleration of adrenaline secretion, and a maximum of 1000 times. The acceleration is due almost entirely to an increase of the concentration, and depends solely on the integrity of the splanchnic nerves.

The latency of oversecretion i.e. the time elapsed from the start of inhalation to the beginning of the secretion rate increase was roughly speaking one minute, and the time when the peak appeared was on an average two

Fig. 9

![Adrenaline secretion vs time](image1)

![Blood sugar fluctuation](image2)

**Fig. 9.** CO-inhalation twice (Wada et al.); adrenaline secretion soon starts to increase, the latency being measured as 1 min.. Adrenaline scale is here taken as 1:10 of the common in this book, and time scale as 2 times.

**Fig. 10.** Blood sugar fluctuation on CO-inhalation (Suzuki, Takahashi & Tamabuti). From top to bottom: CO to normal dogs, CO to medulli-adrenalectomized, and adrenaline hydrochloride saline solution to the medulli-adrenalectomized.
to three minutes after beginning the inhalation. Duration of the inhalation was about two minutes or so.

The hyperadrenalinemic period covered half an hour to one hour, roughly speaking. The total amount of adrenaline, extraordinarily secreted on carbonmonoxide inhalation, conducted in the manner above noted, was 20-30 \( \gamma \) per kg. body weight.\(^1\)

Inhalation of 3% CO in a total amount of 2,500–8,000 cc. causes in normal dogs a hyperglycemia with the mean acme of 0.18–0.19%, and an excess of sugar of 3 g. in 60–90 minutes. The demedullation of adrenals reduces it to 0.14%, and 1.1 g. in 60 minutes.\(^2\) An infusion of adrenaline hydrochloride saline solution in imitation of the natural adrenaline secretion in CO-inhalation in amount and time course, brings about a hyperglycemia with 0.13% peak, 0.6 g. excess amount and 30 minutes duration. (Cf. Fig. 10) Inhalation of the gas in a large amount such as 20,000 cc. of 3% CO is capable of producing a large hyperglycemia both in the normal dog and in one without the adreanl medulla (0.21%, 4 g. and 0.28%, 4 g.).

These figures show, broadly considered, that the blood sugar increase due to CO can be attributed to two factors, one due to the oversecretion of adrenaline, and another to the glycemic mechanism other than the adrenal medulla. Both mechanisms are set into action by the impulse sent through the splanchnic nerves. Only a very small hyperglycemia, for instance 0.11%, is detectable after double splanchnicotomy.\(^1\)

The hyperglycemia due to CO, remaining after double splanchnicotomy seems somewhat larger in rabbits than in dogs.\(^3\)

REFERENCES
1) Wada, Kitahara, Tano, Magoshi, Onodera and Saito, Will be published.
3) Mikami, Ibid., 1926, 9, 113.

POTASSIUM CYANIDE

Potassium cyanide, applied intravenously or subcutaneously, causes an oversecretion of adrenaline.

On i.v. injection of 2–2.5 mg. per kg., the secretion is augmented to the rate of 4 \( \gamma \) per kg.-min., and to the total amount of 3 \( \gamma \) per kg. The maximum rate is measured one minute after injection, and the whole period of oversecretion one and a half minutes.

The blood sugar increases; the arterial pressure elevates for a while on i.v. injection, is soon replaced by a large fall, while subcutaneous injection causes no definite, significant variations.
LOW ATMOSPHERIC PRESSURE

A low pressure, 198 mm. Hg., corresponding to 10 000 meters height, invariably results in an increase of the adrenaline secretion rate and the blood sugar concentration. The maximum was 0.9 γ per kg.-min. and 0.15% respectively. The O₂ and CO₂ content in the chamber was 22% and 0.4%.

A pressure of 267 mm. Hg., corresponding to 8 000 meters height, reached in 40 minutes, is not sufficiently low to bring on such changes.

HEMORRHAGIA

Hemorrhage of certain intensities invariably produces in the normal dog an oversecretion of adrenaline from the adrenals.¹,²

The blood was taken from a femoral or lumbar artery. Usually a few minutes to ten minutes or longer was needed for letting out one-third or a little more of the total blood quantity.

The minimum effective amount for effecting an oversecretion of adrenaline is one-fifteenth of the total blood quantity, and the greater the amount the greater and the longer the oversecretion, generally speaking. One-third or two-fifths might be the maximum effective amount, since too large an amount is detrimental to life.

On bleeding of one-third of the total quantity the dog responds with an adrenaline secretion rate of ten to thirty times as quick as the initial; numerically expressed, the maximum rate is mean 0.5 γ per kg.-min., the actually highest case being 0.8 γ. The oversecretion lasts for, schematically expressed, three hours, and the total amount of oversecretion is mean 60 γ per kg., with the biggest case of 100 γ.¹,²

Adrenaline oversecretion associated with hemorrhage is characterized commonly by the appearance of two peaks, as Fig. 11 indicates. The first peak appears half an hour after bleeding, and the second two hours or more after bleeding.

The blood sugar increases with the peak, detectable ten minutes or later, so that it precedes the first peak of adrenaline secretion. No second elevation occurs in the blood sugar curve.

Narcosis reduces the effects of hemorrhage upon the adrenaline secretion. In the cava pocket experiment on the dog under ether, hemorrhage of one-
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FIG. 11. One-third of the total blood shed in normal dogs; adrenaline secretion, blood sugar, heart rate & anal temperature are estimated. (Saito, Kamei & Tachi)

fifth of the total blood amount can cause a small but definite acceleration of adrenaline secretion. The lumbar route experiment, carried out under ether yields a similar outcome.¹

In the dog, the spinal cord of which was divided between the cervical and thoracic cord, hemorrhage causes an oversecretion of adrenaline of a somewhat smaller degree. About half the rate seen in the normal dog is observable there: the effect is somewhat more pronounced when another stimulant, sensory stimulation for example, has been applied some time before. If the behaviour of the animal after having the cord sectioned before the thoracic be taken into consideration, we see indications that the hemorrhage definitely acts on the central mechanism in the thoracic cord, whereby the adrenaline secretion, above numerically given, can be occasioned.³

Data on the blood sugar will be referred to here so far as they have some bearing upon the adrenaline oversecretion.⁴

One third hemorrhage induces a large hyperglycemia, such as on an average 0.2%, 3 hours duration and 8 mg. excess sugar in toto; the largest cases 0.3%, 3 hours and 20 mg., and the smallest 0.13%, 2 hours and 2 mg.
The glycemic impulse is for the most part sent through the splanchnic nerves. The cutting of nerves reduces the glycemia to 0.12% on an average.\textsuperscript{4}

On the other hand, the removal of the adrenal glands has little effect upon the hemorrhage hyperglycemia, but the clinical symptoms are more severe; the arterial pressure falls largely, and many of our animals died. As to the outcome in hyperglycemia in the adrenalectomized dog, one will remember that the same figure was commonly obtainable in the hands of Stewart and Rogoff in adrenalectomized rabbits; this will be fully discussed in the next chapter.

It is further noteworthy that adrenaline infusion done in imitating the adrenaline oversecretion due to hemorrhage acts, on the contrary, to reduce the increase of blood sugar which should be brought about by bleeding, when the two—the infusion and the bleeding—are conducted simultaneously.\textsuperscript{5} Introduction of saline solution serves as the control to the adrenaline infusion. The latter solution contains adrenaline hydrochloride of Sankyo Co., the saline solution as the vehicle. Adrenaline hydrochloride, intravenously given in the same manner, brings about a sufficient increase in the blood sugar, when applied to a doubly splanchnicotomized dog. (Fig. 13).\textsuperscript{6}

Adrenaline infusion acts to rescue the adrenalectomized dog suffering from bleeding, i.e. the animal survives a severe hemorrhage. This corresponds well with the statement re the effect of medulli-adrenalectomy upon the life and the blood pressure fall after hemorrhage. As to the view that in considering the question of functions of the medulla, it should be kept in mind that no important functions can in any case be assigned to an organ the loss of which causes no symptoms,\textsuperscript{7} we cannot concur.

In rabbits the double splanchnicotomity also considerably reduces the blood sugar increase due to hemorrhage, whereas double adrenectomy reduces it to a lesser degree.\textsuperscript{8,9} Splanchnicotomity can almost prevent a reduction of adrenaline content of rabbit adrenals by bleeding.\textsuperscript{10}
Fig. 13. Blood sugar fluctuation in doubly splanchnicotomized dogs, in imitating the oversecretion of adrenaline causable by bleeding one-third of the total blood volume. (Tachi & Saito)

REFERENCES

2) S. Saito, Kamei and Tachi, Ibid., 1928, 11, 205.
3) W. Takahashi, Ibid., 1932, 18, 339.
4) Tachi, Ibid., 1928, 11, 14.
5) H. Sato, Kaiwa and Wada, Ibid., 1935, 26, 310.
6) Tachi and Saito, Ibid., 1928, 11, 218.
9) Id., Ibid., 307.
10) Id., Ibid., 409.

PEPTONE

Peptone, in an intravenous dose of 0.1–0.3 g. per kg., is capable of accelerating the adrenaline secretion in the normal dog; Type B1. On an average, the maximum rate is 0.4 γ per kg.-min., which appears ten minutes after injection, the oversecretion lasts for thirty minutes, and the total amount
of oversecretion 12γ per kg., schematically stated.

If the spinal cord is cut before the thoracic cord, 0.05–0.1 g. per kg. peptone acts also to accelerate the adrenaline secretion, but this time it is small; three to ten times acceleration is commonly observable, but 0.1γ per kg.-min. was also observable. A greater dose of the drug can not be tried because of the weakness of dogs so operated on.2

What part is played in this oversecretion in peptone intoxication by the central mechanism located cranially is difficult to elucidate from the data given.

Ether narcosis depresses the action of peptone upon the adrenaline secretion, and finally it can nullify the action.1

It is noteworthy that the oversecretion of adrenaline, if any, takes place so long as the depressed state of the animal is perceivable.1

In a dog (No. 34) among 7, in which 0.3 g. per kg. was dosaged, a considerable oversecretion of adrenaline was estimated: the maximum rate 2.4γ per kg.-min. at 10 minutes after injection, the period of oversecretion over five hours, and the whole amount 200γ per kg.1 Adrenalinemia of a similar scale was also detectable in bleeding experiments, though infrequently.

The oversecretion of adrenaline by peptone results through the splanchnic nerves.3

Giving 0.2–0.3 g. peptone per kg. produces a hyperglycemia of such a scale: the maximum 0.15–0.2% in 20–30 minutes after injection, the hyperglycemic period 1.5 hours and the excess sugar 3 (1.5–4.5) g. Five minutes after injection the sugar content starts to increase. In dog 34 of Watanabe, given above, hyperglycemia was also large and of a long duration (0.2%, 10 g.).

Peptone hyperglycemia in dogs is reduced by splanchnicotomy as well as by medulli-adrenalectomy; schematically the reduction is 20% by the former, and 40% by the latter.5,4 The
Fig. 15. Blood sugar fluctuation on peptone in normal dogs (light circles) and in doubly splanchnicotomized. In the latter group of dogs, peptone alone (light triangles), peptone plus adrenaline (triangles with point) or adrenaline alone (solid triangles) was given i.v. Histograms show how adrenaline hydrochloride saline solution was i.v. infused. (Kaiwa)

upper sympathetic ganglia in the abdominal cavity was removed in addition to the medullar adrenalectomy, with about the same outcome.\textsuperscript{5}

Adrenaline-saline solution, intravenously introduced in the splanchnicotomized dog in imitating the secretion in the peptone poisoning in the normal dog is capable of causing hyperglycemia of a certain degree, but it is definitely inferior to one causable by peptone in the splanchnicotomized dogs. And if both the injections, peptone and adrenaline, be combined, the glycemic effect in the dog so operated on is almost similar to that of peptone alone.\textsuperscript{4}

Similar tendencies are also obtainable in rabbits re the glycemia due to peptone, i.e. influence of splanchnicotomy and adrenalectomy thereupon are almost identical with those in dogs. In dogs the adrenal medulla and in rabbits the adrenals were removed. Adrenaline-saline solution was infused intravenously here in a dose taken at random, because there is still no method to estimate the adrenaline secretion rate in rabbits. The outcome can be taken as not much different from that obtained in dogs.\textsuperscript{5,6}

Thus on the one hand ether anesthesia diminishes or abolishes the occurrence of peptone hyperadrenalinemia, while on the other hand the hyperadrenalinemia produced by peptone does not act, at least, to further the hyperglycemia which is produced in the peptone intoxication through the mechanism other than the adrenaline oversecretion. If the oversecretion of adrenaline were taking place in the peptone intoxication in the dog under ether, what figures would result in the matters under test, i.e. those commonly altered by the action of adrenaline? Experiments done with such thoughts in mind show that the adrenaline infusion produces only its usual effects on the arterial pressure and pulse rate, but no definite relationship was established re the blood sugar concentration and the body temperature.\textsuperscript{7}

Here it may be mentioned that in dogs the glycemic effect of histamine is not altered by adjusting the rapidity with which the drug is applied in-
travenously, contrary to the case with peptone and histamine on rabbits. Peptone, intravenously applied, slightly reduces the adrenaline content in rabbits, irrespective of whether the splanchnic nerves are cut or not. When death occurs there very rapidly, no reduction takes place.

**REFERENCES**

7) Makosi, Will be published.

**HISTAMINE**

Histamine produces an oversecretion of adrenaline in a form similar to peptone, namely of Type B, and its degree depends upon doses. The impulse is sent through the splanchnic nerves to the adrenal medulla.

It was found that 1 mg., 2 mg. and 4 mg. histamine per kg. causes an oversecretion with the maximum rate of 0.4, 0.6 & 1 γ per kg.-min. respectively. These appeared 5 minutes after injection; the rate decreased rapidly at first, and the oversecretion almost disappeared 40 minutes to 2 hours later. The total amount of oversecretion was 10, 30, & 45 γ, mean 30 γ per kg. of body weight.

Blood pressure fell rapidly, the maximum fall by 60–80 per cent reached 5 minutes after injection. The pressure fall and the adrenaline secretion increase go quite simultaneously. It is impossible to determine which precedes the other, so far as the methods adapted show. The blood pressure curve recovered somewhat slowly, but the time occupied for the complete recovery was 10, 30, & 45 minutes respectively.

**FIG. 16. Adrenaline secretion on i.v. histamine.** (Wada et al.) Upper curve—5 to 3 mg. histamine per kg.; middle—2 mg. & lower—1 mg.
recovery was almost identical for both events.

The blood sugar content reached the acme 20 minutes after injection, the highest being 0.15% (0.13–0.2%). The heart beats rapidly, the maximum increase being 50% on an average. Changes in blood pressure and pulse rate are not affected by double splanchnicotomy, while neurotomy nearly abolishes the glycemic action of histamine.

Removal of adrenals in rabbits has also no material effect upon the blood pressure fall causable by histamine. It acts to only slightly decrease the minimum effective dose and the lethal dose as well. The medulla is not responsible for the latter fact. Further it may be added: histamine, intravenously injected slowly to rabbits, always produces hypoglycemia. In dogs the drug produces only hyperglycemia, irrespective of whether it is injected rapidly or slowly. The adrenaline content of adrenals in rabbits is reduced by histamine, regardless of the speed of injection.

REFERENCES
1) Wada, K. Fuzii, Sibuta, Sakurai and Li, Tohoku J. Exp. Med., 1940, 37, 442.
2) Ohmi, Ibid., 1933, 21, 323.
3) Oikawa, Ibid., 1931, 18, 27.
4) Hirano, Ibid., 1939, 37, 322.
5) Satow, Ibid., 1938, 32, 239.
7) Tatuji Suzuki, Ibid., 1951, 54, 289.

ANAPHYLACTIC SHOCK

Anaphylactic shock induces in the dog, non-fastened, non-anesthetized, a rapid, large acceleration in the adrenaline secretion of Type B₂, as do peptone and histamine. (See Figs 14 & 16)

Adrenaline secretion reaches its peak, mean 1 γ per kg.-min., about 20–30 times to 100 times the initial rate, 5–10 minutes after the injection of antigen. The hypersecretion lasts for two hours or longer, and the total amount of extra secretion 45 γ per kg. on an average.

The arterial pressure falls almost simultaneously with the acceleration of adrenaline secretion; there was a case witnessed where the fall preceded the acceleration by one minute, among six cases. The lowest level in the blood pressure, say 30 mm. Hg., came simultaneously or some minutes before the peak of adrenaline secretion.

The blood sugar did not begin to elevate until a few minutes after the above two events, and its peak appeared commonly 10 to 30 minutes after injection. The hyperglycemic period is sometimes preceded by a transitory hypoglycemia of a very small scale; the hyperglycemic phase covers 100 minutes on an average.
Double splanchnicotomy as well as double medulli-adrenalectomy reduce the intensity of anaphylaxia hyperglycemia; the former acts weakly and the latter strongly. Roughly speaking, the former reduces it by twenty per cent, the latter by forty. Both operations have no material influence upon the severity of blood pressure fall, but the recovery course seems somewhat slow.

When the hyperglycemia starts, the dog is already in a depressant state, and the blood pressure begins to recover from the fall.

When the poisoning is too severe, profound depression develops accompanied by low pressure and low sugar, and eventually death takes place.

REFERENCES


CAROTID SINUS NERVE

Clamping of the common carotid arteries does not effect in the normal dog any increase in the adrenaline secretion rate or of the blood sugar concentration.

In the cava pocket experiment in the dog under ether, stimulation of the H.E. Hering nerve causes a reduction in the adrenaline secretion. Forty seconds after the start of the stimulation a reduction becomes manifest, and 10–30 minutes are required after stopping stimulation for the complete recovery of the rate. On a 2 minute stimulation the rate is reduced to 1/4-1/3 of the initial, or from 0.5 \( \gamma \) per kg.-min. to 0.15 \( \gamma \) per kg.-min.

REFERENCES

Insulin brings about an oversecretion of adrenaline of B₁ Type. If the blood sugar content goes under 0.06%, the oversecretion of adrenaline sets in, but at first rather slowly, so that 20 minutes after the i.v. injection of insulin in doses of 3–10 units per kg. an oversecretion is now unmistakably observable in almost all cases. The oversecretion reaches its peak one and one hour and a half after injection, and then diminishes slowly to the initial value. The peak is mean 0.5 γ per kg.-min. (0.2–1.5 γ), the duration of oversecretion 3 hours or longer, and the total amount 65 γ per kg., with the greatest case of 80 γ.¹

That the secretion curve presented here has a plateau should not be
taken as a characteristic of insulin, because each curve has a sharp peak commonly.

This action of insulin is also producible in the depancreatomized dog. It should be remembered that the oversecretion is also produced before the blood sugar concentration reaches the limit above noted, if the decrease is taking place very rapidly.2

By way of precaution it may be here added that insulin acts in the pancreatomized animal to cause the blood sugar fall more readily and more rapidly in comparison with the control.

Insulin loses almost or entirely its hyperadrenalinemic action on the dog, after the spinal cord is cut before the thoracic, contrary to bleeding, peptone or sensory stimulation.3

Splanchnicotomy wholly annuls the hyperadrenalinemic ability of insulin. Neurotomy increases the susceptibility of animals to insulin and its hypoglycemic power.4

Hypnotics, such as avertin,5 evipan,6 do not materially interfere with the occurrence and magnitude of insulin hyperadrenalinemia. The blood sugar decreases there considerably, the general blood pressure too, but clinical symptoms such as tremors and convulsions seldom occur, as is to be expected.

The data in rabbits,7 that the hypoglycemic action of insulin is retarded distinctly by a large dose of barbital apparently disharmonize with the above mentioned. Is it to be explained by the different kinds of animals experimented on, of the drugs, or of the amount of drugs applied? A smaller dose of barbital does not cause any retardation.

Insulin reduces the adrenaline content of adrenals in rabbits. Splanchnicotomy annuls this effect. Intravenous introduction of glucose also acts likewise.8 A repeated insulin application to rabbits for a long period, i.e. five weeks, causes an increase of the adrenaline load. It depends upon the intact innervation. If insulin is given i.v., the adrenaline load in adrenals increases slightly and quite transitorily.9

The abolition of adrenalin secretion, i.e. by demedullation of the adrenals, exaggerates in dogs the intensity of insulin hyperglycemia. And the intravenous infusion of adrenaline-saline solution, conducted in a similar manner and magnitude as normally occurring in the insulin poisoning, acts to compensate the medulli-adrenalectomy in respect to the blood sugar fluctuation, if done in addition to the injection into the dog deprived of the adrenal medulla.10

There are some divergent reports re the relation between the adrenalectomy11 or splanchnicotomy and the glycemic action of insulin in rabbits. Either no alteration,12 an earlier appearance of hypoglycemia13 or a largeness of the latter.11

Insulin acts to decrease the body temperature definitely though slightly when applied to the medulli-adrenalectomized dog; and it is well compensated
by the introduction of adrenaline solution in amounts and course corresponding to the adrenaline secretion caused by insulin in the normal animal.10

Contrary to the results given above, the infusion of adrenaline solution carried out in similar experimental conditions has little or no effect on the
arterial pressure or the pulse rate; the reverse action was never discovered on the other hand.¹⁰

REFERENCES

GUANIDINE

Guanidine is a potent drug in accelerating the adrenaline secretion, like insulin.¹ Its course is of B₂. However there are some different figures; first, the guanidine hyperadrenalinemia develops in the normal dog soon after the injection, and more rapidly than in the case with insulin. Twenty minutes after the injection of guanidine the hyperadrenalinemia reaches the peak 0.6 r per kg. per minute, 10 times acceleration on an average on intravenous injection of 0.15 to 0.3 g. per kg. guanidine hydrochloride. Secondly, guanidine causes first a small but long hyperglycemic period, which is replaced by the development of hypoglycemia, arrived at 0.04% 100 minutes further later, while the adrenaline acceleration is of quite the same scale in both sets of experiments.

The oversecretion period covers three hours or longer, and the total amount secreted is computed as 50 r per kg. (in 160 minutes), figures similar to the insulin experiments, given in doses of 3 to 10 units.

When excessive dyspnoea develops a copious oversecretion breaks out. The thick lines in Fig. 20 indicates the two cases with dyspnoea or opisthotonos, whereas the other two cases without dyspnoea are indicated by the thin lines.

Splanchnicotomy deprives the hyperglycemic ability from guanidine. Hypoglycemia of a similar depth as in the normal individual takes place there however.²

The time relation of the adrenalinemia and the glycemia is thus different depending upon the insulin and the guanidine. In the case of insulin the oversecretion of adrenaline can be accounted for the rapid and large development of hypoglycemia, but in guanidine poisoning the adrenaline over-
secretion is already undergoing some reduction at the time when hypoglycemia first makes its appearance. The hyperadrenalinemic action of guanidine must be due to a mechanism other than that for insulin.

In the doubly splanchnicotomized dog, guanidine was injected i.v. and adrenaline hydrochloride-saline solution was also injected i.v. at the rate of secretion, usually presents after guanidine. This procedure produces a hyperglycemia on a scale, standing just between those brought about by each injection when given singly. The hyperglycemia obtainable in the normal dog takes a mediate course between that causable in the splanchnicotomized dog by guanidine alone and that by guanidine and adrenaline. The pattern which was applied here was just that with the greatest acceleration.

In rabbits guanidine (0.24–4 g. per kg. subcutaneously applied) produces a hyperglycemia lasting for some hours in about two thirds of the cases, while a hypoglycemia takes place in all cases, with or without a foregoing hyperglycemia. Splanchnicotomy reduces the hyperglycemia, while adrenalectomy can nullify it entirely. The latter operation reduces the hyperglycemic ability of synthaline there.

REFERENCES

SENSORY STIMULATION & HYPERADRENALINEMIA

SENSORY STIMULATION

(FASTENING, EMOTION AND SLEEP)

Sensory stimulation evokes generally an oversecretion of adrenaline. Usually the acceleration observable in unanesthetized dogs is definitely small compared with other known agencies. In our experiments the strength of faradic stimulation was taken usually as to cause violent aggressive reaction in the animals.

The height of oversecretion due to the stimulation depends upon the preliminary pre-existing rate. Generally speaking, the reflex stimulation increases the secretion by two and a half to three times commonly, irrespective of varied pre-existing rates. The following table illustrates this:

| TABLE XI |
| Influence of Sensory Stimulation upon Adrenaline Secretion Rate in Dogs |
| (per kg. of body weight and per minute) |

| No-narcosis, lumbar route method | 0.07 γ | 0.1 γ | 1:2.5 |
| No-narcosis, cava pocket method | 0.65 γ | 1 γ | 1:2.5 |
| Ether narcosis, cava pocket method |
| Kodama | 0.8 γ | 1 γ | 1:2.3 |
| Sugawara et al. | 0.5 γ | 0.4 γ | 1:1.8 |
| Stewart & Rogoff | 0.2 γ | 0 γ | 1:1 |

Narcosis masks the augmenting effect of sensory stimulation on adrenaline secretion; the fact that accomplished physiologists such as Drs Stewart and Rogoff failed to find any effect at all is due to a too deep anesthesia indeed.

The smallness of the pre-existing rate in the absolute quantity as well as in the limits of fluctuations in the reports from the Cushing Laboratory in Cleveland indicate the deepness of anesthesia. They regard the former as the condition favourable for an increase of secretion and the latter as a proof of the correctness of their cava pocket method. Just the reverse is true, however. They used, it may be added, at that time ether, urethane, etc.

Stimulation was conducted in our cases for 20 or 30 seconds, and we found that the acceleration took place not only during the excitation, but after the cessation in certain instances, as was proved by some samples collected from 5 seconds after the cessation of stimulation—so long the after-action of sensory stimulation.

The greatest acceleration of adrenalin secretion in normal dogs (eight in number), caused by artificial electrical stimulation of a nerve branch was 2 to 5 times, seldom 8 times the pre-existing value, or 0.02 γ–0.2 γ from one
gland, i.e. 0.2 γ per kg.-min. from both glands as the mean. We had the following remarkable experiment: on fastening, the dog (No. 7) cried and struggled very furiously and uninterruptedly throughout fastening. The left lumbar route operation was carried out meanwhile with great difficulty; the adrenal vein blood samples collected twenty minutes later revealed an enormous rate of secretion, such as 6 γ per kg.-min., i.e. 100 times the basal rate. Such a great acceleration has been obtained in dogs only with nicotine (200 times), CO and KCl.

We are still not in a position to elucidate, how the emotional factor is involved in this kind of experiment, like fastening, sensory stimulation, etc. We were at that time very strongly inclined to believe an exceedingly great role is played by the emotional factor in the extraordinary oversecretion of adrenaline just illustrated.

Fastening a normal dog on an operation table, for example, induces a hyperadrenalinemia, though slight and not constantly. About two times acceleration occurs in half of the cases.1

Fastening glyceinia is a classical fact. While it always occurs in cats and rabbits, it is not constantly producible in dogs. The latter fact is in harmony with the adrenaline matter in that kind of animal. How the emotional element intervenes in producing the fastening diabetes has been a much discussed subject for a long time.*

Sensory hyperadrenalinemia occurs also in the dog, the spinal cord of which is sectioned between the cervical region and the thoracic. But the effect is definitely weak, and only seldom does the acceleration take place, then rather small, i.e. at most three times the initial rate. A great contrast to bleeding or peptone.6

Tests show that sensory stimulation, which always produces a paradoxical pupil reaction in normal cats (0.5–2 mm. dilatation), has a weak effect after double splanchnicotomy (in 8 out of ten; 1 mm. in three), and weaker in doubly medulli-adrenalectomized (in 6 out of 10; 0.5 mm. in six). The barking dog is very weak in producing a similar effect; after each operation the dilatation occurs no more.7

Hyperglycemic effect in rabbits subjected to sensory stimulation is largely reduced by double splanchnicotomy, while double adrenalectomy is incapable of doing this.8 The latter fact almost harmonizes with the fact that sensory stimulation contracts in an anesthetized cat a limb or spleen denervated, regardless of whether the adrenals are removed or not.9

During sleep the adrenaline secretion diminishes from the basal rest rate, for example, from 0.02 γ per kg.-min. from one adrenal to 0.01 γ.1

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* Cf. I. Fujii, Tohoku J. Exp. Med., 1920, 2, 9. When Fujii’s paper was published, Dr. W. B. Cannon wrote to me personally saying that the data that the intensity of fastening hyperglycemia varies daily, and in fact does so a form of wave, indicates its emotional origin.
On puncturing the floor of the fourth ventricle, according to Bernard, the adrenaline secretion increase rapidly; in five minutes the rate reaches commonly a high value such as 0.5 r per kg.-min., and further increases though slowly from then on. The peak, such as 0.2 r to 1 r is noted thirty minutes after puncturing, then the rate diminishes slowly; B1-type. The total over-secretion is mean 50 r per kg., and the greatest 90 r; 13 r in the first half hour, 12 r in the second half hour, 15 r in the second hour, and 12 r in the third. Roughly stated, the piqûre increases the adrenaline secretion fifteen times in the rate and five times in the total amount, the whole period of augmentation being over three hours.

The blood flow through the adrenals increases here moderately or slightly; it never decreases. The increase of secretion depends, however, chiefly upon that of the concentration of hormone.

On a closer examination, the blood sugar increase precedes the adrenaline secretion acceleration in some cases, sometimes occurs simultaneously, and in still other cases it follows the acceleration. Usually the peak appears earlier by some minutes in the glycemic curve. Hyperglycemia is noted as 0.15 to 0.2%, mean 0.16%.

Ether anesthesia depresses the increase in both events, but the blood sugar content suffers largely therefrom, so that the hyperglycemia is missed frequently. On the contrary, the adrenaline secretion commonly increases, though on a smaller scale than in non-anesthetized dogs. From 1.5 to 3 times acceleration is common. The pre-existing rate of secretion is 0.1 r per kg.-min. for one gland in a dog under ether, equipped with the lumbar route preparation. Blood pressure fluctuation, observable after the piqûre, also, suffers from narcosis, as explained below.

Piqûre produces hyperglycemia in the dog, deprived of either adrenals or medulli-adrenals, but on a somewhat smaller scale than in the normal individuals. The former operation was carried out acutely in the de-afferented dog; accordingly, neither fastening nor narcosis was needed. The
excess is of one-half of the normal cases; 0.12% against 0.15%. And this inferiority is nearly compensated by infusing adrenaline-saline solution intravenously in the scale similar to the natural secretion of adrenaline in the
normal dog, punctured according to Bernard. Fig. 22 illustrates this.

In these respects the rabbit affords some different figures from those above. Double splanchnicotomy, double adrenalectomy or double medulli-adrenalectomy reduces the magnitude of piqûre hyperglycemia largely. While the piqûre hyperglycemia is of such a scale as 0.25% in normal individuals, three kinds of operation reduce it to 0.12%. The figures of the Cleveland physiologists differ widely from those above referred to; the glycemic height before and after adrenalectomy is almost equal, as 0.41% against 0.45%.

It will be in order to mention here the piqûre experiments with the devervated heart in cats as well as with the denervated pupil in rabbits, in which double adrenalectomy abolishes the paradoxical reaction.

The arterial pressure either ascends or descends abruptly on a large scale on puncturing the fourth ventricle in the normal dog, but soon starts to descend or ascend as the case may be, reaching the initial level about ten minutes after puncture, roughly speaking. Afterwards the pressure fluctuates commonly under the initial level on a small scale. Double medulli-adrenalectomy, with or without accompanying double vagotomy, has some tendency to exaggerate the fall in the later period, and the adrenaline infusion acts to compensate it, though never significantly. Blood pressure fluctuations on the piqûre suffer from narcosis in a similar manner to the adrenaline secretion.

The pulse rate diminishes on puncturing suddenly and largely, approximately 50%, and then at first rapidly and later slowly it tends to recover. In the piqûre experiments it is difficult to elucidate the role of adrenaline oversecretion in the pulse frequency variations. In a few cases the pulse rate increases rapidly, but soon diminishes. No peculiar characteristics show themselves in the further course.

REFERENCES


CEREBELLAR PUNCTURE

An injury of the cerebellum such as destroy the whole lobulus posterior medianus, particularly the vermis, results in an oversecretion of adrenaline and an increase of blood sugar content. The former is similar in form to
SECRETION OF ADRENALINE, PARTICULAR

that due to pique diabétique, but on a decidedly small scale, say one-third in the maximum rate as well as in the total amount; they are 0.15 to 0.35 γ per kg.-min. and 12 γ per kg. respectively.

The blood sugar increase is of much small scale; the greatest excess 0.02%. Blood pressure soon ascends largely on puncturing, but soon to descend and in 10 to 20 minutes completely recovers the initial level.

REFERENCE


MUSCULAR EXERCISE (Exhaustion)

Muscular exercise, as running, for example, on a paved road or in a revolving wheel, does not augment the adrenaline secretion at all in the case of the dog not yet exhausted. When much tired or exhausted, an increase sets in, but only on a small scale, the peak being noted a few minutes to a half-hour after ceasing to work. The maximum rate is mean 0.08 γ per kg.-min., the greatest case being 0.2 γ. The oversecretion lasts for about one hour. The blood sugar content fluctuates only insignificantly; it is apt afterwards to decrease though slightly. Extirpation of the adrenal medullae, cutting of the splanchnic nerves and their combination do not interfere with the scale of decrease.

Muscular exhaustion does not effect to reduce the adrenaline content of adrenals in rabbits, irrespective of whether the innervation be impaired or not.

Normal and doubly medulli-adrenalectomized rabbits behave quite the same re the fatigability of the nerve-muscular preparation in situ, whereas double adrenalectomy shortens it to one-third, 10 hours against 30 hours.

While these three kinds of experiments well harmonize with the above given data re the adrenaline secretion on muscular exercise in the normal dog, there are however other sets of researches which completely disharmonize with them. They are those of Hartman and