BLOOD PRESSURE RESPONSE TO HISTAMINE IN CATS, BEFORE AND AFTER PRE-TREATMENT WITH HISTAMINE.

By: Tihamér Z. Csáky and Arisztíd Gy. B. Kovách.

From the Physiological Institute of the Péter Pázmány University in Budapest and the Hungarian Biological Research Institute, Tihany, Lake Balaton.

With 2 Figures and 1 Table in the Text.
(Received for publication 1st July 1946.)

Tachyphylaxia (Führer, 1912) and histamine desensibilization (H. D.) (Karády, 1936, Rusznyák, Karády, Szabó 1934, 1935) diminish the observed concentration effect curve of histamine on arterial blood pressure. Between the 2 diminishing effects the essentially significant difference is that in histamine tachyphylaxia constantly increasing doses must be given, in intervals of seconds, to cause a smaller blood pressure diminution; H. D. consists of injecting small preliminary doses of histamine once or more per day, over a period of 8—10 days. Control experiments could not confirm that such pre-treatment brought about a lessening in blood pressure diminution. (Kokas, Sarkady, Went, 1938).

The contradiction probably arises from the fact that the response of blood pressure after the same doses shows not only individual variation but, in the same animal, in the same experiment, gives visibly different results. It would therefore only be possible to resolve the problem if there were large groups both of desensibilized and control animals. As the contradiction exists in both schools of thought, both of which worked with small numbers of animals, of those experiments it can only be said that the H. D. does not cause a greatly significant difference in the blood pressure response following on single doses, beyond a large variation.

It would be easier to decide the question if we compared, not groups of animals, but the reactions of the same animal normally and after H. D. The equality of the response is further raised if in place of the response following single H doses we compare concentration

effect curves in which the doses of histamine given were proportioned to each other as 1:10:100.

In this work, with this procedure, we proved that in cats the H. D. does not influence the arterial blood pressure histamine concentration curve. We did not investigate the tachyphylaxic question in this experiment. FÜHNER, in experiments mentioned, seems to have solved the question.

THE EXPERIMENTS.

For the experiments we used 9 cats, of both sexes, weighing 1.5—2.5 kg. The measuring of the blood pressure took place under ether-chloralose narcosis, in such a way that 0.05 g. chloralose per kg. body weight was injected in the veins, and the superficial narcosis deepened

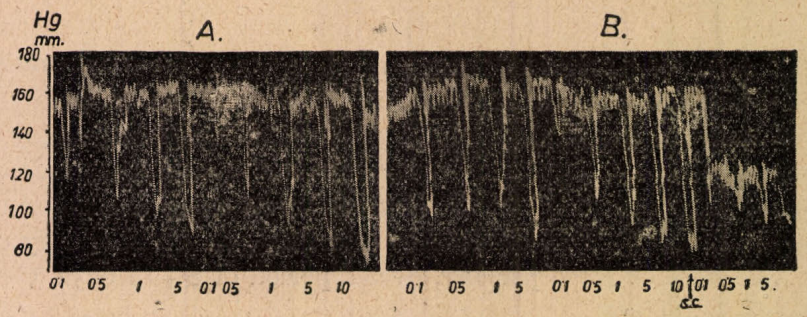

Figure 1. The blood-pressure-diminishing effect of histamine-doses (0.1—10.0 μg) in the same cat before (A) and after (B) 14 days pre-treatment with histamine. At sc. 1 mg histamine was given subcutaneously.

through the constant inhalation of a little ether. In the first experiment, under sterile conditions, we prepared one of the femoral arteries, introduced a canule into it, and registered the blood pressure with the aid of a mercury manometer on a slowly turning kymograph. We injected the histamine in dichlorhydrate form dissolved in a 0.2 ml. physiological salt solution in the femoral vein. We gave the injections at exact 3 minute intervals (BURN 1928). 0.1, 0.5, 1.0, 5.0 and 10 μg. histamine bases were injected one after the other. We got the concentration effect curve through the consequent registration of the blood pressure. After the experiment we removed the canule from the artery, bound up the artery, treated the wound with ultaresptyl-urea powder, and sewed it up.

In the time between the first and second experiments each animal received 3 daily subcutaneous injections of 1—1 mg. histamine of 0.1% solution in its dichlorhydrate form. The effect of the injections on the animals we observed to be as follows: 1—2 minutes after the injection lassitude and weakness, with slavering and in some cases vomiting. These symptoms lasted about 20—30 minutes, after which the cats drank abundantly.

12—19 days after first measuring the blood pressure we again narcotized the animals in the above manner. On this occasion the blood pressure was measured in the carotis and the concentration effect curve taken with histamine injection at 3 minute intervals, exactly as in the first case. Figure 1 shows the graph of some of the concentration effect curves.

In some experiments, after the graphing of the concentration effect curve we injected the animals subcutaneously with 1 mg. histamine, upon which the blood pressure dropped and for a long time remained at a low level. If meanwhile we gave extra doses of histamine intravenously we got much less fall in blood pressure (Figure 1, after s. c. sign).

EXPERIMENTAL RESULTS AND DISCUSSION.

Figure 2 sums up the results of the experiment. In the Figure we show the concentration effect curve of each animal before treatment (straight line) and that after long treatment with histamine (broken line). In some animals both before and after treatment we took only one effect curve, in others two. In this case the mean values appear in the Figure.

The first conspicuous thing about the Figure is that in those experiments where we registered 2 effect curves one after the other, the blood pressure response following on the intravenous histamine administration varied in the same animal. The difference could be as much as 20%. On this difference the increase in dose had no effect. Table I. is a comparison of the concentration effect curve of several animals, and shows the individual variations within the species. In respect to our principal question, whether H. D. brought about a change in the blood pressure, it appeared from our experiments that in not a single animal did the blood pressure fall less after the histamine treatment than before. As far as we can speak of a change in the reactions we must say that a slight degree of increase in the fall of

blood pressure took place, principally in the case of the 0.1 μg doses.

To get an appreciable picture of the consequence of the histamine treatment, in spite of the individual and group variations, we made a statistical valuation of the change in blood pressure fall. In Table I. we have assembled the mean blood pressure values of the single histamine doses, before and after treatment. We reckoned the significant difference between the 2 mean values in the usual way. It appears from the Table that the significant difference between the mean blood pressure values and those effected by the 0.5, 1.0, 5.0 and 10 μg.

TABLE I.
Statistical evaluation of the experimental results.

Histamine dose μg.	Fall in blood pressure in Hgmm.		Significant difference between the blood pressure fall in untreated and treated animals.
	Pre-treated	Untreated	
0.1	17.5 ± 8.4	27.5 ± 12.0	+ 2.75
0.5	35.8 ± 9.53	39.5 ± 12.53	+ 0.91
1.0	43.8 ± 10.9	50.0 ± 10.2	+ 1.45
5.0	59.7 ± 11.4	62.8 ± 11.1	+ 0.67
10.0	71.0 ± 11.28	68.6 ± 17.2	— 0.27

histamine is smaller than 2; that is the amount was exactly the same in the treated and untreated animals. In the untreated animals after a 0.1 μg intravenous histamine injection the blood pressure fell by a mean value of 17.5 Hg. mm., after treatment by 27.5 Hg. mm. The 2.75 significant difference between the two values makes improbable the complete equality; that is, a slight degree more sensibility can be remarked after protracted treatment with histamine on the basis of 0.1 μg intravenous injections.

The fall in blood pressure brought about by intravenous histamine injection is in part the result of the fact that the base widens the arterioles and praecapillaries, besides which it changes the irritability of the centres, inasmuch as, through the blood thickening, the quantity of liquid circulating diminishes.

These effects were also brought about if histamine — in larger doses — was injected subcutaneously. This condition we could observe directly (Figure 1, after s. c.) but we could confirm it indirectly as well, in that after the subcutaneous injection the animals were weak and languid, and thirsty due to the thickening of the blood. In our experiments, after making the first histamine concentration effect

curve, we daily gave the animals 1—1 mg. subcutaneous injections for a period of two weeks. In spite of the fact that during the time beween taking the two effect curves the histamine did cause a fall in blood pressure in the cats on 40—50 occasions, we did not find a diminished sensibility to histamine.

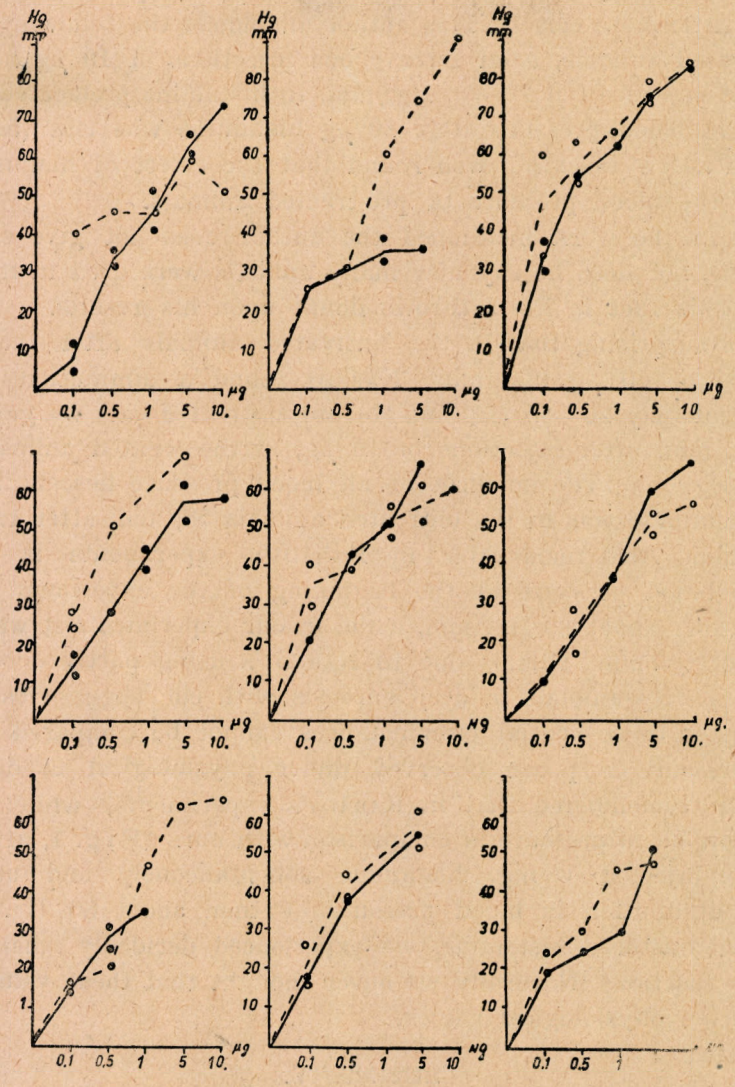

Figure 2. The effect of different histamine-doses in diminishing the blood-pressure, in 9 cats, before (straight line) and after (broken line) pre-treatment. Abscissa: histamine doses given intravenously; ordinata: fall of the blood-pressure in Hgmm. after the histamine doses.

From our experiments we draw the conclusion that cats cannot be desensibilized by lengthy histamine treatments with the effect of reducing blood pressure by histamine administered intravenously. Those mechanisms which cause a fall in blood pressure do not change, even in consequence of long training.

To terminate, we must criticize KARÁDY's experiments (KARÁDY 1936) a little more closely. This author announces the following results: In untreated animals, after intravenous injections of 10 μg histamine, the blood pressure fell 20—40 Hg. mm. In histamine pretreated animals the fall in blood pressure after 10 μg histamine was less (5—10 Hg. mm); in a few cases he even found that the effect of histamine was to raise the blood pressure of pre-treated animals.

But in the work mentioned the author does not give statistical valuations, nor does he say how many animals were used in the experiments. This fact in itself throws doubt upon his results.

It is surprising that in the untreated animals after intravenous injections of 10 μg histamine KARÁDY found a diminution of blood pressure of only 20—40 Hg. mm. In our untreated cats we got a mean 71.0 Hg. mm. after injections of 10 μg, in the treated animals a fall of 68.6 Hg. mm. The smallest of all blood pressure descent following 10 μg histamine was in the untreated animals 58, and, after treatment, 52 Hg. mm. Also remarkable in KARÁDY's experiments is that his animals' blood pressure at the beginning of the experiment was extremely low: about 80 Hg. mm, while in our experiments it was around 120—160 Hg. mm. This is due to KARÁDY's using partly decerebrated animals, partly animals in deep narcosis with cut vagus. Observations made under these special circumstances cannot be compared with the blood pressure response observed under physiological conditions. It should be remembered that in KARÁDY's experiments, while he began with a low blood pressure in comparison with ours (Fig. 1, after s. c.), when we injected 1 mg. histamine subcutaneously and under the lengthy diminution in blood pressure — then about 80 Hg. mm. — again administered histamine, we experienced decidedly smaller blood pressure reactions. Naturally we never thought that these values should be taken as physiological values.

SUMMARY.

We measured the fall in blood pressure of 9 cats in sterile conditions on injecting 0.1, 0.5, 1.0, 5.0 and 10 μg histamine intravenously. Thereafter for 12—19 days we gave the animals 3 daily subcutaneous

injections of 1—1 mg. histamine. After the treatment we again measured the histamine concentration effect curve of the arterial blood pressure.

There is no change in sensibility before and after treatment.

Grateful acknowledgment is made to Mrs. J. THOMPSON VASS for help in the English translation.

REFERENCES.

BURN, J. H. (1928). *Methods of Biol. Assay.* Edinburgh.
FÜHNER, H., (1912). *Münch. Med. Wchschr.* 59, 852.
KARÁDY, St. (1936), *Arch. exp. Pathol. u. Pharmakol.* 180, 283.
KOKAS F., SARKADY L., WENT I. (1938). *Magy. Orv. Arch.* 39, 408,
RUSZNYÁK I., KARÁDY L., SZABÓ (1934), *Orv. Hetilap* 14. — *Deutsch. Med. Wchschr* 60, 1670.
„ „ „ (1935). *Deutsch. Med. Wchschr.* 61, 1111.