Different effects of dopamine and dopexamine on the isolated perfused rat kidney

K. Kirchhoff, M. Leuwer, P. Thum, A. Bornscheuer and S. Piepenbrock

Department of Dermatology and Department of Anaesthesiology, Medical School, OE 6601, Ricklingerstraße 5, D-30449, Hannover, FRG

*Corresponding author

We have investigated the effect of dopamine and dopexamine on the isolated perfused rat kidney. After an equilibration period of 20 min and two control periods of 10 min, dopexamine 1.0, 2.5 or 4.0 μg kg⁻¹ min⁻¹ or dopamine 2.0 μg kg⁻¹ min⁻¹ were perfused for a further 40 min in random order. Renal blood flow, urine volume, glomerular filtration rate, absolute sodium excretion and fractional sodium reabsorption of the isolated perfused kidney were measured every 10 min during the experiment. Dopamine increased significantly urine production from mean 61.54 (SEM 4.7) to 117.2 (9.7) μl min⁻¹ g⁻¹ and absolute sodium excretion from 0.4 (0.1) to 1.2 (0.1) mmol min⁻¹ g⁻¹, and decreased significantly fractional sodium reabsorption from 97.3 (0.5) to 90.7 (0.7)%. Renal blood flow and glomerular filtration rate were not altered. In contrast, dopexamine had no effect on the isolated kidney. These data suggest that the diuretic and natriuretic effects of dopexamine in humans may not result from a direct action on the kidney.

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Dopamine is a dopamine analogue (Fig. 1) which was developed for i.v. treatment of heart failure and low cardiac output states. Its mild inotropic effects are thought to arise from cardiac β₂ adrenoceptor stimulation and noradrenaline reuptake block. In addition, studies in animals and critically ill patients suggest that dopexamine causes a specific increase in splanchnic and renal blood flow as a result of β₂ and dopamine-1 (DA1) receptor agonism. In contrast, in isolated rat kidney, isolated rat pulmonary artery and isolated rat aorta experiments, in addition to DA1 receptor agonism, dopexamine produced a marked α adrenoceptor effect. If these results are applicable to humans, dopexamine should cause systemic vasodilatation in addition to a specific increase in splanchnic and renal blood flow. The reported benefit of dopexamine in patients with renal impairment (e.g. decreased necessity for haemodialysis) may be the net result of improvement in cardiac function together with systemic and splanchnic vasodilatation. In addition, a specific intrarenal effect, increasing diuresis, is possible.

In this study, we have investigated clinically relevant dopexamine concentrations compared with dopamine in an isolated perfused maximum vasodilated rat kidney model.

Materials and methods

Chemicals

Dopamine was purchased from Giuliani Pharma GmbH, FRG and dopexamine (Dopacard) from Fisons Pharmaceuticals, Sweden AB. Thiopental was obtained from Byk Gulden (Konstanz, FRG) and heparin from Hoffmann-La Roche (Grenzach-Wyhlen, FRG). The perfusion medium used was a modification of that reported by Schurek and colleagues and consisted of physiological saline (mmol litre⁻¹: sodium chloride 107.8; potassium chloride 27.5; magnesium chloride 2.1; sodium bicarbonate 27.5; sodium phosphate 0.9; pH 7.4), inulin 1 mg ml⁻¹ (Laevosan), urea 6 mmol litre⁻¹, D-glucose 7.6 mmol litre⁻¹, a mixture of amino acids (Aminoplasmal paed, Braun, Melsungen, FRG), pyruvate 0.3 mmol litre⁻¹, glutamate 0.4 mmol litre⁻¹, ketoglutarate 0.8 mmol litre⁻¹, L-lactate 2.1 mmol litre⁻¹, malate 1 mmol litre⁻¹ and BSA 50 g litre⁻¹ (fraction V, Serva, Heidelberg, FRG). Temperature was maintained at 37.5°C. All chemicals were of analytical grade and purchased from local suppliers.

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Effects of dopamine and dopexamine on the isolated rat kidney

Preparation and perfusion of the isolated rat kidney

Preparation and perfusion of the isolated rat kidney has been described previously. Preparation and perfusion procedure was performed according to the basic description of Schurek and colleagues with some modifications.

Kidneys were obtained from male Wistar rats (250–300 g body weight), anaesthetized with thiopental 100 mg kg⁻¹ i.p. and placed on a heated operating board to maintain body temperature near 38°C. The abdomen was opened by a midline incision and the intestines were moved to the left side and covered with moist saline pads. A small catheter (PE, od 0.6 mm) was inserted into the right ureter for urine collection and the ureter was cut below the catheter. Loose ligatures were placed around the aorta below the left renal artery and above the mesenteric artery. The suprarenal artery was ligated and tied off. In addition, loose ligature threads were placed around the left renal vessel and the mesenteric artery. Heparin 875 u. kg⁻¹ was injected into the liver. The mesenteric and left renal artery were tied off. The arterial catheter (PE, od 1.6 mm; filled with 0.9% saline and closed at the distal end) was inserted into the abdominal aorta below the right kidney and also tied off. Perfusion was started in situ. The kidney was transferred to a warm (37°C) water-jacket chamber. Then the distal end of the catheter was connected to the perfusion system and opened.

The kidney was transferred to a warm (37°C) water-jacket chamber. Then the distal end of the catheter was connected to the perfusion system and opened. The aorta above the mesenteric artery was tied off. Thereafter all connections between the cannulated vessels and the animal were cut off and the animal was removed by lowering the operating table without irrigating the experimental kidney.

Initially, the kidney was perfused for a short period in an open circuit to prevent traces of blood being transferred to the recirculating unit that had a capacity of approximately 400 ml. A schematic drawing of the perfusion system is shown in Figure 2. This system provides an oxygenated medium at a constant pressure, with perfusate flow being set by the renal vasculature. The perfusate enters the renal artery from a thermostatically heated oxygenation chamber. The driving force is provided by a regulated inflow of 95% oxygen and 5% carbon dioxide and perfusion pressure is adjusted by a bubble trap chamber. Immediately proximal
to the kidney, a side arm connects the perfusion circuit with a pressure transducer that constantly records perfusion pressure. The venous effluent is allowed to drain freely into a funnel and to return to the reservoir. The reservoir is gassed continuously with a mixture of 95% oxygen and 5% carbon dioxide and is returned to the pressurized oxygenation chamber through an inline filter (0.8 μm) using a roller pump (Ismatec, Wertheim-Mondfeld, FRG). Renal perfusate flow is recorded by an inline flowmeter (Fohr Medical Instruments, Pohlheim, FRG) interposed in the closed circuit perfusion system.

Effects of dopamine and dopexamine on the function of the isolated perfused kidney

After an equilibration period of 20 min and two control periods of 10 min, dopexamine or dopamine was perfused for a further 40 min in random order. Urine was collected over 10-min intervals in preweighed tubes and perfusate was obtained at the mid-point of each urine collection period. The experimental procedure was as follows: group A (control group), the perfusion medium had no drug (n=4); group B, perfusion medium had dopamine 2.0 μg kg⁻¹ min⁻¹ (n=10); group C, perfusion medium had dopexamine 1.0, 2.0 or 4.0 μg kg⁻¹ min⁻¹ (n=10).

Analytical measurements

To characterize the effects of dopamine and dopexamine on renal function, absolute sodium excretion (U₇NaV), glomerular filtration rate (GFR), and renal flow (mean (SEM)) in the isolated rat kidney before (25 min, baseline) and after (85 min) perfusion of dopamine and dopexamine. *P<0.05 compared with baseline values (ANOVA)

<table>
<thead>
<tr>
<th>Perfusion time (min)</th>
<th>U₇NaV (μmol min⁻¹ g⁻¹)</th>
<th>GFR (ml min⁻¹ g⁻¹)</th>
<th>Renal flow (ml min⁻¹ g⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Dopamine 2.0 μg kg⁻¹ min⁻¹</td>
<td>0.4 (0.1)</td>
<td>1.2 (0.1)*</td>
<td>20.6 (1.2)</td>
</tr>
<tr>
<td>Dopexamine (μg kg⁻¹ min⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>0.4 (0.1)</td>
<td>0.6 (0.1)</td>
<td>17.7 (0.5)</td>
</tr>
<tr>
<td>2.5</td>
<td>0.6 (0.1)</td>
<td>0.7 (0.1)</td>
<td>25.1 (1.0)</td>
</tr>
<tr>
<td>4.0</td>
<td>0.3 (0.1)</td>
<td>0.4 (0.1)</td>
<td>20.8 (1.3)</td>
</tr>
</tbody>
</table>

were considered significant at P<0.05. The study design included planning of each individual experiment in a randomized order.

Results

Effects of dopamine and dopexamine on renal function

Infusion of a clinical dose of dopamine 2 μg kg⁻¹ min⁻¹ resulted in a significant increase in urine flow from 61.54 (4.7) to 117.2 (9.7) μl min⁻¹ g⁻¹ (n=10, P<0.05) (Fig. 3).

There was no significant alteration in renal blood flow or glomerular filtration rate (Table 1). Dopexamine had no significant effect on the isolated rat kidney or on urine flow, fractional sodium reabsorption and absolute sodium excretion, renal flow or glomerular filtration rate.

Discussion

Dopamine significantly increased urine production and absolute sodium excretion and significantly decreased fractional sodium reabsorption. Renal blood flow and glomerular filtration rate were not altered. In contrast, dopexamine had no affect on the isolated kidney at any concentration. This suggests that the diuretic and natriuretic effects of dopexamine in humans may not result from a direct action on the kidney.

Before discussing possible explanations, some basic considerations are necessary. In our isolated perfused rat kidney model, perfusate was delivered at a constant pressure. As no vasoconstrictors were used, the renal vasculature can be supposed to have been in a state of maximum vasodilatation. These experimental conditions were chosen to exclude possible effects of dopamine or dopexamine on renal function mediated by renal vasodilatation as a result of α- and/or DAI receptor agonism or α adrenoceptor block. In an isolated organ, neuronal or humoral influences can be excluded. Therefore, the increase in diuresis and absolute sodium excretion caused by dopamine in our isolated
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perfused rat kidney model most probably was a result of its agonist action on other intrarenal DA receptors. In our experiments, no such effects of dopexamine were seen.

Martin and Broadley demonstrated vasodilatation produced by dopamine, dopexamine and fenoldopam in the isolated perfused rat kidney constricted with the thromboxane analogue, U46619. Their results indicate that this vasodilatation is mediated by DA1 receptors as it was inhibited by SCH23390. However, they did not report natriuretic effects produced by dopamine and dopexamine in the isolated perfused kidney.

In our study, dopamine caused a marked increase in natriuresis whereas dopexamine within the concentration range tested did not affect the function of the isolated perfused rat kidney. A possible explanation is that other dopamine receptor subtypes may be involved. Five dopamine receptors are known to exist as two subgroups, namely DA1-like (DA1a and DA1b, also known as DA5) and DA2-like (DA2, DA3 and DA4). DA1-like receptors have been shown to predominate in the kidney in the afferent arteriole, and presumably mediate vasodilator actions. DA2-like receptors however are also present in the adventitial and endothelial layers of renal blood vessels and mediate inhibition of adenylate cyclase at postsynaptic sites in the walls of rabbit renal arteries. Furthermore, a DA2-like receptor-mediated natriuretic effect has been described in vivo based on reduced sodium excretion by the DA2-selective antagonist metoclopramide, without affecting renal plasma flow. It is conceivable that dopexamine, in common with dopamine, binds to DA2-receptors but may have no intrinsic activity.

Clinical implications

Dopamine is used in low doses (up to 2 mg kg$^{-1}$ min$^{-1}$) to promote natriuresis and diuresis via selective DA1 receptor stimulation, thereby improving renal function. At higher infusion rates dopamine also activates $\beta_1$ and $\alpha_1$ adrenoceptors. The effect of dopamine on urine output by maintaining renal blood flow in low cardiac output states is however associated with wide variations in response and, particularly at high doses, with vasoconstrictor and arrhythmogenic effects. The renal effects of low-dose dopamine have also been used with some success to prevent renal dysfunction in critically ill surgical patients.

In previous reports it was shown that the cardiovascular actions of dopexamine were a result of activation of $\beta_2$ adrenoceptors and DA1 receptors. In comparative studies with dopamine in patients with heart failure, dopexamine was reported to be a more potent vasodilator with a more modest positive inotropic effect. The reason may be that it does not stimulate $\alpha_1$ adrenoceptors, but $\beta_1$ and $\beta_2$ adrenoceptors. Several studies showed that dopexamine produced significant dose-related increases in renal blood flow in patients with mild to moderate hypertension, improving renal function. As the increase in renal blood flow was proportionally greater than the increase in cardiac output, a specific effect on the kidney vasculature has been suggested. A renal vasodilator action may be the result of renal vascular DA1 receptor activation. In human volunteers, dopexamine also increased renal blood flow via a direct vasodilator action although it was less potent in this respect than dopamine. There is some evidence that dopexamine may also be a diuretic and natriuretic agent. In patients with low output ischaemic heart failure, dopexamine increased significantly urine flow and fractional sodium reabsorption. In another study in patients with low output congestive heart failure, dopexamine increased renal blood flow in addition to diuresis and natriuresis.

Our results suggest that the natriuretic effects of dopexamine in humans may be caused mainly by haemodynamic mechanisms (improvement in cardiac output and splanchnic blood flow), whereas dopamine has an additional direct effect on kidney function.

Acknowledgements

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