PRESSOR EFFECT OF HISTAMINE IN THE RABBIT[1]

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The hypotensive effect of histamine upon the arterial blood pressure of the cat and dog has been well known since the first investigations by Barger and Dale (1910) and Dale and Laidlaw (1910). A similar effect has been described in man (Weiss *et al.*, 1932; Katzenstein, 1944; Roth and Kvale, 1954). The problem of the blood pressure effect of histamine in the rabbit has received much less attention. As early as 1927, Feldberg observed that under certain conditions of anesthesia histamine produced a pressor effect, but since then, major interest turned to a more special vascular phenomenon produced by histamine in the rabbit, the constriction of the pulmonary arterioles (Best and MacHenry, 1931; Woodbury and Hamilton, 1941). Only more recently (Naranjo, 1952; Naranjo and de Naranjo, 1953) some attention has been paid to the pressor effect of histamine in the rabbit and to its prevention by antihistamines. The present work was carried out in order to study in this animal species the influence of a) autonomic drugs, b) adrenalectomy and c) anesthesia, on the blood pressure effect of histamine.

METHODS. The experiments were performed with adult rabbits of both sexes, weighing 1.5 to 2 kgm. In the main experiments, they were heparinized and anesthetized with a standard mixture of urethan (700 mgm./kgm.) and pentobarbital sodium (40 mgm./kgm.), administered intraperitoneally. Cannulae were inserted into the right common carotid artery for recording blood pressure, into the external jugular vein for injections, and into the trachea.

Histamine was used as the biphosphate in doses from 0.001 to 0.250 mgm./kgm., and epinephrine HCl in doses from 0.5 to 2.0 microgm./kgm. Successive injections were given after blood pressure had returned to the baseline, histamine being injected 3 to 5 minutes after epinephrine, and epinephrine 5 to 20 minutes after histamine. Both substances, dissolved in 0.9 per cent saline, were administered by rapid intravenous injection (1 to 2 seconds) in a uniform volume of 0.5 ml./kgm.

Other drugs employed were: cocaine HCl, 5 mgm./kgm.; phentolamine methanesulphate (Regitine), 3 mgm./kgm.; dihydroergotamine (DHE), 1 mgm./kgm.; hexamethonium Br, 10 mgm./kgm.; and pendiomide Br, 30 mgm./kgm. They were always administered subcutaneously 15–20 minutes prior to the first subsequent dose of histamine or epinephrine.

In those series of experiments in which dose-effect relationships were studied, the drug was given in progressive doses and no other drug was administered to the animal. In studying the influence of the adrenals on response to histamine, bilateral adrenalectomy was carried out transabdominally after elicitation of control responses in the intact animal.

The influence of anesthesia on the response to histamine was studied with ether, urethan, thiopental Na and the standard urethan-pentobarbital mixture (17:1). The different stages of anesthesia were established with ether by the open drop technique, with the other drugs by varying the dose. Urethan and the mixture of urethan-pentobarbital were administered intraperitoneally and thiopental intravenously.

All numerical data represent averages for groups of 8 to 10 animals.

RESULTS. *Heparinization.* In preliminary experiments it was ascertained that intravenous administration of adequate doses of heparin (50 to 100 units/kgm.) did not modify the blood pressure effect of histamine.

Blood pressure effect of histamine. Doses from 1 to 10 microgm./kgm. failed to cause any change of blood pressure in approximately 75 per cent of animals; in the rest, a slight and transient fall of blood pressure (no more than 5 mm. Hg) was observed. Doses from 10 to 20

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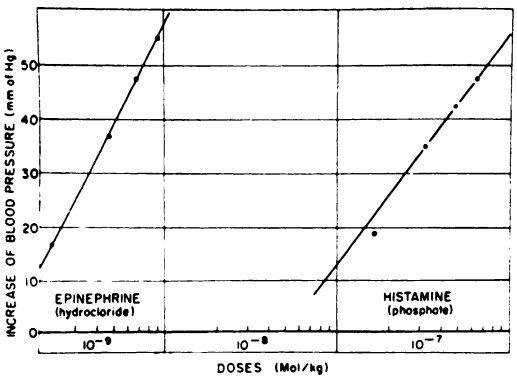

FIG. 1. Dose-pressor effect relationship of epinephrine and histamine in anesthetized rabbits.

microgm./kgm. produced a small rise of blood pressure, varying from 2 to 10 mm. Hg. Higher doses, however, uniformly produced a sharp and marked rise of blood pressure. In the dosage range between 50 and 250 microgm./kgm., the pressor effect of histamine increased (fig. 1) in linear relationship with log dose. Except for a moderate difference in slope, the same relationship prevailed for epinephrine doses approximately 100 times lower than those of histamine.

The pressor phase was followed by a subsequent depressor phase (fig. 3 and 4). In this secondary effect, the two drugs differed in that after doses equieffective in elevating the blood pressure the subsequent drop was greater with histamine. The higher the dose of histamine, the more intense and persistent was the subsequent depression.

Interrelation between histamine and epinephrine. An antagonism between histamine and epinephrine was observed. Depending upon magnitude of dosage, a single epinephrine administration, 3 to 5 minutes prior to histamine, either diminished or reversed the pressor effect of histamine (fig. 2); after repeated doses of epinephrine, (1 to 4 microgm./kgm.) the histamine response was regularly reversed. On the other hand, after a preceding dose of histamine, the pressor effect of epinephrine was diminished but never reversed.

Cocaine by itself did not modify the blood pressure effect of histamine. However the reversal of the histamine pressor effect was obtained with smaller doses of epinephrine in cocainized than in control animals.

Influence of adrenergic blocking agents. Phentolamine (Regitine, 3 mgm./kgm.) and DHE (1 mgm./kgm.), which diminished the pressor effect of 1 microgm./kgm. of epinephrine by 78.0 ± 12 and 81.4 ± 12 per cent, respectively, did not significantly modify the response to histamine (fig. 3). Epinephrine in the same doses as in the former experiments did not reverse the pressor effect of histamine after adrenergic blockade.

Influence of ganglionic blocking agents. Pretreatment with a ganglionic blocking agent increased the pressor response to histamine. The increase amounted to 27 and 32 per cent after 10 mgm./kgm. of hexamethonium and 30 mgm./kgm. of pendiomide, respectively. The subsequent depressor effect of histamine was considerably diminished or abolished after ganglionic blockade.

The mutual antagonism of histamine and epinephrine was not manifest in the presence of ganglionic blockade. Injection of a mixture of histamine and epinephrine resulted in a combined pressor effect which was higher than that of either of the drugs alone. When the dose of one of the substances in the mixture was progressively increased, that of the other substance being kept constant, the increase in pressor effect was proportional to the increased dose.

Influence of adrenalectomy. The pressor effect of histamine was essentially unchanged after

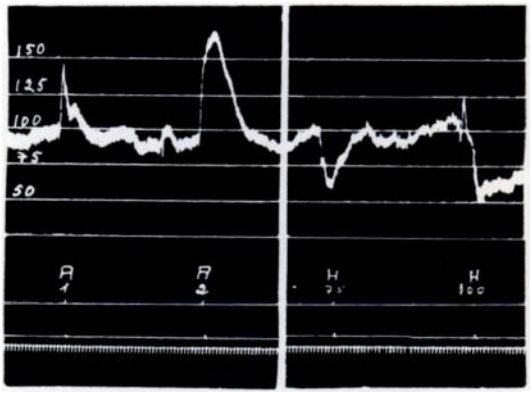

FIG. 2. Reversal of the pressor effect of histamine by epinephrine.

Rabbit, 1.8 kgm., urethan-pentobarbital anesthesia (see text). Blood pressure recorded by means of a mercury manometer. A = epinephrine hydrochloride (successive doses, 1 and 2 microgm./kgm.); H = histamine biphosphate (successive doses, 75 and 100 microgm./kgm.). First dose of histamine 5 minutes after last dose of epinephrine. Time signal: 5 seconds.

adrenalectomy (fig. 4). In six out of ten animals the blood pressure rose to the same peak level before and after adrenalectomy; inasmuch as the removal of the glands produced a deep fall in blood pressure, the histamine-induced rise, in per cent of the baseline value, was even higher after adrenalectomy. In the other four animals even the peak level of blood pressure was 10 to 15 mm higher after adrenalectomy.

In one group of animals, blocking agents were

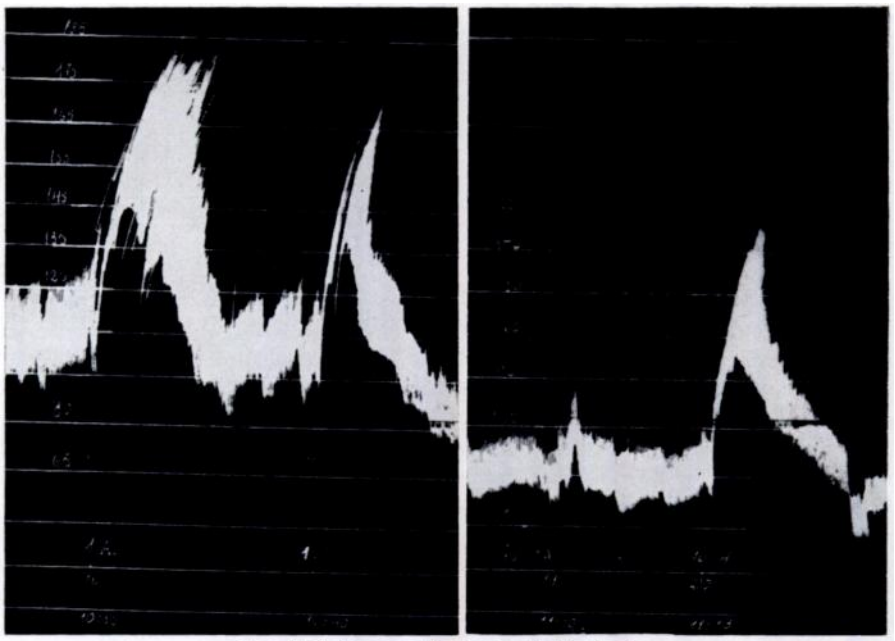

FIG. 3. Influence of adrenergic blockade.

Rabbit, 2.08 kgm., urethan-pentobarbital anesthesia (see text). Recording of the carotid blood pressure by means of a bellows manometer. Left tracing: epinephrine 1 microgm./kgm. and histamine 100 microgm./kgm., respectively. Right tracing: the same drugs and doses, after 20 minutes of subcutaneous administration of 3 mgm./kgm. of Regitine.

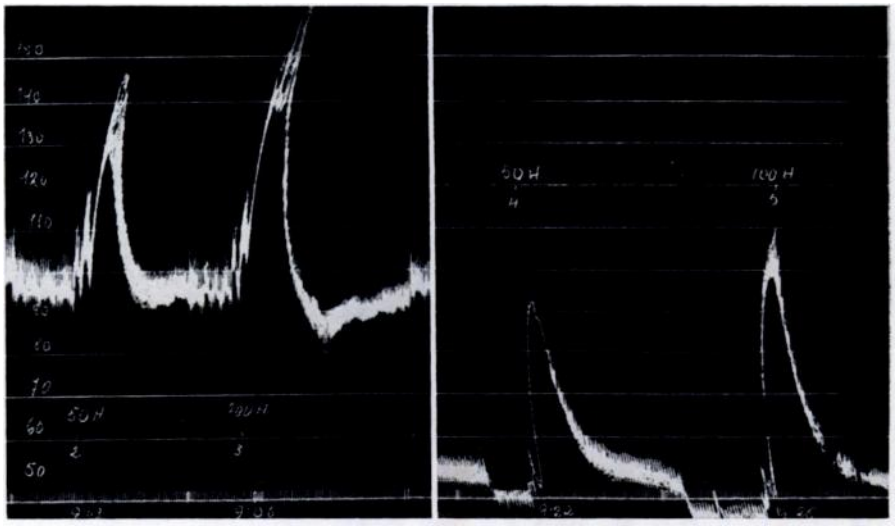

FIG. 4. Pressor effect of histamine before and after bilateral adrenalectomy.

Rabbit, 1.85 kgm., urethan-pentobarbital anesthesia (see text). Recording of the carotid blood pressure by means of a bellows manometer. Left tracing: histamine 50 and 100 microgm./kgm., respectively. Right tracing: the same doses, 10 minutes after adrenalectomy. Time signal: 5 seconds.

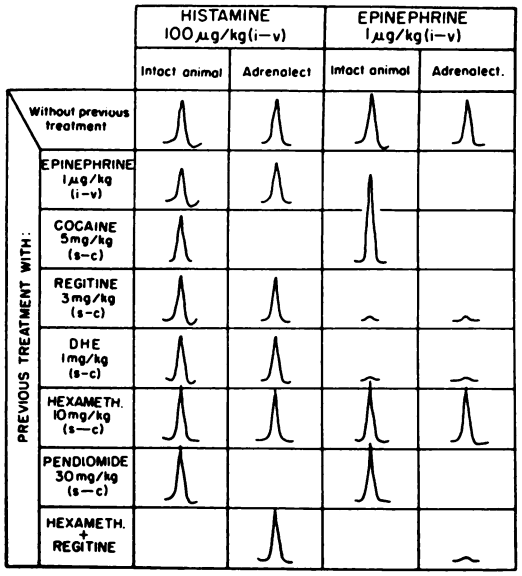

FIG. 5. Pressor effects of histamine and epinephrine after various drugs before and after adrenalectomy.
For explanation see preceding figures and text.

administered immediately before adrenalectomy. Adrenergic blockers, even in a dose capable of abolishing the pressor effect of 1 microgm./kgm. of epinephrine, not only failed to diminish the pressor effect of histamine but rather enhanced it. Ganglionic blockade also enhanced the histamine effect.

Fig. 5 summarizes the major experimental results.

Influence of anesthesia. In unanesthetized animals the blood pressure effect of histamine varied greatly. In some animals a moderate pressor response was observed, followed by a more profound depressor response phase, while in others only a depressor response was produced. Since in the unanesthetized animals histamine elicited very pronounced hypermotility, it was difficult to evaluate to what extent the blood pressure changes were directly induced by histamine and to what extent they were indirect effects due to sequels of histamine action, such as those motor manifestations. Pretreatment with ganglionic blocking agents produced more regularly a pressor response.

Under progressive ether anesthesia it was observed that in the first stage of anesthesia, while the animal still reacted with movements to painful stimuli such as pinching of the skin, the blood pressure effect of histamine was quite the same as in unanesthetized animals. In deeper anesthesia the blood pressure responses were less erratic, and on the third plane of the third stage of surgical anesthesia (Gillespie, 1942) histamine invariably induced a pressor effect.

The results with urethan or the standard urethan-pentobarbital mixture were similar to those described for ether, namely, the deeper the anesthesia, the more prevalent was the pressor response to histamine. With thiopental, although the results were essentially the same, it was not easy to reach an adequate depth of anesthesia; either the anesthesia was too superficial and, consequently, the effect of histamine still variable, or it reached rapidly a toxic and fatal level.

These results suggest that the pressor effect of histamine in the rabbit depends at least in part on the depth of general anesthesia.

DISCUSSION. In rabbits studied under the experimental conditions here reported, histamine produces a rapid and transient rise in arterial blood pressure. Various reports demonstrating that histamine causes depletion of epinephrine from the adrenals in the cat and dog (Elliot, 1912; Houssay and Molinelli, 1925; Burn and Dale, 1926; La Barre, 1927; Szczygielski, 1932), could be interpreted as meaning that, in the rabbit, the histamine pressor effect is mediated by release of endogenous epinephrine. For example, in the spinal cat Burn and Dale (1926) demonstrated that histamine can induce a rise of blood pressure, in contrast to the usual depressor effect seen in the intact animal. However, this pressor effect does not appear after bilateral adrenalectomy. Furthermore, the assumption of release of endogenous epinephrine in the rabbit is eliminated by the present experiments. They demonstrate that the pressor effect of histamine is neither abolished by bilateral adrenalectomy nor diminished or reversed by adrenergic blocking agents in doses capable of diminishing by 80 per cent the effect of 1 microgm./kgm. of epinephrine. These results are most compatible with the interpretation that, in the rabbit, histamine induces a pressor response for which mobilization of epinephrine is not a prerequisite.

Dale and Richards (1918), in one of their earliest studies of histamine found that histamine produced constriction of arterioles in rabbits during artificial limb perfusion. These authors first, and Burn and Dale (1926) later, pointed out that histamine may produce a dual

effect: relaxation of the capillary wall and contraction of the smooth muscle of arteries and arterioles. According to Burn and Dale (1926), in the cat, capillary dilatation would be the most manifest response to histamine but normal capillary tone must previously exist. Factors affecting capillary tone, such as the denervation of an organ, may modify the response to histamine. On the other hand, the same workers demonstrated that histamine relaxed both capillaries and arteries both in the dog and monkey and hence did not elicit such dual effects in these species. These findings were later confirmed by Page and Taylor (1947) in the dog. In the rabbit, as it is well known (Best and MacHenry, 1931), histamine produces constriction of the pulmonary arteries, but this phenomenon does not explain the rise of blood pressure in the carotid artery. It could be assumed that the arterial constriction does not occur exclusively in the lungs but may also occur in other organs to such an extent that this factor would be responsible for the rise of blood pressure. In fact, Feldberg (1927) demonstrated in denervated rabbit ears that arterial constriction can be produced by histamine. He concluded that, in the rabbit also, histamine has dual effects: constriction on the arterial branches including the pulmonary arteries, and dilation on the capillaries. Finally, he advanced the hypothesis that capillary tone in the rabbit would be normally weaker than in the cat or dog and easily depressed or abolished by general anesthetics. When the capillary tone is abolished no more dilatation can be produced by histamine and constriction of arteries may become the only visible response, with the consequent rise of blood pressure.

Our findings confirm that under an appropriate depth of surgical anesthesia the dominant response to histamine in the rabbit is the rapid rise of blood pressure, but the hypothesis of a weaker capillary tone in this animal species than in others still requires confirmation.

The results obtained by Slater and Dresel (1952) are particularly interesting in connection with the problem of the mechanism of vasomotor effects of histamine. These authors found that during ganglionic blockade, histamine elicited a pressor response in the cat but not in the dog. During ganglionic blockade, bilateral adrenalectomy in the cat only slightly diminished the pressor response to histamine. This response was, therefore, not primarily due to mobilization of epinephrine from the adrenals. On the other hand, ganglionic blockade of the sympathetic efferent pathways produced decrease of capillary tone secondary to arterial dilatation. Under such experimental conditions, arteriolar constriction produced by histamine becomes prominent. But in the dog, since histamine dilates arteries as well as capillaries, ganglionic blockade does not reverse the depressor effect of histamine.

In the rabbit, as reported here, ganglionic blockade favors the pressor response to histamine in both anesthetized and unanesthetized animals. Our findings demonstrate that the pressor response is not mediated by mobilization of endogenous epinephrine and confirm indirectly Feldberg's (1927) results, *i.e.*, factors causing a decrease in capillary tone enhance the histamine pressor response.

SUMMARY

Contrary to its depressor effect in cat, dog, monkey and man, histamine produced in the anesthetized rabbit a pressor effect qualitatively comparable to that of epinephrine. This effect was favored by general anesthesia. The deeper the anesthesia the more regular was the pressor effect. In unanesthetized animals or under light anesthesia the responses were erratic, there was even a depressor effect.

In the dose range of 50 to 250 microgm./kgm., the relationship between log dose and pressor effect of histamine was linear. A dose approximately one hundred times that of epinephrine was required to produce an equal pressor effect.

Epinephrine and histamine were mutually antagonistic. Epinephrine given before histamine in a single small dose diminished and, given in a single higher dose or repeated small doses reversed, the pressor effect of histamine. Histamine given prior to epinephrine diminished the epinephrine pressor effect but never reversed it. Adrenergic blocking agents did not modify the pressor response of histamine even in doses strongly blocking the epinephrine effect. By ganglionic blockade the pressor effect of histamine was enhanced and the antagonism between epinephrine and histamine was turned into synergism. Adrenalectomy did not decrease the pressor effect of histamine.

In the discussion of these findings it is pointed out that they are all compatible with the conclusion that the pressor effect of histamine was not due to the mobilization of epinephrine.

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