EFFECT OF HISTAMINE, BRADYKININ AND MORPHINE ON ADRENALINE RELEASE FROM RAT ADRENAL GLAND

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Abstract—Effects of histamine, bradykinin and morphine on adrenaline secretion from rat adrenal gland were investigated by means of fluorometric determination of adrenaline in adrenal-venous blood specimens. Histamine caused marked secretion of adrenaline at doses of more than 2.5 mg/kg i.v. The histamine-induced adrenaline secretion at a dose of 2.5 mg/kg was depleted to about one half by splanchnicotomy. Hexamethonium (C6) and atropine did not prevent histamine-induced adrenaline output. However, antihistaminics antagonized the action of this compound. Bradykinin caused increase of adrenaline secretion from the adrenal gland. Splanchnicotomy scarcely prevented the action of bradykinin. C6, phenylbutazone, and pyridinolcarbamate did not block the bradykinin-induced adrenaline output. Morphine caused significant increase of adrenaline secretion from the chronically and completely denervated adrenal gland.

The author has previously reported a method for the study of drug effects on adrenaline release from rat adrenal medulla (1). Using this method, studies have been performed on the effects of several drugs and on the nature of splanchnic-adrenal transmission. The present paper shows the effects of histamine, bradykinin and morphine on adrenaline release from the adrenal gland in the rat.

MATERIALS AND METHODS

Experiments were carried out with male rats of Sprague-Dawley strain weighing 400–600 g. Details of the methods were demonstrated in a previous paper (1), therefore only a brief explanation will be given here.

Adrenal-venous blood was collected for 15 min under pentobarbital sodium anesthesia or with ether inhalation, and adrenaline contents in the blood specimen were determined fluorometrically. Splanchnicotomy was performed as follows: the left greater splanchnic nerve was incised near the diaphragm either 25 min prior to the onset of blood collection (acute) or a wk. prior to the experiment (chronic). Complete adrenal denervation was performed a week before intended use. In addition to the splanchnicotomy near the diaphragm, the adipose tissue around the left adrenal was excised together with nerves and suprarenal arteries except for the inferior one.

The drugs used were histamine dihydrochloride (Nakarai), bradykinin triacetate (Peptide Center, the Institute for Protein Research, Osaka Univ.) morphine hydrochloride (Shionogi), promethazine hydrochloride (Shionogi), diphenhydramine (Vena—Tanabe),
hexamethonium bromide (Methobromin —Yamanouchi) (C6), phenylbutazone (synthesized in this laboratory) and pyridinolcarbamate (Anginin—Banyu). These drugs except for morphine, phenylbutazone and pyridinolcarbamate were dissolved in 0.9% saline and injected i.v. Phenylbutazone was dissolved in a minimum volume of dil. NaOH, was then diluted with saline and injected i.v. Morphine was injected i.p. as an aqueous solution. Pyridinolcarbamate was suspended in 2.5% gum arabic and injected s.c.

RESULTS

Histamine Adrenaline secretion from the left adrenal gland after injection of histamine is shown in Fig. 1. Histamine caused a marked increase of adrenaline output at doses from 2.5 to 10 mg/kg as hydrochloride salt. Table 1 demonstrates the effect of denervation of the gland on adrenaline secretion in response to histamine. In acute splanchnicotomy, the adrenaline output decreased to about one-third. In chronically splancnichotomized rats, the value of histamine induced adrenaline output was about one-half that of intact rats. Chronic complete denervation gave a result similar to that seen with chronic

![Graph](https://via.placeholder.com/150)

**Fig. 1.** Effect of histamine on adrenaline release from rat left adrenal under pentobarbital anesthesia. Number of experiments is indicated in parentheses. Bars are S.E. of the mean.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Histamine-2HCl (mg/kg i.v.)</th>
<th>n</th>
<th>Adrenaline output (µg/15 min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2.5</td>
<td>6</td>
<td>0.60±0.04</td>
</tr>
<tr>
<td>Acute splanchnicotomy</td>
<td>2.5</td>
<td>4</td>
<td>0.18±0.01</td>
</tr>
<tr>
<td>Chronic splanchnicotomy</td>
<td>2.5</td>
<td>4</td>
<td>0.34±0.03</td>
</tr>
<tr>
<td>Chronic complete adrenal denervation</td>
<td>2.5</td>
<td>4</td>
<td>0.26±0.08</td>
</tr>
</tbody>
</table>

Intact control : 0.04±0.00, Denervated control : Trace
The data represent mean±S.E.
Pretreatment with C6 and atropine did not decrease the hypersecretion of adrenaline caused by histamine (Table 2), although antihistaminics blocked the adrenal response to this compound (Table 3).

<table>
<thead>
<tr>
<th>Pretreatment (mg/kg i.v.)</th>
<th>Histamine·2HCl (mg/kg i.v.)</th>
<th>n</th>
<th>Adrenaline output (Left) (µg/15 min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>2.5</td>
<td>6</td>
<td>0.60±0.04</td>
</tr>
<tr>
<td>Hexamethonium 1.0</td>
<td>2.5</td>
<td>5</td>
<td>0.97±0.19</td>
</tr>
<tr>
<td>Atropine sulfate 1.0</td>
<td>2.5</td>
<td>4</td>
<td>0.65±0.15</td>
</tr>
</tbody>
</table>

Hexamethonium and atropine were administered 5 min before histamine injection. The data represent mean±S.E.

Antihistaminics were administered 5 min before histamine injection. The data represent mean±S.E.

Bradykinin caused hypersecretion of adrenaline at doses of 0.1 to 0.5 mg/kg. Acute splanchnicotomy caused little decrease of adrenaline output in response to bradykinin. The adrenal response to bradykinin was not influenced by pretreatment with C6, phenylbutazone or pyridinolcarbamate (Table 5).

Morphine The effect of morphine on adrenaline secretion from rat adrenals was reported in a previous paper (1). Morphine hydrochloride, 120 mg/kg, was administered, thereafter the rat was anesthetized with ether and adrenal-venous blood was collected from 40 min after the morphine injection. Increase of adrenaline output after administra-
tion of morphine was largely blocked by acute splanchnicotomy, though little residual response was observed. The response of chronically splanchnicotomized adrenal to morphine was a little greater than that seen in the acutely splanchnicotomized gland. When chronic complete denervation was performed, the response was ever greater (Fig. 2).

**TABLE 5. Effects of hexamethonium, phenylbutazone, and pyridinolcarbamate on adrenaline release from rat adrenals in response to bradykinin under pentobarbital anesthesia.**

<table>
<thead>
<tr>
<th>Pretreatment (mg.kg)</th>
<th>Bradykinin•3AcOH (mg.kg i.v.)</th>
<th>n</th>
<th>Adrenaline output (Left) (µg/15 min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>0.25</td>
<td>5</td>
<td>0.37±0.05</td>
</tr>
<tr>
<td>Hexamethonium</td>
<td>1.0</td>
<td>5</td>
<td>0.37±0.02</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>5.0</td>
<td>5</td>
<td>0.32±0.04</td>
</tr>
<tr>
<td>Pyridinolcarbamate</td>
<td>10</td>
<td>5</td>
<td>0.51±0.05</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>5</td>
<td>0.32±0.04</td>
</tr>
</tbody>
</table>

Hexamethonium and phenylbutazone were administered i.v. 5 min before bradykinin injection. Pyridinolcarbamate was administered s.c. 45 min before bradykinin injection. The data represent mean±S.E.

**DISCUSSION**

Wada et al. (2) reported that increase of adrenaline secretion caused by histamine in the dog is due to the action of this compound on the central nervous system. Staszewska and Vane (3) showed that the effect of histamine on the adrenal medullary cells in the dog is mainly indirect, acting through reflex pathways and nerve endings, although in the cat, the effect of this compound is exerted directly upon the adrenal medullary cells. In our experiment, increase of adrenaline secretion was observed after injection of histamine in the rat. The degree of increase was slight at doses of 1.0 mg/kg or less, though it was marked at doses of more than 2.5 mg/kg. The hypersecretion of adrenaline at 2.5 mg/kg was depleted to about one half by splanchnicotomy. C6 showed a tendency to
enhance rather than inhibit the adrenaline secretion caused by histamine. It is concluded that in the rat, histamine has a direct action upon adrenal medullary cells and an indirect effect through splanchnic nerve stimulation, which is conspicuous at doses of more than 2.5 mg/kg. These findings suggest that the ratio of the sensitivity of adrenal medullary cells to that of the central nervous system in response to histamine varies with the species. The histamine induced adrenaline output was blocked by pretreatment with antihistaminics. This result confirmed, in the rat, similar results obtained in the cat and dog by Emmelin and Muren (4), Slater and Dresel (5), and Staszewska-Barczak and Vane (3).

Feldberg and Lewis (6, 7) reported the adrenaline secretion caused by bradykinin and other kinins in the cat. Staszewska-Barczak and Vane (8) indicated the effect of bradykinin and angiotensin on adrenaline release from the adrenal medulla in the dog and cat. On the rat, too, bradykinin caused hypersecretion of adrenaline from the adrenal gland. Splanchnicotomy scarcely prevented the bradykinin induced adrenaline secretion. C6 had no influence on the effect of bradykinin. This shows that as in the cat and dog, bradykinin acts directly upon adrenal medullary cells in the rat. Phenylbutazone antagonizes the contraction of bronchial muscle caused by bradykinin (9, 10) but showed no effect on adrenal medullary response to bradykinin. Pyridinolcarbamate antagonizes the hemorrhage caused by bradykinin (11, 12), but did not block the adrenal medullary response to bradykinin. These results suggest that the action mechanism of bradykinin on adrenal medullary cells differs from that on bronchial muscles and blood vessels.

As shown in a previous paper (1), morphine causes marked hypersecretion of adrenaline from the rat adrenal medulla. Acute splanchnicotomy largely prevented the adrenal response, although some residual response was observed. The response of chronically splanchnicotomized adrenal to morphine was a little greater than that of the acutely splanchnicotomized gland. The response of chronically and completely denervated gland was ever greater. It is concluded that morphine has central and peripheral actions on adrenaline secretion from the rat adrenal medulla, but that the latter is much weaker than the former.

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REFERENCES
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7) FELDBERG, W. AND LEWIS, G.L.: J. Physiol. 178, 239 (1965)