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# The anti-inflammatory effect of catecholamines in the peritoneal cavity and hind paw of the mouse

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## Summary

1. Carrageenin or 5-hydroxytryptamine-induced oedema of the mouse hind paw was antagonized by catecholamines acting on both $\alpha$- and $\beta$-adrenoceptors.

2. Increased permeability of the mouse peritoneum induced by the local injection of acetic acid or pro-inflammatory mediators was antagonized by catecholamines acting predominantly on $\beta$-adrenoceptors.

3. The anti-inflammatory effect of catecholamines was due neither to hyperglycaemia nor to the release of adrenal cortical hormones.

## Introduction

The ability of catecholamines to suppress certain forms of acute inflammation is well documented. Inflammatory responses in which hypersensitivity or anaphylactoid-type states are involved appear to be inhibited by the hyperglycaemic activity of catecholamines (Kellet, 1965). The mechanism of the inhibitory effect of catecholamines in other types of inflammation has not been established. Nevertheless it is widely assumed that catecholamines exert an anti-inflammatory effect by causing vasoconstriction, thereby diverting blood flow away from inflamed tissues. This concept is supported by the ability of the $\alpha$-adrenoceptor blocking agent, dibenamine, to antagonize the anti-inflammatory effects of catecholamines in turpentine-induced pleurisy and in thermal injury (Spector & Willoughby, 1960; Willoughby & Spector, 1964). However, the anti-inflammatory effects of catecholamines in some forms of inflammation appear to be mediated via $\beta$-adrenoceptors, since the $\beta$-adrenoceptor blocking agent, sotalol, antagonizes the suppressive effect of catecholamines in dextran or formaldehyde-induced oedema (McKinney & Lish, 1966; Brown, Mackay, Riggilo & Schwartz, 1968).

The mechanism of the $\beta$-adrenoceptor mediated anti-inflammatory effect of catecholamines is unknown. The present investigation was made in an attempt to clarify the role of $\alpha$- and $\beta$-adrenoceptors in the anti-inflammatory effects of catecholamines and, if possible, to determine the mechanism involved.

## Methods

### *Estimation of peritoneal permeability*

The technique was similar to that described by Northover (1963). Female Schofield mice weighing 25–30 g were injected intraperitoneally by means of a No. 26 gauge needle with 4 ml of 0·05% acetic acid in 0·9% saline warmed to

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38° C. Within the next 30 s, 0·2 ml of a 0·5% solution of Evans blue in saline was administered via a lateral tail vein. Unless otherwise stated, 1 ml of the peritoneal fluid was withdrawn after 1 h, centrifuged, and the optical extinction of the supernatant measured in a Hilger Spekker absorptiometer at 615 mμ. Preliminary results established that the absorption of fluid from the mouse peritoneal cavity in 1 h, under the conditions of the test, was negliglible. The concentration of dye in the peritoneal fluid showed good correlation with the total amount of dye exuded into the peritoneum.

The mean optical extinction for each group was expressed as a percentage of the mean value obtained from control groups of animals, and was called the relative permeability. Dye leakage in drug-treated mice was always compared with dye leakage in control mice obtained at the same time. Unless otherwise stated, drugs were administered either locally into the peritoneal cavity with the 4 ml of acidic saline, or into the subcutaneous tissue of the neck, 30 min before the injection of dye. Animals of control groups were treated similarly, but received injections of saline in place of the drug. Groups of 18–24 mice were used at each dose level.

The effect of pro-inflammatory mediators on the permeability of the peritoneal vascular bed was examined by injecting either bradykinin, histamine or 5-hydroxytryptamine into the peritoneal cavity in 4 ml of Tyrode solution, instead of acidic saline. The peritoneal fluid was recovered after 30 min and its optical extinction determined.

### *Paw oedema induced by carrageenin or 5-hydroxytryptamine*

Mice weighing 25–30 g were injected with 0·025 ml of 1% carrageenin in 0·9% saline into the subplantar tissue of the right hind paw, and with 0·025 ml of 0·9% saline into the left hind paw. The mice were killed 2·5 h after injection, and the paws amputated at the tarsocrural joint and weighed. Catecholamines were administered locally by dissolving the desired dose in the 0·025 ml of carrageenin solution which was injected into the paw. Catecholamines were given systemically by injecting them into the peritoneal cavity with 3 ml of Tyrode solution warmed to 38° C to delay absorption and thus prolong their effect. 5-Hydroxytryptamine-induced oedema was produced by injecting 10 μg of 5-hydroxytryptamine in 0·025 ml of 0·9% saline into the subplantar tissue of the right hind paw. 0·025 ml of 0·9% saline was injected into the left hind paw. The paws were amputated and weighed 30 min after injection.

### *Bilateral adrenalectomy*

Mice were bilaterally adrenalectomized under ether anaesthesia using the dorsal approach, and subsequently given 0·9% sodium chloride solution instead of drinking water until used for experiment 7 days later. In order to assess the effect of the operative procedure on vascular permeability some groups of mice were sham-adrenalectomized.

### *Estimation of blood glucose*

Mice were fasted for 18 h and their blood glucose concentration determined according to the method of Hagedorn & Jensen, as described by Harrison (1957).

*Statistical analysis*

Results are shown as mean ± standard error of the mean. Student's *t* test was used to assess the significance of differences between means.

*Drugs*

The following drugs were used: (−)-adrenaline hydrogen tartrate (B.D.H.); (−)-noradrenaline bitartrate (Koch Light); (±)-isoprenaline sulphate (Abbot); (±)-salbutamol sulphate (Allen & Hanburys); dopamine hydrochloride (Nutritional Biochemicals Corp.); (−)-3,4-dihydroxyphenylalanine (DOPA) (California Corp. for Biochemical Research); (±)-propranolol hydrochloride (I.C.I.); (±)-sotalol hydrochloride, (+) and (−) isomers of sotalol hydrochloride (Mead Johnson); (±)-2-isopropylamino-1-(*p*-nitrophenyl) ethanol hydrochloride (INPEA: Selv); phenoxybenzamine hydrochloride (Smith, Kline & French); phentolamine hydrochloride (Ciba); piperoxane hydrochloride (May & Baker); cortisone acetate (Organon); histamine acid phosphate (B.D.H.); bradykinin triacetate (Sigma); 5-hydroxytryptamine creatinine sulphate (May & Baker); insulin (Burroughs Wellcome); Evans blue (Grübler-Farbstoffe); carrageenin (Viscarin 402: Marine Colloids Inc.).

All doses and concentrations mentioned in the text refer to the salts except for adrenaline, noradrenaline, isoprenaline, salbutamol, dopamine, histamine and 5-hydroxytryptamine which are expressed in terms of the base. (±)-Sotalol was used except where the (−) and (+) isomers are specified.

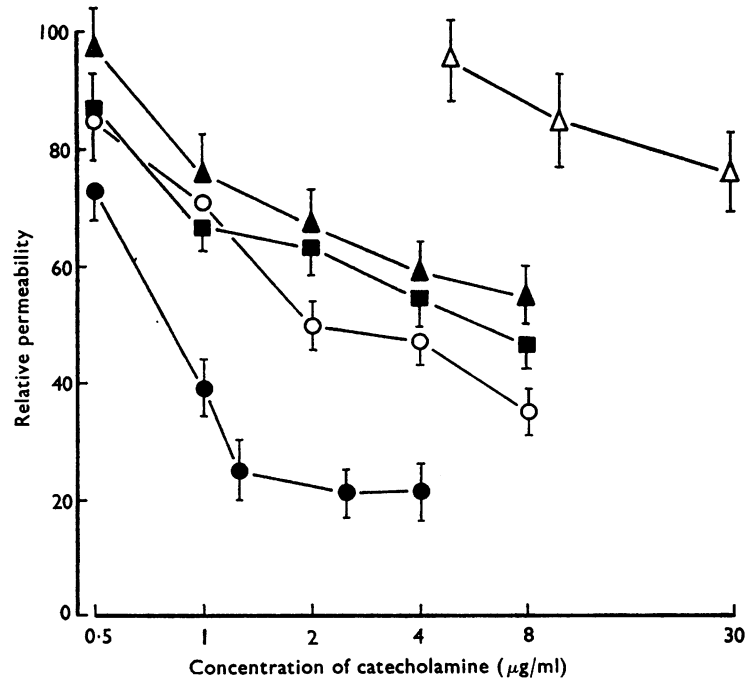


FIG. 1. Relative potency of catecholamines in reducing increased permeability of the mouse peritoneal vascular bed. Adrenaline (●——●); noradrenaline (▲——▲); isoprenaline (○——○); salbutamol (■——■); or dopamine (△——△) were dissolved in acidic saline, the solution warmed to 38° C and 4 ml injected i.p. Doses are expressed as the concentration of drug in the solution injected. Each point is the mean of 26–30 determinations.

## Results

### *Peritoneal vascular permeability*

Mice were injected intravenously with Evans blue and intraperitoneally with 4 ml of 0·05% acetic acid in normal saline. The injection of acidic saline caused an increase in the accumulation of Evans blue bound albumin in the peritoneal cavity, an effect which was antagonized by locally administered sympathomimetic amines, their relative potency being in the order, (−)-adrenaline>(±)-isoprenaline≥(±)-salbutomal≥(−)-noradrenaline≫dopamine (Fig. 1). (−)-DOPA administered in concentrations as high as 320 μg/ml did not reduce the accumulation of Evans blue in the peritoneal cavity.

Bradykinin, histamine or 5-hydroxytryptamine caused a greatly increased exudation of dye into the peritoneal cavity, an effect which was antagonized by adrenaline or isoprenaline (Table 1).

β-Adrenoceptor blocking agents antagonized the permeability-reducing effects of catecholamines, the dose response line for catecholamines being displaced to the right in a parallel manner (Fig. 2, Tables 1 & 2). The potency of β-adrenoceptor blocking agents in antagonizing the permeability effects of catecholamines was in the order propranolol>sotalol=pronethalol>INPEA. This is in accordance with the relative potency of these drugs as β-adrenoceptor antagonists (Black, Duncan & Shanks, 1965; Stanton, Kirchgessner & Parmenter, 1965; Meester, Hardman & Barboriak, 1965; Blinks, 1967; Patil, 1968). The ability of sotalol to antagonize the vascular permeability-reducing effects of catecholamines was found to reside predominantly in the (−) isomer (Table 2). Propranolol (10 mg/kg) failed to antagonize the permeability-reducing effect of phenylbutazone (100 mg/kg), caffeine (80 mg/kg) or aminophylline (80 mg/kg).

TABLE 1. *Inhibitory effect of adrenaline or isoprenaline on increased vascular permeability in the mouse peritoneum induced by bradykinin or 5-hydroxytryptamine (5-HT)*

| Inflammatory agent | Catecholamine | Pretreatment | Dye leakage (μg) | % Inhibition of dye leakage |
|---|---|---|---|---|
| None | (Tyrode solution only) | — | 4·8±0·5 | — |
| Bradykinin | — | — | 41·4±6·9 | — |
| Bradykinin | Adrenaline | — | 6·1±0·9 | 85·3* |
| Bradykinin | Adrenaline | Propranolol | 28·2±6·0 | 31·9* |
| Bradykinin | Adrenaline | Phenoxybenzamine | 6·5±0·9 | 84·3* |
| Bradykinin | Adrenaline | Propranolol +phenoxybenzamine | 44·1±6·9 | —6·5* |
| Bradykinin | Isoprenaline | — | 6·9±1·2 | 83·3* |
| Bradykinin | Isoprenaline | Propranolol | 33·2±6·3 | 19·8* |
| Bradykinin | — | Propranolol | 47·1±8·1 | —11·4* |
| Bradykinin | — | Phenoxybenzamine | 36·8±7·6 | 11·4* |
| 5-HT | — | — | 30·3±6·3 | — |
| 5-HT | Adrenaline | — | 6·0±0·3 | 78·1† |
| 5-HT | Adrenaline | Propranolol | 14·7±3·3 | 51·5† |
| 5-HT | Adrenaline | Phenoxybenzamine | 1·2±0·3 | 96·0† |
| 5-HT | Adrenaline | Propranolol +phenoxybenzamine | 24·5±5·1 | 19·1† |
| 5-HT | — | Propranolol | 27·4±5·7 | 9·5† |
| 5-HT | — | Phenoxybenzamine | 20·1±4·2 | 33·7† |

*Compared with bradykinin control. †Compared with 5-HT control.

4 ml of Tyrode solution containing bradykinin (1·5 μg/ml) or 5-hydroxytryptamine (2·5 μg/ml), with or without the addition of adrenaline (1 μg/ml) or isoprenaline (2 μg/ml), was warmed to 38° C and injected i.p. immediately after the injection of Evans blue. Propranolol (10 mg/kg s.c.) and phenoxybenzamine (10 mg/kg i.v.) were administered 30 min prior to the Evans blue.

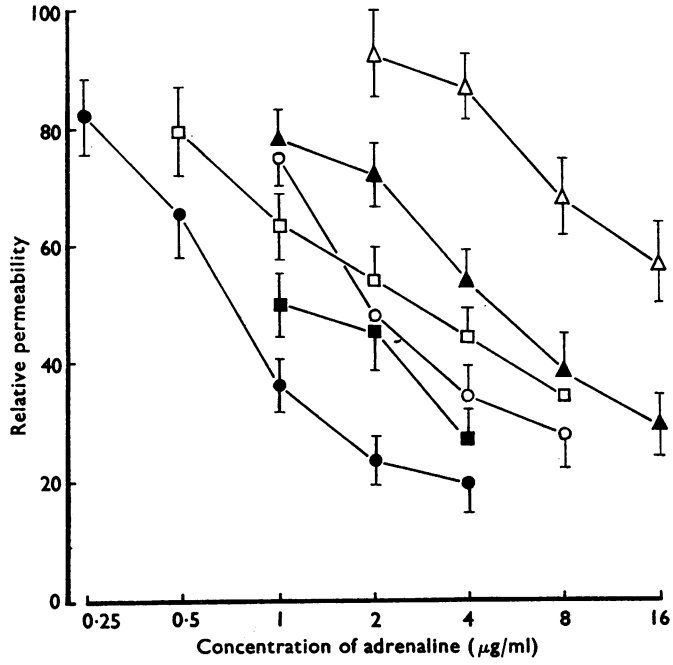


FIG. 2. Antagonism of the vascular permeability-reducing effects of adrenaline by β-adrenoceptor blocking agents. Drugs were dissolved in 4 ml of acidic saline and injected i.p. Doses are expressed as the concentration of drug in the solution injected: adrenaline (●——●); adrenaline+INPEA 20 μg/ml (■——■); adrenaline+sotalol 10 μg/ml (○——○); adrenaline+pronethalol 10 μg/ml (□——□); adrenaline+propranolol 10 μg/ml (▲——▲); adrenaline+propranolol 25 μg/ml (△——△).

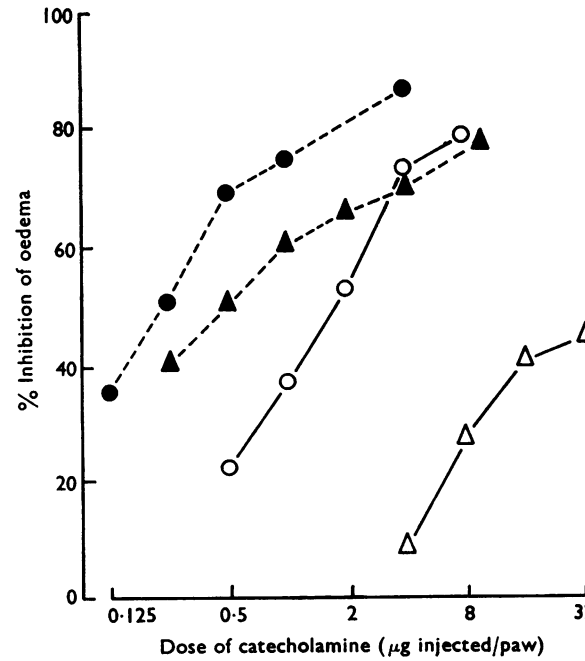


FIG. 3. Inhibition of oedema by adrenaline or isoprenaline injected with carrageenin or 5-hydroxytryptamine (10 μg) into the subplantar tissue of mouse paw. Carrageenin+adrenaline (○——○); carrageenin+isoprenaline (△——△); 5-hydroxytryptamine+adrenaline (●- - -●); 5-hydroxytryptamine+isoprenaline (▲- - -▲). 5-Hydroxytryptamine-induced oedema was measured 30 min after injection and carrageenin-induced oedema was measured 2·5 h after injection.

An attempt was made to antagonize the permeability-reducing effects of catecholamines in the mouse peritoneal cavity with $\alpha$-adrenoceptor blocking agents. The effects of adrenaline or noradrenaline were, however, not significantly antagonized by pretreatment with phenoxybenzamine (2·5 mg/kg, i.v.) or phentolamine (5 mg/kg, s.c.), nor were they antagonized by phentolamine or piperoxane administered locally with the acidic saline in concentrations of 20 $\mu$g/ml and 25 $\mu$g/ml respectively. $\alpha$-Adrenoceptor blocking agents themselves caused a significant reduction in vascular permeability, when administered locally or systemically.

Hyperglycaemia reduces vascular permeability in some forms of experimental inflammation (Brown & West, 1965 ; Kellet, 1965), and hence it was of interest to establish if the hyperglycaemic effects of catecholamines were responsible for their vascular permeability-reducing activity in the mouse peritoneal cavity. However, there appeared to be no correlation between the degree of hyperglycaemia and the suppression of increased vascular permeability (Table 3). In these experiments, the hyperglycaemic effect of adrenaline was partially antagonized by propranolol.

## *Paw oedema*

Adrenaline, noradrenaline, isoprenaline and salbutamol caused a significant reduction in carrageenin-induced oedema in the mouse paw. (−)-Adrenaline was more potent than (±)-isoprenaline in reducing oedema when administered locally

TABLE 2. *Effect of* (+)*-sotalol or* (—)*-sotalol on the vascular permeability-reducing effect of isoprenaline and noradrenaline*

| | Treatment | | Relative permeability | *P* compared with |
|---|---|---|---|---|
| (a) | Isoprenaline | | 44±4 | — |
| (b) | Isoprenaline | + (+)-sotalol | 53±5 | (a) >0·1 |
| (c) | Isoprenaline | + (—)-sotalol | 80±4 | (a) <0·001 |
| (d) | Noradrenaline | | 67±4 | — |
| (e) | Noradrenaline | + (+)-sotalol | 71±4 | (d) >0·4 |
| (f) | Noradrenaline | + (—)-sotalol | 82±5 | (d) <0·01 |
| (g) | (+)-sotalol | | 100±6 | — |
| (h) | (—)-sotalol | | 103±6 | — |

Drugs were injected i.p. after dissolving in 4 ml of acidic saline in the following concentrations: isoprenaline 5 $\mu$g/ml, noradrenaline 2 $\mu$g/ml, (+)-sotalol 5 $\mu$g/ml, (—)-sotalol 5 $\mu$g/ml.

TABLE 4. *Effect of adrenoceptor blocking drugs on the anti-inflammatory activity of systemically administered catecholamines in carrageenin-induced paw oedema*

| Treatment | Increase in paw weight (mg) | % Inhibition of oedema | *P* compared with |
|---|---|---|---|
| (a) Control | 64·5±5·4 | — | — |
| (b) Adrenaline | 25·8±2·4 | 60·0 | (a) <0·001 |
| (c) Adrenaline+propranolol | 36·1±4·1 | 44·0 | (b) <0·05 |
| (d) Adrenaline+phenoxybenzamine | 47·0±4·4 | 27·1 | (b) <0·001 |
| (e) Adrenaline+propranolol +phenoxybenzamine | 59·1±6·4 | 8·4 | (b) <0·001 |
| (f) Isoprenaline | 36·0±2·0 | 44·2 | (a) <0·001 |
| (g) Isoprenaline+propranolol | 63·1±6·5 | 2·2 | (f) <0·001 |
| (h) Isoprenaline+phenoxybenzamine | 39·5±4·1 | 28·8 | (f) N.S. |
| (i) Salbutamol | 27·7±2·9 | 57·1 | (a) <0·001 |
| (j) Salbutamol+propranolol | 49·5±2·7 | 23·3 | (i) <0·001 |
| (k) Propranolol | 64·3±5·6 | 0·3 | (a) N.S. |
| (l) Phenoxybenzamine | 59·7±4·3 | 7·4 | (a) N.S. |

0·025 ml of 1% carrageenin in 0·9% saline was injected into the subplantar tissue of the right hind paw, and 0·025 ml of 0·9% saline into the left hind paw. 3 ml of Tyrode solution, alone or containing isoprenaline (5 $\mu$g), adrenaline (20 $\mu$g) or salbutamol (30 $\mu$g), was warmed to 38° C and injected i.p. Propranolol (10 mg/kg s.c.) and phenoxybenzamine (10 mg/kg i.v.) were injected 30 min prior to the carrageenin. The paws were amputated and weighed 2·5 h after the injection of carrageenin. N.S. Not significant.

TABLE 3. *Effect of changes in the concentration of blood glucose on vascular permeability*

| Group | Treatment | Dose | Route | Time between administration of drug and of dye | *Relative permeability | †Blood glucose (mg/100 ml) |
|---|---|---|---|---|---|---|
| 1 | Normal mice | — | — | — | — | 93±9 |
| 2 | Control mice | — | — | — | 100±7 | 99±10 |
| 3 | Insulin | 0·4 units/kg | s.c. | 30 min | 85±7 | not tested |
| 4 | Insulin | 0·8 units/kg | s.c. | 30 min | 64±5 | 29±5 |
| 5 | Dextrose | 8 g/kg | oral | 30 min | 96±7 | not tested |
| 6 | Dextrose | 16 g/kg | oral | 30 min | 105±8 | 158±12 |
| 7 | Adrenaline | 0·16 mg/kg | i.p | 30 sec | 36±4 | 135±13 |
| 8 | Adrenaline | 0·16 mg/kg | s.c. | 10 min | 94±9 | 187±14 |
| 9 | Propranolol | 1 mg/kg | s.c. | 30 min | 98±7 | 107±8 |
| 10 | Adrenaline +propranolol | | As groups 8 and 9 | | 98±8 | 134±9 |

* Mean of 26-30 determinations. † Mean of 12 determinations.

Blood samples were taken from mice which had been starved for 18 hours. Mice in groups 2-10 were injected i.p. with 4 ml of 0·05% acetic acid in 0·9% saline, and i.v. with 0·2 ml of 0·5% Evans blue in 0·9% saline. Blood samples were taken 1 h later, immediately after the collection of peritoneal fluid.

with the carrageenin (Fig. 3), but (±)-isoprenaline was more potent when given systemically (Fig. 4). This difference in relative potency, depending upon the route of administration was not unexpected, since isoprenaline and adrenaline are absorbed and inactivated at different rates.

In contrast to their effect in the mouse peritoneal cavity, α-adrenoceptor blocking agents showed no anti-inflammatory activity in paw oedema induced by carrageenin. Systemically administered adrenaline appeared to exert its anti-oedema effects through both α- and β-adrenoceptors (Table 4), while the effects of locally injected adrenaline were antagonized by phenoxybenzamine but not substantially affected by propranolol. The oedema-reducing effect of isoprenaline was prevented by propranolol, suggesting an effect mediated via β-adrenoceptors but propranolol (10 mg/kg) did not interfere with the anti-inflammatory activity of

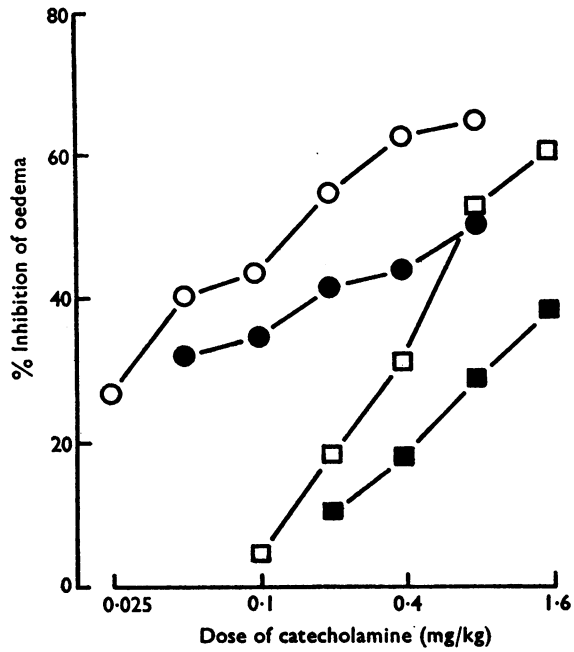


FIG. 4. Anti-inflammatory effect of catecholamines in carrageenin-induced paw oedema. Adrenaline (□——□); noradrenaline (■——■); isoprenaline (○——○), or salbutamol (●——●) in 3 ml of Tyrode solution, were injected i.p. immediately after the subplantar injection of carrageenin.

TABLE 5. *Effect of adrenaline or cortisone on carrageenin-induced paw oedema in normal and bilaterally adrenalectomized mice*

| | Treatment | | Increase in paw weight (mg) | % Inhibition of oedema | *P* compared with |
|---|---|---|---|---|---|
| | Sham-adrenalectomized | | | | |
| (a) | ,, ,, | Control | 71·1±5·3 | — | — |
| (b) | ,, ,, | Adrenaline | 16·0±1·2 | 87·6 | (a) <·001 |
| (c) | ,, ,, | Cortisone | 32·7±3·8 | 56·3 | (a) <·001 |
| | Adrenalectomized | | | | |
| (d) | ,, | Control | 83·7±8·6 | — | (a) N.S. |
| (e) | ,, | Adrenaline | 19·2±1·4 | 87·1 | (b) N.S. |
| (f) | ,, | Cortisone | 27·7±3·8 | 66·9 | (c) N.S. |

Bilateral adrenalectomy was performed 7 days prior to experiment. 0·025 ml of 1% carrageenin in 0·9% saline, with or without adrenaline (5 μg), was injected into the subplantar tissue of the right hind paw. The left hind paw was injected with 0·025 ml of 0·9% saline. Cortisone acetate (20 mg/kg s.c.) was given 12 h before the injection of carrageenin. The paws were amputated and weighed 2·5 h after the injection of carrageenin. N.S. Not significant.

indomethacin (5 mg/kg) or phenylbutazone (200 mg/kg) administered systemically 30 min before the injection of carrageenin.

5-Hydroxytryptamine-induced paw oedema was inhibited by lower doses of adrenaline or isoprenaline than carrageenin-induced oedema (Fig. 3). The effect of adrenaline on 5-hydroxytryptamine-induced oedema was antagonized partly by phenoxybenzamine and partly by propranolol. The effect of isoprenaline was antagonized by propranolol (Table 4).

Bhalla, Sinha, Tangri & Bhargava (1970) found that adrenaline failed to inhibit carrageenin-induced paw oedema in bilaterally adrenalectomized rats. However, in the present experiments, bilateral adrenalectomy did not affect the anti-inflammatory activity of adrenaline in carrageenin-induced paw oedema (Table 5). Bilateral adrenalectomy also failed to prevent the permeability-reducing effect of adrenaline in the mouse peritoneal cavity inflamed by the injection of 0·05% acetic acid. In the mouse, therefore, it seems unlikely that the anti-inflammatory effect of adrenaline is due to the release of corticosteroids.

## Discussion

The antagonistic effect of $\alpha$- and $\beta$-adrenoceptor blocking agents on the anti-inflammatory activity of catecholamines in paw oedema induced by carrageenin or 5-hydroxytryptamine, suggests that at this site catecholamines mediate their effect through both $\alpha$- and $\beta$-adrenoceptors. Blood vessels supplying the skin are very sensitive to the vasoconstrictor effects of adrenaline and it seems likely that the anti-inflammatory effect of adrenaline in the paw is partly due to a decrease in blood flow to the paw.

Conversely, increased vascular permeability in the peritoneal cavity induced by the injection of acetic acid or pro-inflammatory mediators appears to be suppressed by catecholamines acting almost exclusively via $\beta$-adrenoceptors. Thus isoprenaline was more potent than noradrenaline in reducing vascular permeability and the vascular permeability effects of catecholamines were antagonized by $\beta$-adrenoceptor blocking agents but not by $\alpha$-adrenoceptor blocking agents. Doubt has been cast on the specificity of $\beta$-adrenoceptor blocking agents in antagonizing the anti-inflammatory activity of drugs by the report of Riesterer & Jaques (1968) that $\beta$-adrenoceptor blocking agents antagonize the anti-exudative effect of both steroidal and non-steriodal anti-inflammatory drugs in turpentine-induced pleurisy. These observations are in contrast with those of Kellet (1966), Brown, Kissel & Lish (1968), and Northover & Northover (1969), who found that the antagonism of anti-inflammatory activity by $\beta$-adrenoceptor blocking agents is limited to those drugs which are known to activate $\beta$-adrenoceptors. In the present investigation, the specificity of the $\beta$-adrenoceptor blocking agent, sotalol, was indicated by the fact that the (−) isomer of sotalol inhibited the permeability effects of isoprenaline but the (+) isomer at the same dose was inactive. This is in agreement with reports that (−)-sotalol is more active than (+)-sotalol as a $\beta$-adrenoceptor blocking agent (Lish, Weikel & Dungan, 1965). The specificity of $\beta$-adrenoceptor blocking agents was also shown by their failure to antagonize the vascular permeability effects of phenylbutazone, indomethacin, caffeine or aminophylline which are believed to mediate their effects via non-adrenergic mechanisms.

The permeability-reducing effects of catecholamines in the peritoneal vascular bed do not appear to be due to hyperglycaemia, since there was no correlation between blood glucose concentration and the leakage of dye into the peritoneal cavity. The ability of catecholamines to exert an anti-inflammatory effect in bilaterally adrenalectomized animals indicates that the effect is not due to the release of corticosteroids. Since the vascular permeability effects of injected bradykinin, histamine and 5-hydroxytryptamine were antagonized by catecholamines acting on $\beta$-adrenoceptors, it is possible that the $\beta$-adrenoceptor mediated anti-inflammatory effect of catecholamines is due to a direct effect on vascular endothelium.

Majno, Shea & Leventhal (1969) have suggested that endothelial cells respond to pharmacological agents in a manner similar to smooth muscle cells. From electronmicrographs it appears that histamine and similarly acting permeability factors increase vascular permeability by causing endothelial cells to contract and pull apart from one another, thereby forming gaps through which plasma proteins escape. Catecholamines, by activating the adenyl cyclase system, might be expected to cause relaxation of endothelial cells and oppose the contractile activity of pro-inflammatory mediators. Catecholamines exert a similar $\beta$-adrenoceptor mediated effect in the lungs, where they tend to oppose the bronchoconstrictor effects of histamine, bradykinin and 5-hydroxytryptamine (Collier, James & Piper, 1965; Piper, Collier & Vane, 1967). The ability of smooth muscle relaxant drugs to inhibit certain types of inflammation (McKinney & Lish, 1964; 1966) might also be due to antagonism of endothelial contraction.

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