Dopamine natriuresis in salt-repleted, water-loaded humans: a dose-response study

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Aims The purpose of the present study was to define the dose-response relationship between exogenous dopamine and systemic haemodynamics, renal haemodynamics, and renal excretory function at infusion rates in the range 0 to 12.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$ in normal volunteers.

Methods While undergoing water diuresis, eight subjects were infused with 0, 1, 2, 3, 5, 7.5, 10 or 12.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$ over 2 h in a randomized and double-blind fashion. On each study day, renal clearance studies were performed during a 1 h baseline period and subsequently during the second 1 h infusion period. Lithium clearance (CL_{Li}) was used to estimate proximal tubular outflow.

Results Cardiac output increased with the four highest doses. Mean arterial pressure followed a biphasic pattern with a decrease during the two lowest doses and a dose-dependent increase from the 7.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$ dose onwards. Effective renal plasma flow increased with all doses of dopamine, but peaked with the 3 $\mu\text{g kg}^{-1} \text{min}^{-1}$ infusion rate [from 617 (585–649) ml min^{-1} with placebo to 915 (824–1006) ml min^{-1} (means with 95% CI, $P < 0.001$)]. None of the doses changed glomerular filtration rate (GFR). Sodium clearance (CL_{Na}) and CL_{Li} were elevated with the four lowest doses but increased further from 7.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$ onwards. Compared with placebo, the percentage increase in CL_{Na} with increasing dose was 77 (5–159), 93 (13–172), 107 (24–190), 121 (60–181), 253 (65–441), 284 (74–494), and 212 (111–312) %, respectively. There were only small, inconsistent decreases in absolute proximal reabsorption rate ($\text{APR} = \text{GFR} - \text{CL}_{\text{Li}}$). Fractional distal reabsorption of sodium ($\text{FDR}_{\text{Na}} = (\text{CL}_{\text{Li}} - \text{CL}_{\text{Na}}) / \text{CL}_{\text{Li}}$) decreased with all doses, reaching its nadir with 7.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$ [from 95.9 (94.6–97.2) % with placebo to 91.5 (90.0–93.0) % ($P < 0.01$)] whereafter a flat dose-response curve was observed.

Conclusions In conclusion, the renal vasodilating effect of dopamine was maximal with 3 $\mu\text{g kg}^{-1} \text{min}^{-1}$. The dose-dependent attenuation seen with higher doses is consistent with an increased α -adrenergic stimulation opposing the effect on dopaminergic receptors. The present CL_{Li} studies confirm that dopamine increases proximal tubular outflow. The results suggest that the natriuretic effect of depressor doses of dopamine was primarily caused by attenuation of the increase in distal sodium reabsorption normally seen after an increase in proximal tubular outflow. Pressor doses further increased sodium excretion, indicating the presence of pressure natriuresis at these high doses.

Keywords: renal haemodynamics, kidney function, natriuresis, dopamine, dose-response, tubular function, lithium clearance, sodium

Introduction

In anaesthetized dogs [1] and rats [2], low doses of dopamine decreased renal vascular resistance, whereas higher doses caused vasoconstriction. α -adrenergic receptor blockade abolished the vasoconstriction so that vasodilation was observed with all doses of dopamine [2]. These dose-dependent effects have been confirmed in studies using isolated renal microvessels of the rabbit [3] and the split

hydronephrotic kidney of the rat [4], thus supporting the concept of a vasodilating effect of specific dopaminergic D_1 -receptor activation, which at higher doses is opposed by an action of α -adrenergic receptors [5, 6]. Another important effect of dopamine, which does not occur with other catecholamines, is the increase in sodium excretion [5–7]. Stimulation of D_1 -receptors in proximal tubular brush-border membranes inhibits the $\text{Na}^+ - \text{H}^+$ antiport [8]; in basolateral membranes of both the proximal tubule and the ascending limb of the loop of Henle, D_1 -receptors inhibits $\text{Na}^+ - \text{K}^+ - \text{ATPase}$ activity [9–11]. Based on this evidence, and because the highest density of renal D_1 -receptors is

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found in the proximal tubules [7, 12], it has been suggested that the natriuresis is mainly caused by inhibition of sodium transport mechanisms in this segment of the nephron [7]. Dopamine was found to decrease fluid reabsorption in the microperfused pars recta of the proximal tubule [13], but data in experimental animals [14, 15] and humans [16, 17] also imply an effect of dopamine and the D_1 -receptor agonist fenoldopam on more distal parts of the nephron. However, the dose-response relationship between exogenous dopamine doses and segmental tubular sodium transport has not been investigated in humans.

In the kidney, adrenergic α -receptor stimulation has a pronounced depressing effect on the excretory function [18]. Because an effect of dopamine on α -receptors may become significant at infusion rates of $5\text{--}10\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$ [19], dopamine natriuresis could be expected to be maximal at relatively low infusion rates. However, in previous dose-response studies in humans with doses up to 8 [20] and $10\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$ [21], sodium excretion continued to rise progressively. The infusion rate at which a functional transition occurs between dopaminergic and adrenergic mediated renal effects has not been established in humans. Earlier studies used an incremental method [20, 21], but randomized, controlled studies with the use of fixed doses of dopamine on separate occasions previously have not been reported.

The purpose of the present study was to define the dose-response relationship between exogenous dopamine and systemic haemodynamics, renal haemodynamics, and renal excretory function at infusion rates in the range 0 to $12.5\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$ in normal volunteers. In addition, hormonal responses were recorded, and the renal clearance of lithium (CL_{Li}) was used to estimate whole kidney segmental tubular reabsorption rates of sodium [22–24].

Methods

Subjects and experimental protocol

Eight healthy male subjects, 22–40 years of age, entered the study after they had given their written informed consent. The study was approved by the regional scientific ethics committee. Weight and height (means $\pm$ s.d.) were $83.0 \pm 12.2\text{ kg}$ and $186 \pm 6\text{ cm}$, respectively. Each subject was investigated on eight different occasions, separated by intervals of at least 7 days. The subjects were instructed to maintain the same diet ($140\text{--}150\text{ mmol sodium/day}$) and to avoid strenuous physical activity for 3 days prior to each study day. A test dose of lithium carbonate (300 mg) was given orally at 22.00 h before each investigation. The protocols for the 8 study days were identical and were conducted on the same time of the day. After an overnight fast, water diuresis was induced by oral intake of water with a rate of $200\text{--}300\text{ ml}$ every 30 min without an initial load. The subjects abstained from nicotine and caffeine-containing drinks. A venous catheter was inserted into an antecubital vein in each arm for infusion and blood sampling, respectively. Except for briefly standing when voiding every 30 min, the subjects were confined to a supine position. Steady state was considered to have been achieved when urine flow rates approximately equaled water intake.

Thereafter, 11–12 h after the administration of the lithium test dose, a 1 h control period (baseline) was followed by an intravenous infusion ($0.15\text{ ml kg}^{-1}\text{ h}^{-1}$) of either 0 (placebo), 1, 2, 3, 5, 7.5, 10, or $12.5\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$ of dopamine, which was given during two consecutive 1 h periods. The solutions were prepared for double-blind administration in a randomized order. On each study day, measurements were obtained during the baseline period and subsequently during the second 1 h infusion period.

Haemodynamic and systemic measurements

Cardiac output was measured by the CO_2 -rebreathing method using a cardiopulmonary gas exchange monitoring device (CPX, Medical Graphics Corporation, St. Paul, USA) according to the principles described previously [25, 26]. Cardiac output was determined at baseline and in the second infusion period as the mean of at least two measurements. Arterial blood pressure (measured manually by sphygmomanometry) was determined in duplicate at baseline and in the second infusion period. ECG rate was recorded continuously. Packed cell volume (PCV) was measured in each period. Plasma renin activity (PRA), and plasma concentrations of aldosterone (PAC), atrial natriuretic peptide (ANP), nor-adrenaline, adrenaline, and dopamine were measured at the end of the second infusion period. In each infusion period, the subjects were specifically asked for the experience of side-effects: headache, palpitations, dizziness, and/or nausea. Incidences of vomiting and cardiac arrhythmias were also recorded.

Renal measurements

Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were measured by a constant infusion technique with urine collections, using ^{131}I -hippuran and $^{99\text{m}}\text{Tc}$ -diethylenetriaminepentacetate (DTPA) in a total average dose of 0.10 mCi (3.6 MBq) and 0.73 mCi (27.0 MBq), respectively. After an equilibration period of at least 1 h, renal clearances of ^{131}I -hippuran, $^{99\text{m}}\text{Tc}$ -DTPA, lithium, and sodium (CL_{Na}) were determined at baseline and during the second hour of dopamine infusion. Each clearance value was calculated from the 1 h urinary excretion rates and the mean of plasma values from two samples drawn at 15 and 45 min, respectively, during each 1 h clearance period.

Analytical methods

Activities of ^{131}I -hippuran and $^{99\text{m}}\text{Tc}$ -DTPA in plasma and urine were determined in a well-counter. Plasma and urinary lithium concentrations were measured by atomic absorption spectrophotometry (Model 403; Perkin-Elmer, Norwalk, CT, USA). Plasma sodium was measured with a Technicon RA 1000 instrument, and urinary sodium with a Technicon RA-XT instrument (Tarrytown, NY, USA). PRA was measured by a two site, two monoclonal antibody immunoradiometric assay with plastic beads for solid phase (Nichols Institute, San Juan Capistrano, CA, USA). Limit of detection was 2 mIU l^{-1} . Intra- and interassay coefficients of variation were 4% and 5%, respectively. PAC was measured by

radioimmunoassay in unextracted serum (Diagnostic Products Corporation, Los Angeles, CA, USA). Limit of detection was 41 pmol l^{-1} . Intra- and interassay coefficients of variation were 10% and 15%, respectively. α -ANP was measured by an ^{125}I radioimmunoassay system from Amersham International PLC (Amersham, UK). The chromatographic extraction of ^{125}I -tagged α -ANP was 90%, and the analytical recovery of α -ANP when added to a control sample was 82%. Minimal detectable concentration was 1 pmol l^{-1} . Intra- and interassay coefficients of variation were 5% and 15%, respectively. Plasma concentrations of noradrenaline, adrenaline, and dopamine were measured by a radioenzymatic method with separation by high performance liquid chromatography (h.p.l.c.). Intra- and interassay coefficients of variation (calculated by measurements on a plasma pool ($n=35$), where concentrations of noradrenaline, adrenaline, and dopamine (means $\pm$ s.d.) were $2.01 \pm 0.13 \text{ nmol l}^{-1}$, $0.34 \pm 0.03 \text{ nmol l}^{-1}$, and $0.84 \pm 0.11 \text{ nmol l}^{-1}$, respectively) were 5.5% and 5.0% for noradrenaline, 7.6% and 7.4% for adrenaline, and 13.0% and 13.0% for dopamine, respectively. Limits of detection were 0.03 nmol l^{-1} and 0.02 nmol l^{-1} for noradrenaline and adrenaline, respectively, and 0.4 nmol l^{-1} for dopamine.

Calculations

Total peripheral resistance was determined as mean arterial blood pressure (MABP) divided by cardiac output. ERPF, GFR, CL_{Li} and CL_{Na} were calculated using standard formulae. Renal vascular resistance was estimated as MABP divided by the renal blood flow calculated as $\text{ERPF}/(1-\text{PCV})$. Segmental renal tubular reabsorption rates were calculated based on the assumption that CL_{Li} provides a valid measurement of the rate of end-proximal delivery of fluid to the thin descending limb of Henle's loop [23]: absolute proximal reabsorption rate = $\text{GFR} - \text{CL}_{\text{Li}}$; fractional proximal reabsorption = $1 - (\text{CL}_{\text{Li}}/\text{GFR})$; absolute distal reabsorption rate of sodium = $(\text{CL}_{\text{Li}} - \text{CL}_{\text{Na}}) \times \text{P}_{\text{Na}}$ (where P_{Na} is plasma sodium concentration); fractional distal reabsorption of sodium = $(\text{CL}_{\text{Li}} - \text{CL}_{\text{Na}})/\text{CL}_{\text{Li}}$. Fractional excretion of sodium (FE_{Na}) was calculated as $\text{CL}_{\text{Na}}/\text{GFR}$. The total clearance of dopamine was calculated by dividing the infusion rate with the steady state serum concentration. Presence of linear pharmacokinetics was examined for by investigating the correlation between infusion rates and steady state concentrations. A Lineweaver-Burk plot was used to calculate the maximal effect (E_{max}) and the dose producing half-maximal effect (K_d) of the percentage increase in CL_{Na} .

Statistical analysis

Differences within and between study days were analyzed by a one-way analysis of variance for repeated measures. If unequal ($P < 0.05$), paired t -tests were used to analyze differences between placebo and dopamine, and differences within study days between the baseline period and the second hour infusion period. All values are presented as means (95% confidence intervals).

Results

Pharmacokinetic and pharmacodynamic variables

In the second 1 h infusion period with 1, 2, 3, 5, 7.5, 10 and $12.5 \mu\text{g kg}^{-1} \text{ min}^{-1}$, plasma concentrations of dopamine were 41 (21–60), 89 (61–117), 152 (103–200), 261 (212–311), 305 (222–389), 428 (368–488), and 571 (445–697) nmol l^{-1} , respectively. On the study day with placebo, concentrations of (endogenous) dopamine were below the detection limit of 0.4 nmol l^{-1} , except in one subject where it was 1.1 nmol l^{-1} . With increasing doses, total clearances of dopamine were 153 (110–196), 134 (93–175), 114 (81–148), 106 (84–128), 145 (99–190), 126 (110–142), and 121 (97–144) $\text{ml kg}^{-1} \text{ min}^{-1}$, respectively. There were no significant differences between study days, and the correlation coefficient between coherent values of infusion rate and mean steady state serum concentration was 0.99. Estimated as the mean of pooled values ($n=54$), total clearance of exogenous dopamine was 129 (118–140) $\text{ml kg}^{-1} \text{ min}^{-1}$. E_{max} and K_d for the percentage increase in CL_{Na} were 231% and $2.3 \mu\text{g kg}^{-1} \text{ min}^{-1}$, respectively (correlation coefficient = 0.89).

Side-effects (Table 1)

None of the infusion rates caused cardiac arrhythmias, except in one subject in whom supraventricular extrasystoles ($4\text{--}10 \text{ min}^{-1}$) were observed during the first 20 min with the infusion of $5 \mu\text{g kg}^{-1} \text{ min}^{-1}$.

Catecholamines, renin, aldosterone, and ANP (Table 2)

Noradrenaline and adrenaline levels rose progressively with increasing doses of dopamine and were significantly elevated from the $3 \mu\text{g kg}^{-1} \text{ min}^{-1}$ dose onwards. The different dopamine infusion rates had no effects on PRA, PAC, and plasma concentrations of ANP.

Table 1 Number of subjects with side-effects.

	Dopamine infusion rate ($\mu\text{g kg}^{-1} \text{ min}^{-1}$)							
	Placebo	1	2	3	5	7.5	10	12.5
Headache	1	1	3	1	2	5	4	5
Palpitations				1	5	5	7	8
Dizziness					1	1	1	2
Nausea			1	1	4	3	6	6
Vomiting					1	3	3	3

Figure 1 Renal vascular resistance (RVR), effective renal plasma flow (ERPF), and glomerular filtration rate (GFR) at baseline periods (open bars) and during the second 1 h infusion periods with placebo and increasing doses of dopamine (hatched bars). Means (95% CI), $n=8$ except at 3 and $12.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ where $n=7$; values of GFR have $n=7$ at placebo and $3 \mu\text{g kg}^{-1} \text{min}^{-1}$ and $n=6$ at $12.5 \mu\text{g kg}^{-1} \text{min}^{-1}$. ⁺, $P<0.05$; [‡], $P<0.01$; ^{*}, $P<0.001$ compared with placebo.

Cardiovascular effects (Table 3)

Heart rate increased with the lowest infusion rate and increased in a dose-dependent manner with the four highest doses of dopamine. Cardiac output rose progressively with increasing doses of dopamine, but only values at the highest infusion rate were significantly higher compared with placebo. Compared with the corresponding baseline period, cardiac output increased with the four highest doses. MABP followed a biphasic pattern with a decrease during the two lowest doses and a dose-dependent increase from the $7.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ dose onwards. Systolic blood pressure remained unchanged with the three lowest dopamine doses and thereafter increased at and above $5 \mu\text{g kg}^{-1} \text{min}^{-1}$. Diastolic blood pressure decreased with doses in the range of $1\text{--}5 \mu\text{g kg}^{-1} \text{min}^{-1}$ and thereafter remained unchanged until it increased with $12.5 \mu\text{g kg}^{-1} \text{min}^{-1}$. The two lowest doses decreased total peripheral resistance compared with the baseline period.

Renal haemodynamics (Figure 1)

Renal vascular resistance decreased at dopamine doses below $7.5 \mu\text{g kg}^{-1} \text{min}^{-1}$, reaching its nadir with $3 \mu\text{g kg}^{-1} \text{min}^{-1}$. ERPF increased with all doses of dopamine. The maximal value was observed with $3 \mu\text{g kg}^{-1} \text{min}^{-1}$. At this dose values were significantly higher than with $1 \mu\text{g kg}^{-1} \text{min}^{-1}$ ($P < 0.05$), $10 \mu\text{g kg}^{-1} \text{min}^{-1}$ ($P < 0.05$), and $12.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ ($P < 0.005$). None of the different dopamine infusion rates induced significant changes in GFR.

CL_{Li} and segmental tubular function (Table 4)

CL_{Li} was elevated with the four lowest doses. From $7.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ onwards C_{Li} increased further. Compared with placebo, none of the dopamine doses caused significant changes in absolute proximal reabsorption rate (APR), but as compared with the corresponding baseline period APR did decrease with 1, 2, and $7.5 \mu\text{g kg}^{-1} \text{min}^{-1}$, respectively. All doses decreased fractional proximal reabsorption, but with $3 \mu\text{g kg}^{-1} \text{min}^{-1}$ only the difference from the baseline period before infusion reached statistical significance. Absolute distal reabsorption of sodium increased with all infusion doses. Fractional distal reabsorption of sodium decreased with all doses, reaching its nadir with $7.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ whereafter a flat dose-response curve was observed.

Excretion of sodium and water (Figure 2)

CL_{Na} in the eight baseline periods averaged $1.37 (1.25\text{--}1.49) \text{ml min}^{-1}$; Values did not differ significantly between study days. The dopamine-induced changes in CL_{Na} and FE_{Na} followed the same pattern as for C_{Li}. CL_{Na} with the four lowest doses did not differ significantly. Values at $12.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ were significantly higher than those with $5 \mu\text{g kg}^{-1} \text{min}^{-1}$ ($P < 0.02$), $3 \mu\text{g kg}^{-1} \text{min}^{-1}$ ($P < 0.02$), $2 \mu\text{g kg}^{-1} \text{min}^{-1}$ ($P < 0.001$), and $1 \mu\text{g kg}^{-1} \text{min}^{-1}$ ($P < 0.002$). CL_{Na} with the three highest doses did not differ significantly. With placebo CL_{Na} was $1.58 (1.12\text{--}2.03) \text{ml min}^{-1}$. Compared with placebo, the

Table 2 Effects of dopamine on plasma catecholamines, plasma renin activity (PRA), and plasma concentrations of aldosterone (PAC) and atrial natriuretic peptide (ANP). Means (95% CI), $n = 8$ except at 3 and $12.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ where $n = 7$. ^a: $P < 0.05$, ^b: $P < 0.01$, ^c: $P < 0.001$ compared with placebo.

	Dopamine infusion rate ($\mu\text{g kg}^{-1} \text{ min}^{-1}$)							
	Placebo	1	2	3	5	7.5	10	12.5
Noradrenaline, (nmol l^{-1})	1.22(0.94–1.50)	1.33(1.08–1.58)	1.54(1.29–1.79)	1.70(1.43–1.97) ^a	1.73(1.29–2.16) ^b	2.55(2.00–3.10) ^c	2.88(2.00–3.76) ^b	3.07(2.45–3.69) ^c
Adrenaline, (nmol l^{-1})	0.22(0.17–0.27)	0.27(0.21–0.33)	0.29(0.23–0.34)	0.32(0.24–0.41) ^a	0.31(0.24–0.38) ^a	0.40(0.33–0.46) ^c	0.44(0.33–0.55) ^b	0.46(0.34–0.57) ^b
PRA (mmHg min^{-1})	16(11–21)	14(9–19)	17(6–27)	19(14–25)	19(9–29)	14(8–20)	15(11–19)	15(9–20)
PAC (pmol l^{-1})	215(116–314)	169(133–204)	193(126–259)	230(180–280)	175(132–218)	229(136–321)	229(174–283)	251(160–342)
ANP (pmol l^{-1})	6.0(4.0–7.9)	6.1(3.6–8.5)	6.4(4.3–8.6)	5.7(4.2–7.1)	5.2(3.5–6.9)	8.2(2.8–13.5)	7.5(3.3–11.6)	8.3(4.5–12.1)

Table 3 Cardiovascular effects of dopamine. Means (95% CI). $n=8$, except at 3 and 12.5 $\mu\text{g kg}^{-1} \text{ min}^{-1}$ where $n=7$. *: $P<0.05$, +: $P<0.01$, #: $P<0.001$ compared with the corresponding baseline period; ^a: $P<0.05$, ^b: $P<0.01$, ^c: $P<0.001$ compared with placebo.

	Dopamine infusion rate ($\mu\text{g kg}^{-1} \text{ min}^{-1}$)									
	Placebo	1	2	3	5	7.5	10	12.5		
<i>Heart rate (beats min^{-1})</i>										
Baseline	52(47–57)	52(48–55)	52(49–55)	54(50–59)	53(45–61)	51(45–56)	50(46–54)	51(45–56)		
Infusion	50(47–53)	58(53–64) ^a	57(48–66)	57(50–65)	55(50–60) ^a	57(49–65) ^a	61(52–70) ^a	62(53–71) ^b		
<i>Cardiac output (l min^{-1})</i>										
Baseline	4.0(3.2–4.9)	4.5(3.5–5.5)	4.7(3.6–5.8)	4.5(3.6–5.4)	4.5(3.5–5.5)	4.0(2.7–5.4)	4.3(3.8–4.9)	4.0(3.3–4.7)		
Infusion	4.2(3.2–5.2)	4.8(3.6–6.0)	5.0(3.9–6.1)	5.0(3.7–6.2)	5.6(4.2–7.0) [*]	5.8(3.7–8.0) [*]	5.6(3.9–7.3) [*]	6.0(4.8–7.1) ^a		
<i>Systolic blood pressure (mmHg)</i>										
Baseline	121(111–131)	122(109–135)	118(106–130)	119(110–128)	116(108–124)	115(106–124)	120(110–129)	118(110–127)		
Infusion	117(110–124)	118(106–130)	121(110–131)	125(107–144)	133(120–146) ^b	155(131–179) ^{+b}	172(142–202) ^{+b}	179(163–195) ^{#c}		
<i>Diastolic blood pressure (mmHg)</i>										
Baseline	74(65–82)	74(66–82)	70(62–79)	73(67–79)	71(64–79)	70(61–79)	70(62–79)	73(65–81)		
Infusion	73(67–78)	64(59–69) ^a	64(57–71) ^{*c}	67(55–79) ^a	66(60–71) ^{+a}	76(61–91)	74(66–83)	81(75–86) ^a		
<i>Mean arterial blood pressure (mmHg)</i>										
Baseline	89(81–98)	90(81–100)	86(77–96)	88(82–95)	86(79–93)	85(76–94)	87(78–96)	88(80–96)		
Infusion	87(82–93)	82(76–88) ^a	83(75–91) ^a	86(73–100)	88(81–95)	102(85–120) [*]	107(92–122) ^{+a}	113(105–121) ^{#c}		
<i>Total peripheral resistance (mmHg min l^{-1})</i>										
Baseline	22(17–26)	21(16–26)	19(16–23)	20(17–24)	22(17–27)	23(18–28)	21(19–23)	22(19–26)		
Infusion	21(15–28)	18(14–23) [*]	17(15–20) [*]	19(14–24)	17(12–23)	19(14–23)	20(15–25)	19(17–22)		

Table 4 Effects of dopamine on lithium clearance (CL_{Li}) and on calculated values of absolute proximal reabsorption rate ($APR = GFR \cdot CL_{Li}$), fractional proximal reabsorption ($FPR = (GFR \cdot CL_{Li}) / GFR$), absolute distal reabsorption rate of sodium ($ADR_{Na} = (CL_{Li} - CL_{Na}) \cdot xP_{Na}$), and fractional distal reabsorption of sodium ($FDR_{Na} = (CL_{Li} - CL_{Na}) / CL_{Li}$). Means (95% CI). $n = 8$, except at 3 and 12.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ where $n = 7$. $^*P < 0.05$, $^+P < 0.01$, $^{\#}P < 0.001$ compared with the corresponding baseline period; $^aP < 0.05$, $^bP < 0.01$, $^cP < 0.001$ compared with placebo.

	Dopamine infusion rate ($\mu\text{g kg}^{-1} \text{ min}^{-1}$)							
	Placebo	1	2	3	5	7.5	10	12.5
<i>CL_{L1}</i> (<i>ml min</i> ^{−1})								
Baseline	38(34–42)	39(33–46)	36(33–39)	38(33–43)	37(32–41)	39(34–44)	38(32–44)	35(30–41)
Infusion	39(36–43)	49(41–57) ^{#a}	49(45–53) ^{#c}	48(41–55) ^{*a}	52(47–57) ^{#c}	54(44–65) ^{+b}	58(53–62) ^{#c}	58(49–67) ^{+b}
<i>APR</i> (<i>ml min</i> ^{−1})								
Baseline	93(84–102)	97(89–106)	93(85–101)	107(75–139)	95(86–103)	99(80–119)	97(86–108)	89(77–101)
nfusion	89(78–100)	87(78–96) [#]	85(76–94) ⁺	96(77–115)	88(81–96)	83(71–94) ⁺	87(76–97)	79(61–97)
<i>FPR</i> (%)								
Baseline	70(68–73)	71(68–75)	71(66–75)	72(69–76)	72(69–75)	71(69–73)	72(70–74)	71(67–75)
Infusion	69(66–72)	64(60–68) ^{#a}	63(59–66) ^{+b}	66(59–72) [*]	63(59–67) ^{#a}	61(57–64) ^{#b}	60(57–63) ^{#b}	58(52–64) ^{+a}
<i>ADR_{Na}</i> (<i>mmol min</i> ^{−1})								
Baseline	5104(4516–5692)	5221(4364–6079)	4857(4414–5300)	5079(4367–5792)	4923(4268–5577)	5263(4542–5985)	5127(4229–6024)	4742(4014–5470)
Infusion	5279(4853–5705)	6419(5406–7432) ^{+a}	6472(5905–7039) ^{#b}	6324(5490–7157) ^{*a}	6790(6058–7523) ^{#c}	7057(5664–8449) ^{+b}	7317(6628–8006) ^{+c}	7371(6187–8555) ^{+b}
<i>FDR_{Na}</i> (%)								
Baseline	96.2(94.8–97.8)	96.5(95.2–97.8)	96.5(95.4–97.6)	96.4(95.1–97.7)	96.6(95.4–97.8)	95.6(94.0–97.2)	96.6(95.6–97.5)	96.5(95.1–97.9)
Infusion	95.9(94.6–97.2)	94.7(92.8–96.6) ⁺	94.4(93.1–95.7) ^{#a}	94.0(92.0–96.0) ^{*a}	93.6(91.7–95.5) ^{#b}	91.5(90.0–93.0) ^{+b}	91.4(89.6–93.2) ^{#b}	91.5(89.7–93.3) ^{#c}

Figure 2 Sodium clearance (C_{Na}), fractional excretion of sodium (FE_{Na}), and urine flow rate at baseline (open bars) and during the second 1 h infusion periods with placebo and increasing doses of dopamine (hatched bars). Means (95% CI), $n=8$ except at 3 and $12.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ where $n=7$. ⁺, $P<0.05$; [‡], $P<0.01$; ^{*}, $P<0.001$ compared with placebo.

percentage increase in CL_{Na} with increasing dose was 77 (5–159), 93 (13–172), 107 (24–190), 121 (60–181), 253 (65–441), 284 (74–494), and 212 (111–312) %, respectively. None of the changes in urine flow rates reached statistical significance.

Discussion

The present study investigated the dose-dependent effects of dopamine on systemic and renal hemodynamics, tubular function, and sodium excretion in salt-repleted, water-loaded subjects. The small variation between the baseline sodium excretion before infusion of each dose confirms that the sodium intake of the subjects was successfully adjusted. Comparisons between different dopamine doses, however, should be interpreted with caution because of the small sample size.

Dopamine had a biphasic effect on MABP with a decrease during the two lowest doses and a dose-dependent increase from the $7.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ dose onwards. The depressor effect of dopamine resulted from a decrease in diastolic blood pressure, whereas the pressor effect was mainly caused by an increase in systolic pressure. This is consistent with a predominant activation of peripheral D_1 -receptors producing vasodilation in the arterial vascular bed during infusions of low doses, and, when infusion rates are increased, with an increasing stimulation of cardiac β_1 -receptors [6, 27, 28]. Pressor doses did not affect total peripheral resistance suggesting that dopamine doses higher than $12.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ are necessary to produce α -adrenergic receptor mediated vasoconstriction.

The renal vasodilating effect of dopamine was maximal with $3 \mu\text{g kg}^{-1} \text{min}^{-1}$. With higher doses the effect progressively declined but was still significantly expressed with $12.5 \mu\text{g kg}^{-1} \text{min}^{-1}$. The present results are consistent with a direct vasodilating action of dopamine via specific D_1 -receptors in the renal vasculature which at higher doses is attenuated by increasing stimulation of α -adrenergic receptors. However, the upper dose necessary to cause renal vasoconstriction could not be defined, suggesting that in humans doses above $12.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ may still improve renal perfusion. None of the doses used increased GFR. This is in accordance with previous results indicating that dopamine only causes small changes in GFR [16, 17, 20, 28–30].

The well known natriuretic effect of dopamine was expressed already with the lowest dose ($1 \mu\text{g kg}^{-1} \text{min}^{-1}$). With increasing doses of 0.25, 0.5, and $2.0 \mu\text{g kg}^{-1} \text{min}^{-1}$, Smit *et al.* [20] found that the first natriuretic response appeared with $2.0 \mu\text{g kg}^{-1} \text{min}^{-1}$, suggesting that in normal, sodium-repleted humans the threshold dose for producing a natriuretic effect is between 0.5 and $1 \mu\text{g kg}^{-1} \text{min}^{-1}$. Although increases in ERPF with or without concomitant increases in GFR most probably contribute to the natriuretic response to nonpressor doses of fenoldopam and dopamine [31], it has been demonstrated that natriuresis can occur in the absence of renal haemodynamic changes [14, 31, 32] and that this action can be attenuated by specific D_1 -receptor antagonists [32]. D_1 -receptors have been identified in both brush-border and basolateral tubular membranes [7, 33]. In the human kidney, the highest density of receptors was observed in the proximal tubule and the

macula densa followed in descending order by the ascending limb of the loop of Henle, the distal tubule, and the descending limb of Henle [12]. Strong evidence indicates that dopamine via D_1 -receptors inhibits $\text{Na}^+ \text{--} \text{H}^+$ exchange in the brush-border membrane of the proximal tubule [8] and $\text{Na}^+ \text{--} \text{K}^+ \text{--} \text{ATPase}$ activity in the basolateral membrane of both the proximal tubule and the medullary thick ascending limb of Henle [9–11].

The CL_{Li} method was used in this study to assess the functional effects of dopamine on the segmental tubular reabsorption of sodium. For CL_{Li} to be an accurate measure of the delivery of tubular fluid from the proximal tubule to the descending loop of Henle, two premises should be fulfilled: 1) lithium is reabsorbed in parallel with water in the proximal tubule, and 2) lithium is neither secreted nor reabsorbed in more distal segments [22–24]. Recent studies indicated that CL_{Li} may slightly overestimate the end-proximal tubular outflow and that a small amount of lithium (<10%) is reabsorbed within the loop of Henle [22]. Thus, although none of the assumptions on which the CL_{Li} method is based seem to be entirely correct, the error factors will affect CL_{Li} in opposite directions and may tend to cancel out. Amiloride-sensitive lithium reabsorption beyond the loop of Henle has not been found in humans even during extreme sodium depletion [34]. Lithium test doses may increase sodium excretion [29, 35]. However, the renal response to dopamine and fenoldopam remained unchanged [29, 30, 36]. A test dose of 300 mg was chosen in the present study since such a dose has only small, if any, natriuretic effects on the following study day [35], but still results in plasma concentrations that can be measured with acceptable precision. Therefore, it cannot be excluded that the present lithium test doses increased baseline values of CL_{Na} ; however, experimental conditions were similar on all study days.

The present findings confirm the results from several earlier CL_{Li} studies indicating that dopamine increases proximal tubular outflow [16, 17, 28–30]. Direct micropuncture measurements demonstrated a similar effect of fenoldopam in the rat [15]. The dopamine-induced increase in CL_{Li} may either derive from an increased filtered load or a decreased proximal tubular reabsorption or both. The associated increase in FE_{Li} and decrease in the estimated fractional proximal reabsorption, invariably found during infusions of dopamine and fenoldopam [16, 17, 28–30, 37], has previously been interpreted as being indicative of a tubular mechanism solely [37]. However, since load dependency of the reabsorption of sodium and fluid in the proximal tubule seems to be of minor importance [24, 38], the calculated absolute proximal reabsorption rate ($\text{APR} = \text{GFR} - \text{CL}_{Li}$) should be more suited to reflect changes in proximal tubular transport capacity. In the present study, dopamine only elicited small, inconsistent decreases in APR. This is in agreement with previous studies in humans in which APR either slightly decreased [16, 17] or remained unchanged [28]. In micropuncture studies in rats and dogs fenoldopam [15] or dopamine [14] did not change fluid reabsorption in the proximal convoluted tubule. On the other hand, *in vitro* studies by Bello-Reuss *et al.* [13] demonstrated that D_1 -receptor stimulation with dopamine can inhibit fluid reabsorption in the isolated, microperfused

pars recta of the proximal tubule in the rabbit. The use of the CL_{Li} method very much depends on accurate and precise measures of GFR to enable reliable estimates of APR. Even with the use of ideal markers in technically optimal renal clearance studies with urine collections, changes in GFR less than 10–15% may not be detected. Because of the numeric difference between GFR and CL_{Li} , and in view of the small effects of dopamine on GFR, significant decreases in estimated fractional proximal reabsorption may well appear in the presence of non-significant increases in GFR without changes in APR. Thus, although a functional role of the high density of D_1 -receptors in the proximal tubule has been suggested by *in vitro* studies [13], the present results confirm that the natriuretic effect of D_1 -receptor agonists in humans and intact animals may occur without marked depression of APR [14–17, 28].

Sodium reabsorption in the distal segments of the nephron is directly load dependent, and therefore changes in distal tubular reabsorption rate should be evaluated in relation to the end-proximal delivery of sodium [39]. In CL_{Li} studies, the fractional distal reabsorption of sodium (FDR_{Na}), estimated as a fraction of sodium delivered from the end of the proximal tubule, may best reflect the distal tubular effects of dopamine. The present increase in absolute distal reabsorption of sodium (ADR_{Na}) is consistent with a load-dependent response to the dopamine-induced increase in end-proximal delivery. FDR_{Na} progressively decreased with depressor doses of dopamine, reaching its nadir with $7.5 \mu\text{g kg}^{-1} \text{ min}^{-1}$. When compared with infusions of amino acids and dopexamine in doses producing a similar increase in CL_{Li} , only dopamine elicited a natriuretic response [16, 17, 40]. This was associated with a significant decrease in FDR_{Na} not observed with the other interventions [16, 17, 40]. It is therefore possible that the natriuretic effect of depressor and nonpressor doses of dopamine is caused, at least in part, by attenuation of the mechanisms which normally increase distal sodium reabsorption in response to an increased delivery. Such an effect may be secondary to inhibition of $\text{Na}^+ - \text{K}^+ - \text{ATPase}$ activity in the ascending loop of Henle [10], and, perhaps, to stimulation of D_1 -receptors in cortical collecting ducts [41]. In addition, alterations in medullary haemodynamics and/or renal interstitial pressure secondary to a dopamine-induced increase in medullary blood flow [2] might also decrease fluid and solute reabsorption in the loop of Henle [42], but further studies are needed to clarify this latter issue.

Concomitant with the dose-dependent increase in MABP, sodium excretion further increased from $7.5 \mu\text{g kg}^{-1} \text{ min}^{-1}$ onwards. This response occurred in spite of a decreasing ERPF and unchanged GFR, suggesting the contribution of a component of pressure natriuresis. Although the exact tubular mechanisms responsible for the phenomenon of natriuresis remain unsolved, the present results are in accordance with previous CL_{Li} studies in rats and dogs showing that pressure natriuresis involves a decrease of fractional sodium reabsorption in both proximal and distal tubules [43, 44]. Thus, the additional natriuresis seen with the three highest doses most likely reflect indirect effects of β_1 -receptor mediated increases in cardiac contractility and renal perfusion pressure. CL_{Na} seemed to level off with $10 \mu\text{g kg}^{-1} \text{ min}^{-1}$. FE_{Na} continued to rise throughout the

pressor range, and the infusion rate at which adrenergic α -receptor mediated inhibition of sodium reabsorption becomes significant could not be defined.

Dopamine progressively increased plasma levels of noradrenaline and adrenaline. The rise in plasma catecholamines may either be secondary to conversion of exogenous dopamine to noradrenaline in adrenergic neurons or to an increased release from endogenous sources or both. Previously, 25% of an infused dose of radio-labelled dopamine could be recovered in the urine as noradrenaline or metabolic products of noradrenaline [47]. In accordance with other studies [45, 46, 48], the present plasma clearance of dopamine greatly exceeded hepatic blood flow and GFR. These data support the hypothesis of a peripheral metabolism of exogenous dopamine. In healthy subjects, plasma noradrenaline concentrations in excess of $1,800 \text{ pg ml}^{-1}$ ($10.64 \text{ nmol l}^{-1}$) were necessary to produce measurable haemodynamic changes [49]. This is about eight-fold over basal levels [49]. In the present study, the highest dose of dopamine increased the mean plasma noradrenaline concentration only two to three-fold over basal values to 3.07 nmol l^{-1} . Therefore it is unlikely that the present dopamine-induced increases in noradrenaline levels subserved a hormonal function; rather the changes in systemic haemodynamics were primarily caused by a direct action of dopamine on adrenergic receptors. However, the threshold level of circulating noradrenaline necessary to produce significant changes in renal haemodynamics and tubular function remains unknown. Recently, infusion of noradrenaline resulting in a median plasma concentration of 3.55 nmol l^{-1} was found to decrease ERPF, GFR, and CL_{Li} [50]. Within the renal circulation, increased plasma noradrenaline levels may therefore play a role in mediating the attenuation of ERPF observed with pressor doses of dopamine.

In summary, the present study demonstrated that the renal vasodilating effect of exogenous dopamine follows a bell-shaped dose-response curve. The maximal increase in ERPF was seen with $3 \mu\text{g kg}^{-1} \text{ min}^{-1}$. Higher doses caused a dose-dependent attenuation of the renal vasodilation, consistent with an increased α -adrenergic stimulation opposing the effect on dopaminergic receptors. Although the present CL_{Li} studies confirmed that depressor doses of dopamine increase proximal tubular outflow, the results do not support the hypothesis that inhibition of proximal tubular sodium transport play a major role for the natriuretic effect of dopamine. Rather the results suggest that the natriuresis, at least in part, was caused by attenuation of the increase in distal sodium reabsorption normally seen after an increase in proximal tubular outflow. Pressor doses further increased sodium excretion suggesting the contribution of pressure natriuresis at these high doses.

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