Effect of Histamine upon the Blood Pressure in Suprarenal- ectomized Rabbits.

By

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Working with rabbits, Fujii¹ came to see invariably an elevation in the blood pressure on an intravenous injection of histamine in doses varying from 0.002 to 0.005 mgrm. per kilo of body weight after the suprarenals had been excluded from the blood circulation. No transitory fall occurred before the onset of elevation, judging from the curves theregiven. Ligating the suprarenal vessels was performed under light anaesthesia with ether, no other narcosis was resorted to throughout the entire course of experiment. In a rabbit, blank operated and normal rabbits, not or only slightly anaesthetized, histamine was always proved to decrease the pressure. And further when a steady perfusion of a diluted adrenaline solution into the circulation was combined with it, histamine elicited only a decrease of the blood pressure. Whether histamine induces an elevation or a decrease in the blood pressure in rabbits, not or only slightly anaesthetized, depends thus upon the condition whether or not there exists epinephrine in the circulation. The blood pressure in his rabbits after ligating the suprarenal vessels was very low as 10 to 70 mms. Hg; and when combined with the adrenaline infusion it was high in one example, but in another 60-70 mms. Hg were given, even in the latter case histamine acted depressoric.

A few years later a similar kind of experiment, but with another kind of animal, in fast with cats, was reported by Burn and Dale.² Cats were decapitated under preliminary anaesthesia, and when the arterial pressure thus fell to a low level, a small dose of histamine still caused a definite, though often relatively trivial, further fall of the

¹) Michio Fujii, Namman Igakukai Zasshi, 19(23-24), 12, 487 (Presented before the Japanese Physiological Meeting at Fukuoka, 1923, April.).
²) Burn and Dale, Jour. of Physiol., 1926, 61, 185.
pressure, and then a secondary extensive rise of the pressure. The secondary rise was accompanied by pronounced acceleration of the heart and pronounced shrinkage of the limb volume. Extirpation of the suprarenals practically nullified this secondary rise of the pressure or application of ergotamine prior to histamine produced a secondary depressor action in place of the pressor phase. These experimenters thus brought about evidence that this secondary pressure elevation is due to the sudden accelerated output of epinephrine. Similar results were given later by MacKay. The usual effect of histamine, in both dogs and cats, was a fall in the blood pressure, but when the drug failed to cause salivary secretion in cats, the secondary rise occurred in the blood pressure and removal of the suprarenals abolished this rise.

Similar experiments were also performed subsequently by Feldberg with the same species of animal as Dale, viz. cats, the medulla oblongata and the spinal cord of which were destroyed. On injecting histamine before and after closing the suprarenal veins he came to see the secondary rise in the blood pressure, only it was of much smaller degree when the veins were closed. (Curves 5 & 6 of Feldberg show that the magnitude of the secondary elevation after closing the veins was in that case much more than the half of that before it.) In reading the paper of Feldberg we have understood the data presented there as such as quoted above, but we are not certain whether he came to see some outcome similar in nature with that of Burn and Dale, who were able practically to abolish the secondary rise of the arterial pressure by removing the suprarenal glands, in spite of his description: „Zunächst konnte ich öfters nach Histamininjektion dieselbe Blutdruckänderung beobachten, wie sie Burn und Dale vor und nach Nebennierenexstirpation erhalten haben.“

In the same laboratory with Feldberg, Alexiú observed in cats, narcotized with ether-chloroform-chloralose and with a low arterial pressure as 60–40 mms. Hg., a rise of the pressure by giving a large doses of histamine as 10–20 mgrms., which occurred also even after the double suprarenalectomy.

Quite recently Wyman and Suden measured the arterial pressure in rats, normal, bilaterally suprarenalectomized with or without autoplastic transplants of cortical tissue, etc. under urethane anaesthesia. Only a depressor action was seen. While as to small doses capable of depressing the pressure there was little difference in the control and suprarenalectomized ones, the minimal dose of histamine

3) MacKay, Jour. of Pharm. & Exp. Ther., 1929, 37, 349.
4) Feldberg, Arch. f. exp. Path. u. Pharm., 1929, 140, 156.
necessary to produce a permanent fall of blood pressure was proved distinctly different for both kinds of animals, decapsulated or not, 0.05 to 0.1 mgm. per 100 grms. body weight for the former and 0.3 to 0.5 mgm. being determined for the latter.

In reviewing the previous reference in respect to the relation between vascular action of histamine and removal of the suprarenals, we find thus several controversies there, it is rather puzzling. Fox example, Fujii and Dale agree in pointing out the rôle of the suprarenal glands in vascular response to histamine, but the pressure elevated on histamine when Fujii excluded the glands from the circulation, while the secondary rise disappeared when Dale did so. When they did so narcosis was no longer used and the blood pressure was low. Is such a difference to be accounted by the difference in kinds of animal? Some writers would refuse to explain the differences in the vascular action of the drug by different kinds of animal species. Since the vascular action of histamine, might vary, generally speaking according to species of animal, depth of narcosis, vascular tone preliminarily existing, etc., etc., the results above referred to can only with difficulty be compared with each other in criticizing. Only those of Burn and Dale on one side and those of Feldberg and probably of Alexiò were obtained with the same species of animal and under more or less similar conditions, and the results apparently do not harmonize with each other.

In utilizing rabbits, long surviving double suprarenalectomy the present writer has attacked the same problem with the above references. No narcosis was used, that is the following data have been originated from non-anaesthetized rabbits only.

Experimental Data: The arterial blood pressure was recorded from the carotid artery by means of a mercury manometer and 0.2 per cent histamine base (Grübler) solutions were injected into the marginal vein of ear, previously denervated, with a uniform speed. Histamine was given to the normal rabbits in doses varying from about 0.1 mgm. to about 0.5 mgm. per kilo, and to the decasulated in those from 0.04 to 0.3 mgm. per kilo. No narcosis was resorted to but the animal was fastened on the table during the whole experimental course. The following results were obtained from a number of normal rabbits and long surviving double suprarenalectomized.

Normal rabbits:

Experiment 1. 24. II. 1932. Female rabbit, 2.74 kilos. 0.85 c.c. of 0.2% histamine solution (0.6 mgm. histamine per kilo) occasioned a fall from

102 mms. Hg to 44 mms. Hg with a slow recovery, so that 15 minutes later the recovery was still incomplete. Convulsive seizures were seen about two minutes after the injection. 30 minutes later 0.5 c.c. (0.35 mgrm. per kilo) caused a fall from 100 mms. Hg. to 52 mms. Hg. ad maximum; this time a complete recovery was seen 8 minutes later. 20 minutes later 0.1 c.c. i.e. 0.07 mgrm. histamine per kilo was injected with no effect; 0.3 c.c. (0.21 mgrm. per kilo) produced a fall from 92 mms. Hg. to 54 mms. Hg. and convulsive attacks. For recovery 8 minutes were needed; some minutes later 0.2 c.c. i.e. 0.15 mgrm. per kilo was capable of producing a small and transitory decrease in the blood pressure.

**EXPERIMENT 2.** 25. II. '32. Male rabbits weighing 2.29 kilos. Initial arterial pressure 118 mms. Hg. 0.1 c.c. 0.2 percent histamine solution, i.e. 0.087 mgrm. per kilo had no effect upon the pressure. 0.2 c.c. (0.17 mgrm. per kilo) and 0.15 c.c. (0.13 mgrm. per kilo) caused a small fall, that is from 114 mms. to 102 and from 116 mms. to 102 mms. respectively, and the recovery quickly set in, as in three minutes. 0.3 c.c. (0.26 mgrm. per kilo) was capable of producing a somewhat large fall and convulsions. Before injection 120 mms. and after 100 mms. Hg. and 10 minutes later the recovery still incomplete.

**EXPERIMENT 3.** 26. II. '32. Female rabbit, with body weight of 2.15 kilos. 0.1 c.c. 0.2% histamine solution (0.093 mgrm. per kilo) no effect. 0.2 c.c. (0.18 mgrm. per kilo) were injected three times, always a fall (from 100 mms. to 72 mms. from 90 mms. to 76 mms. and from 70 mms. to 40 mms.) was preceded by a transitory rise as from 30 to 40 mms. Hg. 0.3 c.c. (0.28 mgrms. per kilo) were given twice; once only a pure fall occurred (from 80 mms to 60 mms.), and on the later occasion a preliminary rise and a long lasting fall (50 mms. rise and 40 mms. fall), and in the latter case the recovery still incomplete 3 minutes later. About 3 minutes were sufficient to see a nearly complete recovery when the small dose was given. With 0.3 c.c. convulsions occurred.

**EXPERIMENT 4.** 8. III. '32. Male rabbit weighing 1.83 kilos. 0.1 c.c. 0.2 per cent histamine solution (0.11 mgrm. per kilo) no visible action, and 0.2 c.c. (0.22 mgrm. per kilo) had a quite transitory and small depressant effect; but when 0.25 c.c. (0.27 mgrm. per kilo) were intravenously administered, severe convulsions occurred, the arterial pressure descended largely, 1.5 minutes later the pressure elevated a little, but was soon replaced by a conspicuous fall and eventually the animal died.

**EXPERIMENT 5.** Female rabbit, 2.15 kilo, 27. II. '32. This rabbit proved highly refractory to histamine. 0.1, 0.2 and 0.35 c.c. (0.32 mgrm. per kilo) 0.2% histamine solution had no effect at all. 0.75 c.c. was responded to by a transitory rise only, and first 0.85 c.c. i.e. 0.78 mgrm. per kilo occasioned a transitory rise and a decrease in the blood pressure lasting eight minutes.

**EXPERIMENT 6.** 29. II. Male rabbit with 2.04 kilos body weight. 0.1 c.c. (0.098 mgrm. per kilo) no effect; 0.2 c.c. first no effect, but about 10 minutes later convolution-attacks occurred with a sudden rise in the blood pressure. The elevation continued about five minutes then was replaced by a decrease. On a later occasion 0.3 c.c. (0.29 mgrm. per kilo) produced only a small and quite brief depression in the blood pressure, and further 0.5 c.c. (0.49 mgrm. per kilo) a fall from 90 mms. to 62 mms. About 3 minutes later the pressure regained the level before the injection.
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**Experiment 7.** 29. II. Male rabbit, 2.63 kilos. 0.1 c.c., 0.2 c.c., 0.3 c.c., 0.4 c.c. and 0.5 c.c. were injected; when 0.3 c.c. and 0.5 c.c. were applied a small decrease was recorded in the blood pressure curve.

**Experiment 8.** 10. III. Male rabbit, 1.95 kilos. 0.1 c.c. 0.2 per cent solution wholly ineffective, 0.2 c.c. (0.21 mgrm. per kilo) scarcely effective, to cause a blood pressure fall. When 0.3 c.c. (0.31 mgrm. per kilo) intravenously applied, the pressure decreased from 120 mms. Hg. to 76 mms. Hg. and about eight minutes were needed in order to see the initial height again.

**Doubly suprarenalectomized rabbits:**

**Experiment 9.** Male rabbit, 8. XII. '31 r. gland removed, 15. I. '32 l. gland. 3. III. 2.08 kilos. The initial blood pressure 129 mms. Hg. 0.05 c.c. and 0.1 c.c. 0.2% solution no effect, 0.2 c.c. (0.19 mgrm. per kilo) 0.3 c.c. (0.28 mgrm. per kilo) also almost no alteration in the blood pressure level or only a quite small depression. 30 minutes usually were allowed to pass before the next injection.

**Experiment 10.** Female rabbit, 8. XII. '31 r. gland removed, 8. I. '32 l. gland. 4. II. 1.98 kilos. Initial pressure 126 mms. Hg. 0.2 c.c. (0.2 mgrm. per kilo) 0.2 per cent histamine solution caused a fall of the arterial pressure from 126 mms. Hg. to 98 mms. About 30 minutes 0.1 c.c. (0.1 mgrm. per kilo) no effect; 0.2 c.c. were again given after a lapse of 20 minutes with a rather gradual, small decrease.

**Experiment 11.** Male rabbits; 26. IX. '31 r. gland, 7. XI. 1. gland extirpated. 7. III. 2.17 kilos. Initial blood pressure 147 mms. Hg. 0.1 c.c. 0.2% histamine (0.1 mgrm. per kilo) occasioned a temporary rise and a rather slow and somewhat long lasting descent in the blood pressure as from 146 mms. Hg. to 114 mms.

**Experiment 12.** Female rabbit, 26. IX. '31 r. gland, 5. XII. 1. one removed. 8. III. 32 1.70 kilos. Initial level 124 mms. Hg. 0.1 c.c. (0.12 mgrm. per kilo) and 0.2 c.c. (0.24 mgrm. per kilo) no visible effect, 0.3 c.c. which were injected about thirty minutes later, caused a fall from 152 mms. Hg. to 96 mms. Hg. with a preceding transitory elevation to 172 mms. Hg., five minutes later the recovery was almost complete.

**Experiment 13.** Male rabbit, 10. XII. '31 r. gland removed, 23. I. '32 l. gland. 8. III. 2.5 kilos. Initial arterial pressure 86 mms. Hg. 0.1 c.c. (0.08 mgrm. per kilo) occasioned a fall from 86 mms. Hg. to 66 mms., 0.05 c.c. had no effect at all. 0.2 c.c. injected thirty minutes later, caused a conspicuous fall from 78 mms. to 18 mms., which was reached about 60 seconds after ending the injection. 0.1 c.c. was tried with a decrease occurring slowly.

The outcome was thus rather inconsistent, but some definiteness can be drawn from the data above quoted: Firstly it is beyond doubt that the suprarenalectomy did not qualitatively alter the vascular reaction against histamine. In the normal rabbits histamine, given in doses varying from less than 0.1 mgrm. per kilo of body weight to 0.5 mgrm. or more, caused as a rule a fall in the blood pressure, seldom
preceded by a transitory elevation. The drug was dosaged to the rabbits long surviving double suprarenalectomy as from 0.04 to 0.3 mgrm. per kilo, and produced only a similar alteration in the blood pressure. Alteration of sign, as decrease before the removal and elevation after removal,\(^1\) or decrease and secondary elevation before and decrease only after removal,\(^2\) was never met with in the present experiments, rather in accordance with the outcome in cats of Feldberg and of Alexiú and in rats of Wyman and Suden.

Secondly, the minimal effective dose to cause the vascular response was apparently small in the doubly suprarenalectomized rabbits. 0.1 mgrm. histamine per kilo of body weight never effected any fluctuation in the blood pressure in the normal rabbits, and the doses between 0.13 to 0.2 mgrm. were sometimes non-effective, sometimes powerful in causing the fall. Doses above 0.2 mgrm. per kilo were capable of decreasing the pressure on a large scale. Cases Nos. 5, 6 & 7 were more insensitive against histamine. Two decapsulated rabbits showed rather a small vascular reaction when 0.2 mgrm. or 0.3 mgrm. was dosaged, but the rest a distinctly great sensibility; 0.1 mgrm. per kilo caused a conspicuous decrease in Nos. 11 & 13, and 0.3 mgrm. in No. 12. An increased sensibility of the doubly suprarenalprived rabbits against histamine in respect to the vascular response agrees well with the findings of Oikawa\(^8\) about the maximum non-lethal dose and minimum lethal dose.

It is rather superfluous to say that the initial blood pressure of the doubly decapsulated animals is of the same degree with the normal, in accordance with the previous reference.\(^9\)

**Summary.**

Effect of histamine upon the blood pressure in the rabbits long surviving double suprarenalectomy was compared with that in the normal. No narcosis was resorted to at all. The usual response was the decrease in both sets of animals, normal and decapsulated; seldom a transitory elevation occurred before the onest of the decrease, but in both the sets. No alteration was thus noted in the vascular response by removal of the suprarenals, as decrease before removal and rise after. Only the minimum effective dose appeared a little small in the decapsulated.

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8) Oikawa, Tohoku Jour. of Exp. Med., 1931, 18, 27 (At this opportunity a mistake in the legend to Table XIII on p. 52 may be corrected: it should be "*indicates the doses for suprarenalectomized rabbits" instead of "normal.")