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SOME ACTIONS OF ISOPRENALINE AND ORCIPRENALINE ON PERFUSED CAT KIDNEYS

BY

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Small doses of (±)-isoprenaline (0.5 to 1.0 μg) given subcutaneously to rats (150 to 200 g body weight) decreased the rates of urinary excretion of water (Botting & Lockett, 1961), sodium and potassium (Botting, Farmer & Lockett, 1961), chloride, ammonia and hydrogen ion (Farmer & Lockett, 1961) during the first hour of water diuresis. The qualitatively similar but greater effects of larger subcutaneous doses of isoprenaline (2 to 4 μg) were accompanied by measurable decrease in the clearance of inulin (Farmer & Lockett, 1961) whereas those caused by smaller doses were not. The sympathetic β-receptor blocking drug pronethalol (1 mg per rat, intramuscularly) was itself without action during water diuresis and completely antagonized the antidiuretic and vascular actions of 2 μg of (±)-isoprenaline (Lees & Lockett, 1963).

Our present purpose has been to test the assumption that the β-receptors through which isoprenaline causes these urinary changes are sited in the kidney and to discover whether these changes are due solely to a renal vascular action of the drug. Cat isolated perfused kidneys have been used for these purposes. In addition, the renal actions of a second β-receptor blocking drug, orciprenaline (Alupent), have been compared with those of (±)-isoprenaline.

METHODS

Twenty-eight heart-lung-kidney preparations were made in spinal animals as described by Davey & Lockett (1960) and Lockett & Roberts (1963). Blood used to fill the perfusion circuit was obtained from male, female or neutered spinal animals and contained 50 mg of creatinine hydrochloride and 1,000 U of heparin per 100 ml. Osmotic diuresis was induced, when required, by infusion of 0.9% saline containing 20 g of mannitol and 40 mg of creatinine hydrochloride per 100 ml. at a rate of 48 ml./hr until the minute volume of urine had risen to the required level, maintained by an infusion rate of 6 to 12 ml./hr.

Functional renal dead space was measured during mannitol diuresis as the accumulated weight of the serial samples which emerged from the ureteric cannula after release of an obstruction of 2.75 min duration and which preceded a fall in the ratio of urine sodium to plasma sodium concentration divided by the ratio of urine creatinine to plasma creatinine concentrations (de Lima & Lockett, 1963).

Chemical procedures. Concentrations of sodium, potassium and creatinine in urine and plasma were estimated as described by Davey & Lockett (1960). The *p*H of urine samples was measured by means of a

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Stadie glass electrode and Pye *p*H-meter. No corrections have been made for renal and ureteric dead space in estimates of renal clearance and electrolyte excretion.

Drugs. (±)-Isoprenaline hydrochloride (Winthrop Laboratories, New York), (±)-orciprenaline sulphate (Alupent, Boehringer Ingelheim) and pronethalol hydrochloride (Alderlin, I.C.I.) were freshly dissolved in 0.9% saline shortly before use.

The resulting solutions were added to the blood in the vencus reservoir. Doses refer tc the salts.

RESULTS

Actions of isoprenaline and orciprenaline on cat kidneys perfused at constant temperature and pressure

Cat kidneys perfused at constant temperature and pressure from heart-lung circuits usually attained almost steady levels of blood and urine flow and of creatinine clearance (glomerular filtration rate) within an hour. Thereafter, the addition of isoprenaline (0.3 to 1.0 μg/150 ml.) to the circulating blood produced an immediate increase in the renal blood flow and inhibition of ureteric peristalsis (Figs. 1, 2 and 3). The maximum renal blood flow was reached in 3 to 5 min and was maintained for 5 to 15 min before declining gradually to reach the baseline in a further 15 to 30 min. Pelvic and ureteric peristalsis re-appeared as the renal blood flow declined. An increase in renal blood flow was always accompanied by a decrease in glomerular filtration rate and antidiuresis. Occasionally a transient slight initial polyuria preceded the antidiuresis. Restoration of the urine flow and of the glomerular filtration rate synchronized with the fall of the renal blood flow back to baseline and was almost always complete when the concentration of isoprenaline used

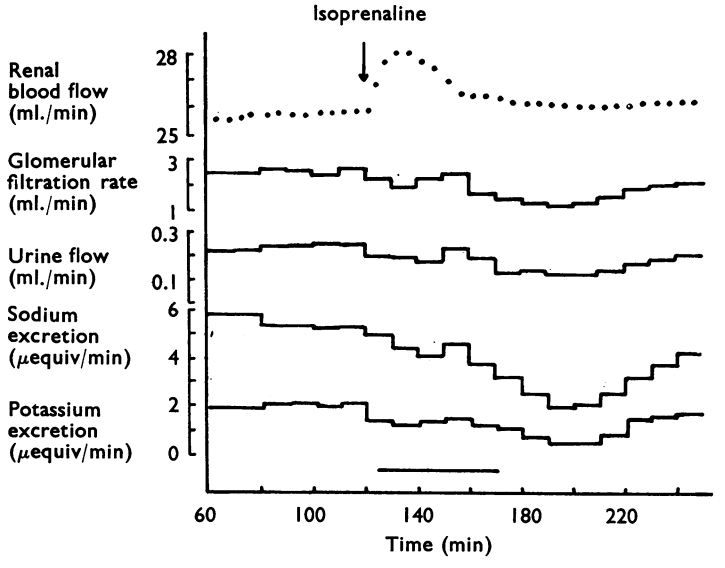

Fig. 1. The diphasic action of isoprenaline on a cat kidney, 8.4 g, perfused at 36° C and 120 mm Hg with blood from a heart-lung circuit. Ordinates from above down: renal blood flow (ml./min); creatinine clearance (glomerular filtration rate, ml./min); urine flow (ml./min); rates of urinary excretion of sodium and potassium (μequiv/min). Abscissa: time in minutes from the start of the perfusion. At the arrow, 1.0 μg cf isoprenaline was added to 150 ml. of circulating blood. The horizontal line indicates the duration of inhibition of pelvic peristalsis.

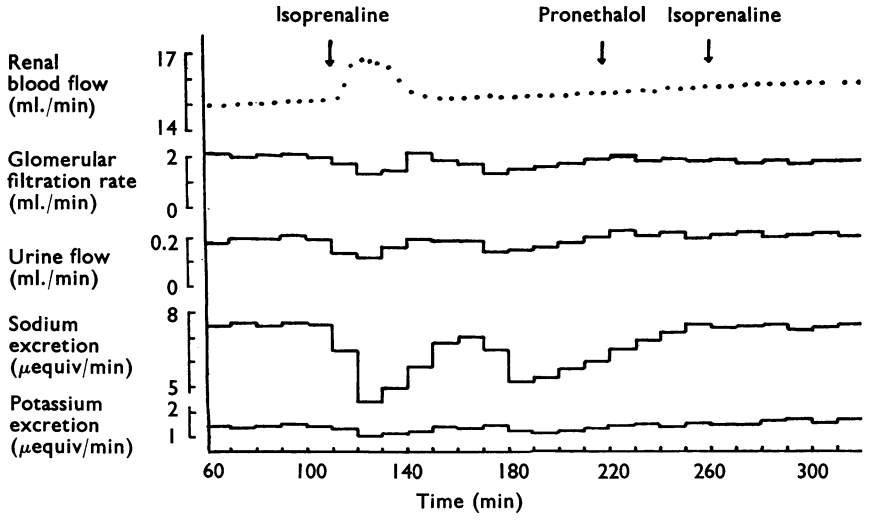

Fig. 2. The action of isoprenaline (0.3 μg/150 ml. of blood) is prevented by 20 μg of pronethalol. The graph shows results from an experiment on a cat kidney, 6.2 g, perfused at 37° C and 116 mm Hg with blood from a heart-lung circuit. Ordinates and abscissae, as in Fig. 1. At the first and third arrows, isoprenaline hydrochloride and, at the second arrow, the inhibitor, were added to the blood in the venous reservoir.

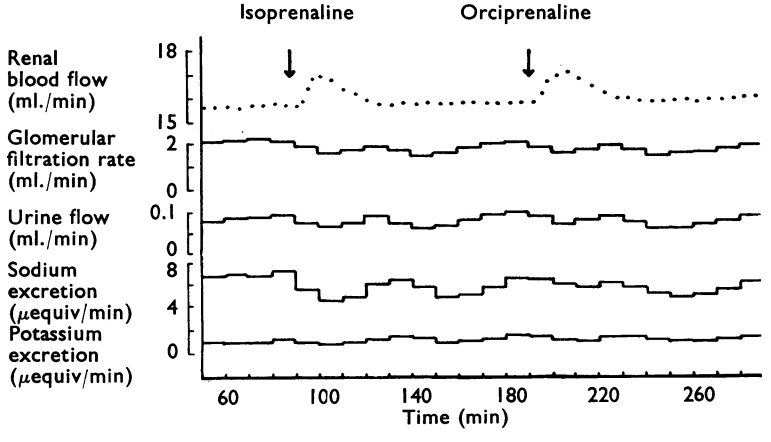

Fig. 3. The actions of isoprenaline (0.3 μg/150 ml. of blood) (first arrow) are equal to those of 1.0 μg of orciprenaline (second arrow) on a cat kidney, 7.2 g, perfused at 37° C and 121 mm Hg from a heart-lung circuit. Ordinates and abscissae as in Fig. 1. The heart was driven at a constant rate of 162 beats/min by impulses of 0.75 msec duration and 6 V delivered through electrodes lightly screwed to the right auricular appendage throughout.

did not exceed 0.3 μg/150 ml. of blood (Figs. 2 and 3). Then, within 5 or 10 min, a second phase of antidiuresis began; the glomerular filtration rate fell, but the renal blood flow remained unchanged. The peak intensity of this second phase was reached in 20 to 30 min and was maintained for 10 to 30 min before it gradually lessened. Restoration of the urine flow and glomerular filtration rate proceeded in parallel over 30 to 80 min

(Figs. 1, 2 and 3). The higher the concentration of isoprenaline used the greater the duration of this second phase of antidiuresis. Complete separation of these two phases of antidiuresis occurred only at low concentrations of isoprenaline: at higher concentrations, 0.6 to 1.0 μg/150 ml., the second phase usually tended to merge with the first because its onset preceded recovery from the action of the drug on total renal blood flow. Rhythmic ureteric peristalsis was maintained throughout the second antidiuretic phase.

Concentrations of sodium and potassium in the urine usually remained unchanged throughout both phases of antidiuresis: occasionally they rose during the second phase but by less than 10%. The *p*H of the urine also tended to rise during this phase but rarely by more than 0.4 units.

Pronethalol (20 μg/150 ml.) did not induce change in any of the parameters of renal function under study but prevented all the actions of isoprenaline hydrochloride (0.3 μg/150 ml. of blood) (Fig. 2).

The actions of orciprenaline on the perfused kidney were qualitatively indistinguishable from those of isoprenaline; 0.6 and 2.0 μg had equal action to 0.3 and 1.0 μg of isoprenaline respectively (Fig. 3).

The actions of isoprenaline hydrochloride and orciprenaline on the cat kidney during osmotic diuresis

The renal actions of isoprenaline and of orciprenaline were not essentially altered by osmotic diuresis (Fig. 4). In general, however, the separation of the antidiuretic effect of these drugs into two distinct phases tended to be more clearly demonstrable under these

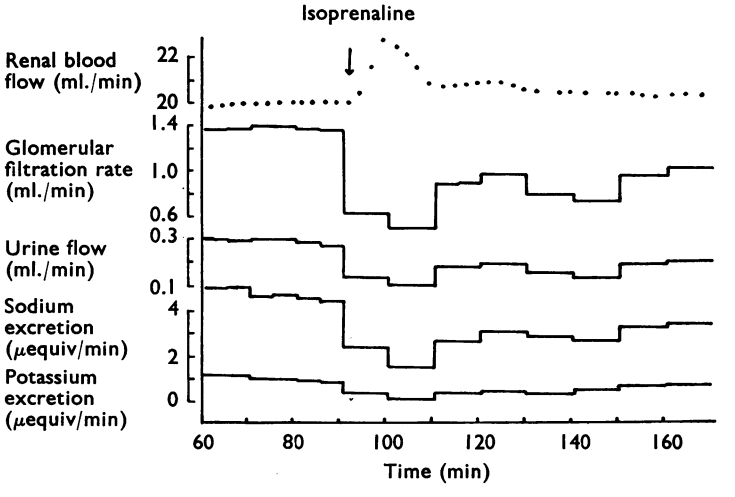

Fig. 4. The diphasic renal action of isoprenaline during mannitol diuresis. The graph shows results from an experiment on a cat kidney, 7.8 g, perfused at 37° C and 108 mm Hg from a heart-lung circuit. Ordinates and abscissae as in Fig. 1. At the arrow, isoprenaline (0.6 μg/150 ml. of blood) was added.

conditions. The functional renal dead space, measured by ureteric stop-flow analysis, was not significantly altered by isoprenaline (1 μg/150 ml. of blood) during either antidiuretic phase (see Methods).

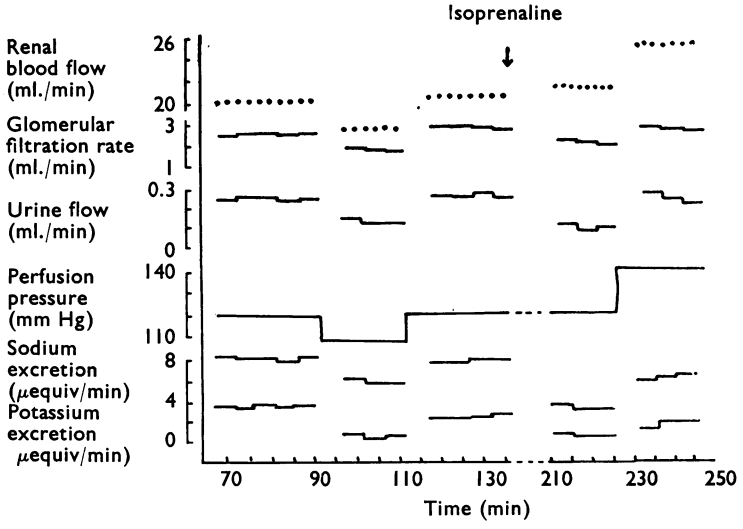

Fig. 5. Isoprenaline causes a fall in filtration rate which outlasts the action of the drug on renal blood flow: restoration of the filtration rate at this stage by increase in perfusion pressure results in a renal blood flow greater than control and restoration of the urine flow. The graph shows results of an experiment on a cat kidney at a steady level of mannitol diuresis, 5.9 g, perfused at 36.5° C at varied pressures. Ordinates from above down: renal blood flow (ml./min); glomerular filtration rate (ml./min); perfusion pressure (mm Hg); urine flow (ml./min); rates of urinary excretion of sodium and potassium. Abscissa as in Fig. 1. At the arrow, 1.0 μg of isoprenaline was added to 150 ml. of blood.

Fig. 5 demonstrates that restoration of the rate of urine flow to control levels by raising the perfusion pressure caused restoration of glomerular filtration rate during the second phase of antidiuresis. The resultant total renal blood flow then greatly exceeded control values: the filtration fraction was greatly reduced.

DISCUSSION

Very low concentrations of isoprenaline, 0.3 to 1.0 μg/150 ml. of blood, immediately decreased the vascular resistance of the kidney; consequently, the blood flow through the kidney increased since all were perfused at constant pressure. The vasodilation effecting these changes will probably prove to be cortical rather than medullary since the glomerular filtration rate fell but the concentrating processes in the kidney were not measurably altered (Wirz, Hargitay & Kuhn, 1951). Such changes might result from dilatation of the efferent glomerular arterioles alone. The duration of the vascular action and of inhibition of ureteric peristalsis synchronized with the duration of the action of isoprenaline on the cat heart-lung preparation (Lockett, 1957).

The second, more prolonged, reduction in the filtration rate, dissociated from the vascular actions of the drug, was clearly related in duration to the dose of isoprenaline used. Since at constant perfusion pressure the concentrations of sodium and potassium in the urine remained almost unchanged throughout this phase and were also unchanged when the filtration rate was artificially restored by increase in the perfusion pressure (Fig. 5), it is

probable that the drug influenced the structure of the membrane filters of the glomeruli, and the testing of this hypothesis is well advanced.

The prolonged actions of very low concentrations of isoprenaline on cat kidneys perfused from heart-lung circuits accord with the prolonged urinary changes induced in conscious rats by subcutaneous injections of isoprenaline (2 to 4 μg/150 g body weight) (Botting & Lockett, 1961; Botting *et al.*, 1961). The urinary changes caused by the action of isoprenaline on the perfused kidney are not, however, identical with those produced in conscious rats, for isoprenaline failed to influence the concentration of sodium in the urine excreted by the isolated kidney, but decreased the sodium concentration in the urine of these rats. This difference is attributed to some extrarenal influence of the drug.

SUMMARY

1. Some effects of isoprenaline and orciprenaline have been demonstrated on cat kidneys perfused at constant temperature and pressure in heart-lung preparations.

2. Isoprenaline (0.3 to 1.0 μg/150 ml. of blood) immediately increased the renal blood flow, decreased rates of filtration, urine flow and urinary excretion of sodium and potassium, and inhibited pelvic peristalsis. These immediate effects declined as the blood flow returned to control level in 15 to 30 min.

3. A second phase of antidiuresis accompanied by reduction in rates of filtration and of excretion of sodium and potassium began after (0.3 μg) or shortly before (1.0 μg of isoprenaline) restoration of control blood flow. Restoration of the resting levels of urine flow and rates of filtration and electrolyte excretion was achieved during this second phase, which lasted 30 to 90 min, by raising the perfusion pressure. Renal blood flow then exceeded the control.

4. Osmotic diuresis did not prevent the diphasic effects of isoprenaline.

5. The renal changes induced by 1.0 and 2.0 mg of orciprenaline were qualitatively similar to and equal to those of 0.3 and 0.6 μg of isoprenaline respectively.

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