SPECIFICITY OF BLOCKADE OF RENAL RENIN RELEASE BY PROPRANOLOL IN THE CAT

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SUMMARY

1. The anaesthetized cat, unilaterally nephrectomized and with renal nerves sectioned, has been used in a study of the specificity of the inhibitory effect of propranolol on renin release.

2. The effect of (+)-propranolol on the rise in plasma renin activity (PRA) induced by renal nerve stimulation has been examined. When administered at approximately the same dose as the racemic mixture which blocks renin release in response to this stimulus, (+)-propranolol did not significantly reduce the magnitude of the response. Therefore the action of racemic propranolol in blocking the response to neural stimulation can be attributed to the (−)-isomer.

3. Renal artery constriction, producing blood flow changes similar to those resulting from renal nerve stimulation, also induces a rise in PRA. (+)-Propranolol, in amounts which block the rise in PRA observed with renal nerve stimulation, did not prevent the increase seen with renal artery constriction.

4. Reduction of renal perfusion pressure within the autoregulatory range for 20 min resulted in a rise in PRA in all experiments. (+)-Propranolol did not significantly affect the response.

5. It is concluded that the release of renin in response to renal nerve stimulation cannot be attributed to associated changes in renal blood flow. The evidence is compatible with a direct action of the neurotransmitter on renin-containing cells via a β-adrenergic receptor. When renin release is induced by non-adrenergic mechanisms propranolol blockade has no significant effect on the response.

Key words: propranolol, renin, renal nerves, renal perfusion pressure.

In a recent study we observed that on stimulation of the renal nerves there was a close correlation between the timing of the fall in renal blood flow and the rise in plasma renin activity.

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Constriction of the renal artery mechanically, to induce blood flow changes similar in magnitude to those seen with renal nerve stimulation, caused a similar rise in plasma renin activity (PRA). Our results also indicated that administration of propranolol completely blocked the release of renin resulting from stimulation of the renal nerves, without altering the pattern of renal blood flow. It was suggested that renal nerve stimulation might have produced its effect on renin release through some change induced by the reduction in renal blood flow, which was sensitive to and inhibited by propranolol. However, the data presented in our study were insufficient to suggest a clear mode of action of propranolol.

Although there is considerable evidence that propranolol blocks the action of catecholamines (Ueda, Yasuda, Takabatake, Iizuka, Iizuka, Ihori & Sakamoto, 1970; Assaykeen, Clayton, Goldfein & Ganong, 1970; Meurer, 1971; Vandongen, Peart & Boyd, 1973) or renal nerve stimulation (Passo, Assaykeen, Goldfein & Ganong, 1971; Loeffler, Stockigt & Ganong, 1972) on renin release, these studies do not give a clear indication of its mechanism of action. Although the results suggest that propranolol is acting on a typical β-receptor, some published evidence has cast doubt on this interpretation. Winer, Chokshi & Walkenhorst (1971) have reported that both isomers of propranolol could suppress isoprenaline-induced renin release. On the other hand, Reid, Schrier & Earley (1972) have queried the presence of a β-receptor in the kidney as isoprenaline appeared to have a greater effect on renin release when injected intravenously than when injected into the renal artery.

In the present study we have attempted to resolve the question of the importance of changes in renal blood flow in mediating renin release after neural stimulation. We have done this by determining whether propranolol influences the renin-releasing effect of reduction of renal blood flow induced by renal artery constriction. The object of the reduction was to mimic the overall pattern of blood flow change observed with renal nerve stimulation. We have also examined the specificity of the renin-inhibitory effect of propranolol by studying its influence on another stimulus normally associated with renin release, i.e. reduction of renal perfusion pressure within the autoregulatory range of flow. Finally, we have attempted to identify more precisely the receptor which mediates renin release due to renal nerve stimulation by determining whether (+)-propranolol, which does not exhibit typical β-receptor blocking activity, can block the response.

**METHODS**

*General preparations*

Male cats in the weight range 2.7-4.5 kg were anaesthetized with sodium pentobarbitone, 168 μmol/kg intraperitoneally, with further small doses administered intravenously as required. Blood pressure was monitored from the carotid artery with a pressure transducer (Statham P23DiC) connected to a polygraph (Grass model 7). A jugular vein was cannulated to allow administration of drugs. Renal blood flow was measured by means of a non-cannulating flow probe placed on the left renal artery connected to a flowmeter and linked to a pen recorder (Medical and Biological Instrumentation flowmeter and Devices M2 recorder, or S.E. Laboratories M275 flowmeter and Grass Polygraph). The flow probe was calibrated at the end of the experiment by using the excised vessel and saline perfusion. The values given in this report represent saline (154 mmol/sodium chloride solution) equivalents. To convert these into blood
flow the values must be multiplied by a factor of 1.16 (for blood with a typical haematocrit of 44%). Heart rate was monitored with a tachograph (Grass) triggered by the arterial pulse wave. The right kidney was removed retroperitoneally in all experiments and the left kidney exposed similarly.

In order to overcome any fall in blood pressure caused by the administration of propranolol, a cotton thread was passed around the aorta approximately 2 cm below the left renal artery and then passed through a short length of polythene tubing (Portex PP290). The thread could be tightened around the aorta by being pulled up through the polythene tubing by means of a screw device, which enabled a reasonable control of constriction. Heparin (1000 units/kg) was administered intravenously between 30 and 45 min before the first blood sample was removed.

Renal experiments

Renal nerve stimulation. The renal nerves were dissected and prepared for stimulation as described previously (Coote et al., 1972). The distal cut ends of the nerves were placed over silver wire stimulating electrodes. A 10 min period of stimulation was used with square-wave stimuli of 15 V, 15 Hz and 0.2 ms duration available from a stimulator (Grass S8).

Reduction of renal blood flow by renal artery constriction. In all experiments the kidney was denervated by cutting the renal nerves close to their origin from the coeliac ganglion as well as cutting any small nerves observed entering the kidney. A cotton thread was passed around the renal artery, distal to the flow probe, but proximal to the bifurcation of the renal artery. This thread then passed through a short length of polythene tubing (Portex SH90), clamped into position immediately above the artery, and was attached to another screw device similar to that described above. The degree of constriction was adjusted as required by observing changes on the blood flow record.

Reduction of renal perfusion pressure by aortic constriction. The kidney was denervated as described above. A cotton thread was placed around the aorta between 1 and 2 cm above the level of the renal artery and the aorta constricted as indicated above. Renal perfusion pressure was recorded with a pressure transducer (Statham) connected to a cannula (Portex PP90) whose tip was approximately at the level of the renal artery. This cannula was manipulated into position via the femoral artery, or was introduced via the right renal artery prior to removal of the right kidney.

Blood sampling

The first blood sample was taken not less than 2 h after completion of renal denervation. When propranolol was used the first blood sample for PRA estimation was taken at least 30 min after the start of the continuous infusion of propranolol. Blood samples (3-5 ml) were taken from the carotid artery, immediately centrifuged at 0°C and the plasma was removed and stored in the deep freeze at –8°C until required for PRA estimation. In the initial experiments the blood removed for sampling was immediately replaced with an equal volume of blood freshly removed from an anaesthetized donor animal. In the later experiments the blood sample was replaced with the erythrocytes of the previous sample resuspended in 2-2.5 ml of Lomodex 70 (dextran 70 in 154 mmol/l sodium chloride; Fisons). At 30 min before the removal of the first experimental sample, a blood sample (3-5 ml) was removed and centrifuged; the plasma was mixed with 2 ml of Lomodex 70 and reinfused, and the cells were resuspended in Lomodex.
70 and used to replace the first experimental blood sample. Experiments were designed to allow an interval of at least 20 min between two consecutive blood samplings. This procedure permitted the intermittent removal of up to twelve blood samples without significant effect on basal PRA values.

**Assay of renin**

Plasma renin activity was estimated by bioassay of angiotensin I generated on incubation of plasma with an excess of homologous renin substrate by the previously described method (Coote *et al.*, 1972). Results are expressed as pmol of angiotensin I generated h⁻¹ ml⁻¹ of plasma. Changes in PRA are interpreted as reflections of changes in the rate of release of renin from the remaining kidney.

**Infusion solutions**

Both (+)- and (±)-propranolol were dissolved in saline (154 mmol/l sodium chloride solution). The maximum volume used for induction of blockade was 1 ml/kg. When infused continuously, the drugs were injected at the rate of 6 ml/h. In some experiments in animals not receiving a drug, saline was administered in the same manner as was used for propranolol administration. The infusion of these small volumes of saline did not significantly affect either the basal PRA or the magnitude of the response. Drug concentrations are given in the appropriate results section.

**RESULTS**

**Effect of (+)-propranolol on renin release induced by renal nerve stimulation**

These experiments were performed to determine whether the effect of racemic propranolol on the response to renal nerve stimulation previously observed was related to the membrane-stabilizing or other effect possessed by both isomers. The dose selected was 15.4 µmol kg⁻¹, as approximately this amount of the racemic mixture (13.6 µmol kg⁻¹) was previously found to effectively block the renin-releasing effect of renal nerve stimulation. With this dose of the racemic mixture, the effect on the heart rate of an injection of at least 2.89 nmol kg⁻¹ of isoprenaline was completely prevented, whereas normally, before propranolol administration, the response to 0.361 nmol kg⁻¹ (0.1 µg/kg) of isoprenaline was easily observed. With the (+)-propranolol, the heart rate was considerably reduced (by approximately 25 beats/min) after administration of the drug but the response to the same amount of isoprenaline was still observed, though reduced in magnitude.

The (+)-propranolol was given intravenously over 15–20 min. The effect of an injection of isoprenaline (0.361 nmol kg⁻¹) on the heart rate was checked before and after the administration of the (+)-propranolol. The propranolol was then infused continuously at the rate of 15.4 µmol h⁻¹ kg⁻¹ until the end of the experiments, when the heart rate response to isoprenaline (0.361 nmol kg⁻¹) was again checked.

Stimulation of renal nerves, in the manner described, causes a prompt fall in renal blood flow to about one-tenth of that at the start of the stimulation. However, in spite of continued stimulation, flow gradually returns toward control values over the next 8–12 min (see Fig. 1b). PRA values, studied 10 min after the start of stimulation, were always elevated compared with control values (Coote *et al.*, 1972). These experiments have been repeated in the present
FIG. 1. Effect of renal nerve stimulation on (a) plasma renin activity and (b) renal blood flow in the absence and presence of (+)-propranolol. (a) The propranolol (15.4 µmol kg⁻¹) was administered slowly, intravenously, in a volume of 1 ml kg⁻¹. This was followed by a continuous i.v. infusion of the drug (15.4 µmol h⁻¹ kg⁻¹) for the rest of the experiment in a volume of 6 ml h⁻¹. The first blood sample was taken 30 min after the start of the continuous infusion. (b) ○, Without drug; □, with (+)-propranolol. Mean values (± SEM, n=9 in both groups) are shown.
study and compared with results obtained after the administration of (+)-propranolol. Nine experiments were performed in four cats in the absence of the drug, and nine experiments were performed in four other cats in its presence. Each experiment yields three values of PRA: a control value, a value after 10 min of renal nerve stimulation, taken 20 min after the first, and a third, taken 20 min (or 30 min in three instances) after the end of renal nerve stimulation. A maximum of three periods of renal nerve stimulation was performed in any one animal.

The results of these experiments are presented in Fig. 1(a). In all cases, without (+)-propranolol, there was a rise in PRA after 10 min of renal nerve stimulation. The individual increases over control values ranged from 150% to 1037%, with a mean increase of 423%. This variation in response is attributed, in part, to variation from animal to animal in the number of renal nerve fibres which can be placed on the stimulating electrodes and also to the fact that the blood sample was taken after exactly 10 min of nerve stimulation whether the blood flow had returned to prestimulation level or not. The mean PRA rose from 3.51 pmol h⁻¹ ml⁻¹ (SEM 0.60, n=9), before stimulation, to 15.2 pmol h⁻¹ ml⁻¹ (SEM 1.59, n=9) at the end of the stimulation period, with a fall to 5.79 pmol h⁻¹ ml⁻¹ (SEM 0.78, n=9), 20 (or 30) min later.

The administration of (+)-propranolol generally resulted in a small fall in blood pressure which was effectively counteracted by constriction of the aortic loop below the origin of the renal artery. The mean blood pressure before the start of stimulation in these experiments was 103 mmHg, compared with 105 mmHg in those performed without the drug. (+)-Propranolol did not affect the basal renal blood flow under the conditions of these experiments, nor was there any apparent modification in the responses in renal blood flow produced by stimulation of renal nerves (Fig. 1b).

PRA in these experiments rose in response to 10 min of renal nerve stimulation (Fig. 1a). The individual increases over the prestimulation level ranged from 92% to 1792%, with a mean of 498%. In this group of tests, the mean PRA rose from 1.39 pmol h⁻¹ ml⁻¹ (SEM 0.16, n=9) before stimulation, to 8.10 pmol h⁻¹ ml⁻¹ (SEM 2.00, n=9) after stimulation, with a fall to 2.09 pmol h⁻¹ ml⁻¹ (SEM 0.27, n=9) 20 min later.

The mean prestimulation PRA values in the (+)-propranolol-treated animals were significantly lower than the equivalent values obtained in the animals not receiving the drug (3.51 versus 1.39, P<0.02), suggesting that the (+)-propranolol had an inhibitory effect on the basal level of renin secretion from the denervated kidney. However, as PRA was not estimated in these animals before the administration of propranolol, it cannot be concluded with certainty that this difference in basal levels is not due to animal variability. The response to renal nerve stimulation was quantitatively smaller than it was without the drug, although in terms of percentage increase over prestimulation level it was not significantly different (mean increase of 423% versus 498%, P>0.7). It is possible that the observed modest attenuation in the rise in PRA may be due to the high dose of (+)-propranolol, which will have some β-adrenergic action.

Effect of (+)-propranolol on the response to reduction in renal blood flow by renal artery constriction

When renal blood flow is reduced by constriction of the renal artery to mimic the effects of renal nerve stimulation, a comparable rise in PRA is observed (Coote et al., 1972). The present experiments were designed to examine whether the mechanism involved in this renin release after mechanical reduction of renal blood flow is similar to that of nerve stimulation by deter-
Fig. 2. Effect of renal artery constriction on (a) plasma renin activity and (b) renal blood flow before and after propranolol blockade. (a) (+)-Propranolol (9.95-13.6 µmol kg⁻¹) was administered slowly, intravenously, in a volume of 1 ml kg⁻¹. This was followed by a continuous i.v. infusion of the drug (13.6 µmol h⁻¹ kg⁻¹) for the rest of the experiment in a volume of 6 ml h⁻¹. The first blood sample was taken 30 min after the start of the continuous infusion. For details of the test for confirmation of β-receptor blockade see text. (b) Mean values (±SEM, n = 6 in both groups) are shown. ●, Without drug; ○, with (+)-propranolol.

mining whether the response can be inhibited by propranolol blockade. After a momentary stoppage of blood flow, the flow rate was held at one-tenth of the control rate for 2 min. Flow was gradually allowed to return over approximately the next 8 min until the constriction was fully removed (Fig. 2b). Blood samples were taken 10 min before the start of the constriction, 10 min after the start of constriction and 20 min after the end of constriction. In this group of experiments, one or two periods of artery constriction were carried out to obtain PRA responses in the absence of the drug; propranolol was then administered and a further one or two periods of artery constriction were undertaken. Before administration of propranolol the
increase in heart rate in response to isoprenaline (0.361 nmol kg\textsuperscript{-1}) was recorded; blockade was then induced by the gradual intravenous injection of propranolol over the next 15–20 min. The amounts of propranolol used varied from 9.95 µmol kg\textsuperscript{-1} to 13.6 µmol kg\textsuperscript{-1}. In all cases it was confirmed that the effect of 3.61 nmol kg\textsuperscript{-1} of isoprenaline on the heart rate was blocked. Immediately after blockade was confirmed, a further infusion of 13.6 µmol h\textsuperscript{-1} kg\textsuperscript{-1} was commenced and continued until the end of the experiment, when effectiveness of the blockade was again checked. The mean blood pressure before the start of renal artery constriction was 118 mmHg in the experiments performed before the administration of propranolol and 106 mmHg after the administration of propranolol. Renal blood flow was not affected by the administration of propranolol in these experimental conditions. Modest rises in systemic blood pressure were observed during renal artery constriction in all experiments, reaching a mean increase of 20 mmHg by the end of the constriction period. The values had generally returned to pre-constriction levels when the post-constriction blood sample was taken.

The results of the effect of renal artery constriction on PRA before and after propranolol blockade are presented in Fig. 2(a). Twelve experiments were carried out in five cats. In the absence of propranolol, PRA rose from a mean of 2.18 pmol h\textsuperscript{-1} ml\textsuperscript{-1} (SEM 0.42, n=6) to 15.4 pmol h\textsuperscript{-1} ml\textsuperscript{-1} (SEM 3.81, n=6) after 10 min constriction and 20 min later had fallen to 3.51 pmol h\textsuperscript{-1} ml\textsuperscript{-1} (SEM 0.60, n=6). There was a wide variation in response of the animals, PRA after 10 min of constriction ranging from 3.89 to 32.2 pmol h\textsuperscript{-1} ml\textsuperscript{-1}. Administration of propranolol (with the precaution described to maintain renal perfusion pressure) had no significant effect on the base-line values of PRA in these experiments. Before constriction the mean value was 2.80 pmol h\textsuperscript{-1} ml\textsuperscript{-1} (SEM 0.81, n=6), which rose to 13.0 pmol h\textsuperscript{-1} ml\textsuperscript{-1} (SEM 2.37, n=6) and fell to 4.31 pmol h\textsuperscript{-1} ml\textsuperscript{-1} (SEM 1.10, n=6) 20 min later. Although there was considerable variation in response, it was not as large as in the experiments in the absence of the drug, PRA 10 min after the start of constriction ranging from 5.82 to 23.5 pmol h\textsuperscript{-1} ml\textsuperscript{-1}. However, the mean values of PRA observed after 10 min of renal artery constriction are very similar in both groups of experiments (P>0.3).

The stability of the basal PRA and reproducibility of the responses in a typical set of experiments is illustrated in Fig. 3, in which two renal artery constrictions were performed before, and two after, the administration of propranolol. Fig. 3 includes details about timing of the procedures, and the changes in blood pressure, heart rate and renal blood flow observed before and after induction of \(\beta\)-receptor blockade.

**Effect of (±)-propranolol on the response to reduction in renal perfusion pressure within the autoregulatory range**

These experiments were performed to determine whether propranolol could block the release of renin induced by a mechanism which involved neither stimulation of renal nerves nor reduction in renal blood flow. Experiments were carried out in which renal perfusion pressure was reduced to 100 mmHg and held at this value for 20 min. The object of the procedure was to study the effect of a fall in renal perfusion pressure of approximately 25 mmHg. In order to do this it was occasionally necessary to raise the blood pressure before the experiment by constriction of the aortic loop below the renal artery. This was done at least 20 min before the experiment. In several instances up to three experiments were performed in an animal either entirely in the absence of, or entirely in the presence of, propranolol. In other cases, one or two experiments were performed before propranolol administration, and then a further one or two
Renin release and propranolol blockade

(a) Before propranolol

<table>
<thead>
<tr>
<th>Blood pressure (mmHg)</th>
<th>98</th>
<th>88</th>
<th>120</th>
<th>100</th>
<th>88</th>
<th>113</th>
<th>88</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
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<td>185</td>
<td>160</td>
<td>180</td>
<td>185</td>
<td>165</td>
<td>175</td>
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<tr>
<td>Renal blood flow (ml/min)</td>
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<td>24</td>
<td>27</td>
<td>26</td>
<td>30</td>
<td>27</td>
<td>27</td>
</tr>
</tbody>
</table>

Renal blood flow is expressed as saline equivalents (see the Methods section). Solid blocks indicate periods of constriction of the renal artery. In the tests of effects of isoprenaline, doses of isoprenaline used were: test 1, 0.361 nmol kg\(^{-1}\); test 2, 3.61 nmol kg\(^{-1}\); test 3, 3.61 nmol kg\(^{-1}\).

(b) After propranolol

<table>
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<tr>
<th>Blood pressure (mmHg)</th>
<th>88</th>
<th>75</th>
<th>75-88</th>
<th>90</th>
<th>122</th>
<th>88</th>
<th>87</th>
<th>130</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
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<td>160</td>
<td>160</td>
<td>175</td>
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<td>165</td>
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<td>150</td>
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<td>Renal blood flow (ml/min)</td>
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<td>27</td>
<td>24</td>
<td>25</td>
<td>25</td>
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<td>26</td>
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</table>

**FIG. 3.** Effect of renal artery constriction (a) before and (b) after (±)-propranolol blockade. Sequential responses in one cat are presented. Heparin and propranolol were given in a volume of 1 ml kg\(^{-1}\); saline and propranolol infusions were given in a volume of 6 ml h\(^{-1}\). Renal blood flow is expressed as saline equivalents (see the Methods section). Solid blocks indicate periods of constriction of the renal artery. In the tests of effects of isoprenaline, doses of isoprenaline used were: test 1, 0.361 nmol kg\(^{-1}\); test 2, 3.61 nmol kg\(^{-1}\); test 3, 3.61 nmol kg\(^{-1}\).

Experiments performed. Propranolol blockade was confirmed by the isoprenaline test as described in the previous section. The amount of propranolol used was between 10.3 and 13.6 \(\mu\)mol kg\(^{-1}\). A continuous infusion of 13.6 \(\mu\)mol h\(^{-1}\) of the drug was begun immediately after blockade was confirmed. The mean pressure before the start of the experimental fall to 100 mmHg was induced at the kidney was 126 mmHg in the absence of propranolol and 125 mmHg in the presence of propranolol blockade. Renal blood flow was not affected by the administration of propranolol in these experiments.

Fifteen experiments were performed in five animals, seven in the absence of propranolol and
Fig. 4. Effect of reduction of renal perfusion pressure, within the autoregulatory range, on PRA and the influence of (±)-propranolol on this response: (a) control; (b) with (±)-propranolol. Propranolol was administered as described in Fig. 2(a). The broken lines indicate results obtained from four experiments in one animal, two before and two after induction of propranolol blockade.

eight in its presence. Blood samples were taken 5 min before the reduction in perfusion pressure was started, after 20 min of reduced perfusion pressure and 20 min after the end of the period of reduced renal perfusion pressure. In all experiments changes in renal blood flow immediately after reduction of renal perfusion pressure to 100 mmHg were slight (no more than 5–10% of the total renal blood flow), and of a transitory nature due mainly to the lag in autoregulatory response. Otherwise renal blood flow was steady throughout the period of constriction, with occasional small, slow upward or downward drifts as are also seen at normal pressures.

The effect of reduction of renal perfusion pressure on PRA is illustrated in Fig. 4. It is evident that this is a much smaller stimulus to renin release, as assessed by the change in PRA, than the other experimental procedures included in the present study. For this reason, results have also been considered in terms of the absolute or percentage increase above base-line activity in each individual experiment. These experiments show that at the end of a 20 min period of reduced renal perfusion pressure there was a rise in PRA whether propranolol was administered or not. The response was demonstrated in all cases regardless of the initial PRA. In one animal with a high initial PRA two experiments were performed before and two after the administration of propranolol (illustrated by the broken lines in Fig. 4). The increases in PRA in these tests are comparable. In all the experiments, the mean absolute increase in PRA over respective control activities was 1.41 pmol h⁻¹ ml⁻¹ in the absence of propranolol compared with 1.43 pmol h⁻¹ ml⁻¹ in the propranolol-blocked animal. These changes represent a mean increase of 128% over initial values in the experiments performed without propran-
olol as compared with a mean increase of 159% in the propranolol-blocked animals. The effects in propranolol-blocked animals were not significantly different from those obtained in untreated animals whether they are expressed in terms of absolute increase \((P>0.95)\) or percentage increase \((P>0.99)\). Twenty minutes after the pressure was allowed to revert to normal the PRA values were 16% above control value in the untreated animals and 14% above control value in the propranolol-blocked animals.

**DISCUSSION**

In the present investigation we have found that (+)-propranolol was hardly effective in attenuating the rise in PRA observed after renal nerve stimulation. Thus it cannot be responsible for the complete blockade of the renin-releasing effect of renal nerve stimulation which we observed previously with (±)-propranolol. The results indicate that this effect must be attributable to the (−)-isomer, which possesses typical β-blocking activity (Fitzgerald, 1969). The present experiments do not support the report of Winer, Chokshi & Walkenhorst (1971) that (+)-propranolol was as effective as (±)-propranolol in blocking the response to isoprenaline. A similar conclusion to the present one was reached by Tobert, Slater, Fogelman, Lightman, Kurtz & Payne (1973), who reported that racemic propranolol inhibited the rise in PRA in response to orthostatic stress in man whereas (+)-propranolol had no significant effect.

The information obtained in the present study may be used to reassess the effect of renal nerve stimulation. This stimulus resulted in a rise in PRA and a fall in renal blood flow, and (±)-propranolol completely blocked the rise in PRA but had no effect on renal blood flow (Coote et al., 1972). The present report indicates that when the renal artery is constricted to mimic the flow changes observed with neural stimulation, (±)-propranolol did not significantly inhibit the resulting rise in PRA. Clearly two different stimuli must be mediating the renin release induced by these two procedures. The present results rule out the previous suggestion that the release of renin in response to renal nerve stimulation was related to some consequence of the reduction in renal blood flow produced by this stimulus. As propranolol only inhibited the response to the stimulus which was associated with catecholamine release, and as the renin-inhibiting effect is possessed only by the (−)-isomer, the likeliest explanation for the action of the renal nerves is that the transmitter is acting on the renin-containing cells through a β-adrenergic receptor. The receptor may also respond to α-receptor blockers, although there is some controversy on this point (Assaykeen et al., 1970; Passo et al., 1971; Winer et al., 1971).

In our previous study we found that phentolamine blocked the blood flow and PRA responses to renal nerve stimulation (Coote et al., 1972). In view of the timing of our sampling, it is possible that the lack of effect of nerve stimulation on blood flow, in the presence of phentolamine, may have resulted in an earlier release of renin which was not detected. This point merits further investigation.

Regarding the stimulus to renin release when blood flow is reduced by renal artery constriction, a current view suggests that the stimulus is mediated by a change in sodium load and/or transport at the macula densa (Vander & Carlson, 1969). However, the present results indicate that this is unlikely. If it is accepted that renal nerve stimulation leads to renin release by an action of transmitter on the renin-containing cells, and not by the accompanying fall in blood flow with associated reduction in sodium transport at the macula densa, then it is unlikely that a comparable reduction in sodium transport produced by renal artery constriction will mediate
renin release by this mechanism. A more likely explanation would appear to be related to a local baroreceptor mechanism operating at the afferent arterioles (Tobian, 1960). An evaluation of this suggested mechanism has been reported by Eide, Løyning & Kill (1973), who found a close relation between renin release and degree of afferent arteriolar dilatation produced by stepwise reduction in renal perfusion pressure. They observed no further increase below the autoregulatory range. Such a mechanism could, at least in part, be responsible for renin release observed during the renal artery-constriction experiments. This mechanism would, presumably, not be operating during renal nerve stimulation when the afferent arterioles are constricted.

Several mechanisms may be mediating renin release during reduction of renal perfusion pressure within the autoregulatory range. Reduction in perfusion pressure within this range leads to a reduction in urinary sodium excretion (Selkurt, 1951), which is probably associated with a reduction in sodium load at the macula densa. Vander & Miller (1964) have reported that they could reverse the renin-releasing effect of reduction of renal perfusion pressure to about 90 mmHg with diuretics. They concluded that their stimulus was acting at the macula densa and that the diuretics were reversing this action by increasing the amount of sodium delivered to the macula densa. Eide et al. (1973) have recently re-examined this point. Their results suggest that the macula densa may be mediating the rise in PRA seen during modest reductions in perfusion pressure such as those used by Vander & Miller (1964) and by us in the present experiments, but that at lower pressures a baroreceptor mechanism may predominate.

Although the present experiments do not indicate the mechanism by which renin is released after reduction of renal perfusion pressure or flow, it is clear that the response to these non-adrenergic stimuli cannot be inhibited by propranolol. Another non-adrenergic stimulus to renin release which is not blocked by propranolol is the administration of furosemide (Johns & Singer, 1973). The demonstration that the inhibitory effect of (+)-propranolol on the response to renal nerve stimulation cannot be attributed to the (+)-isomer clearly indicates the importance of the β-adrenergic mechanism in mediating renin release.

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REFERENCES


Renin release and propranolol blockade


