ATRIAL NATRIURETIC HORMONE IS NOT ELEVATED DURING DOPAMINE INDUCED NATRIURESIS

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Summary

To evaluate the possibility that atrial natriuretic hormone (ANH) is
involved in dopamine induced natriuresis and diuresis, we studied
five normal male volunteers. Each was studied on two occasions.
During the first two hours of each study, normal saline, 25 ml/hr,
was infused. During the second two hours either normal saline, 25
ml/hr, or dopamine, 4 µg/kg/min, in normal saline, was infused.
Dopamine infusion caused prominent and significant natriuresis and
diuresis but plasma levels of immunoreactive ANH levels did not
change. We conclude that the ANH is not involved in dopamine
induced natriuresis and that dopaminergic stimulation is not
responsible for ANH secretion.

Dopamine infusion causes increased diuresis and natriuresis (1). A
physiologic natriuretic function of dopamine was postulated by Cuche et al (2)
following studies in which they analyzed urinary catecholamines in correlation
with sodium excretion. This natriuresis could be mediated by vasodilatory
actions of dopamine (3) or other mechanisms may be involved. The recently
derived natriuretic peptides, known collectively as atrial natriuretic hormone
(ANH), have potent natriuretic effects in animals (4,5) and humans (6,7). To
evaluate a possible role of this hormone in dopamine induced natriuresis, we
measured the levels of immunoreactive ANH (IR-ANH) in humans during dopamine
infusion.

Materials and Methods

Human subjects

Five healthy male volunteers aged 25-37, all within 10% of ideal body
weight, were studied. Their blood pressure was measured twice before the
study and was found to be below 140/90.

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Protocol of the study

The subjects were studied after a 10 hour fast and were kept supine for
the entire 4 hours of the study with exception of assuming the upright
position for one voiding. At 8 a.m. (0' minute of the study), after the
subjects emptied their bladders, a butterfly needle was inserted into the
vein of each forearm. One line was used for infusion and the other line,
which was kept open by flushing with heparinized saline, was used for blood
sampling. The total amount of heparin used did not exceed 500 units. Blood
pressure and heart rate were monitored every hour and continuous ECG
monitoring was maintained.

Blood samples for immunoreactive ANH (IR-ANH), plasma aldosterone,
plasma renin activity (PRA), and plasma dopamine levels were drawn at 0,
120, 180, and 240 minutes. A serum sample for sodium and potassium was
drawn at 0 minute. Two urine samples were collected at 10:00 and 12:00
a.m., the volume was recorded and samples were analyzed for sodium and
potassium. To assure appropriate urine flow subjects drank 100 ml of tap
water every hour.

During the first two hours of study (between 8:00 and 10:00 a.m.)
25 ml/hr of normal saline was infused using a Harvard infusion pump. During
the second two hours the infusion syringe was switched to either another
syringe of normal saline or to solution of dopamine in normal saline. The
infusion was continued at the same rate of 25 ml/hr and the dose of dopamine
was calculated so that 4 µg/kg/min was infused during those two hours. Each
subject was studied on two separate days; once using placebo (normal saline)
infusion for the entire 4 hours and once using dopamine infusion for the
last two hours of the study. The protocol was designed as a double blind
study and the code was broken only after completion of all the infusions.
The side effects were minimal and included nausea and one episode of
vomiting in one volunteer and multiple supraventricular premature beats in
another volunteer. These side effects occured during dopamine infusion.
The study was approved by the Human Studies Committee of the University of
Michigan Hospital.

Assay methods

Serum and urinary sodium and potassium were measured using flame
photometry. Plasma aldosterone and PRA were measured by radioimmunoassay
(8,9). Dopamine concentration was determined radioenzymatically by the
method of Peuler and Johnson (10).

The radioimmunoassay for IR-ANH has been described (11). In brief,
blood samples drawn into EDTA tubes were put on ice and plasma was separated
within 30 minutes of sampling. Plasma was extracted through C_{18} Sep Pak
cartridges (Waters Associates, Milford, MA) and IR-ANH levels were measured
by radioimmunoassay. All samples were measured in the same assay.
Intraassay variation for IR-ANH was 8.6%.

Statistical methods

All the data are expressed as mean ± standard error. Repeated measures
analysis of variance (ANOVA) with Newman-Keuls test (NKT) was used for
comparisons of mean blood pressure, heart rate, plasma aldosterone, PRA,
plasma dopamine, IR-ANH, urinary volume, urinary sodium and potassium.
Paired t test was used for comparisons of serum sodium and potassium.

Results

Mean blood pressure and heart rate were not significantly different during placebo and dopamine administration (not shown). The results of plasma aldosterone, PRA, urinary potassium, serum sodium, and serum potassium are shown in Table 1. No significant variability or difference were found. The results of urinary sodium, plasma dopamine and IR-ANH levels are shown in Figure 1. Urinary volume and sodium excretion (both p<0.025) and plasma dopamine levels (p<0.01) were increased following dopamine infusion. Plasma IR-ANH levels were not significantly altered by dopamine infusion (p=0.24).

TABLE I

Plasma Hormone Levels, Urinary Potassium and Serum Electrolytes During Infusion of Placebo and Dopamine.

	0'	120'	180'	240'
Aldosterone (ng/dl)				
Control	6.8 ± 0.9	6.1 ± 1.2	5.0 ± 0.9	4.9 ± 1.0
Dopamine	9.3 ± 2.5	7.3 ± 1.0	8.0 ± 1.7	6.7 ± 1.1
PRA (ng/ml/hr)				
Control	2.80 ± 1.32	2.94 ± 0.94	2.60 ± 0.63	1.39 ± 0.38
Dopamine	2.87 ± 1.04	3.60 ± 1.38	2.52 ± 0.44	3.47 ± 1.14
Urine K (meq)				
Control		11 ± 2		11 ± 1
Dopamine		9 ± 2		11 ± 1
Serum Na (meq/l)				
Control	143 ± 1			
Dopamine	142 ± 1			
Serum K (meq/l)				
Control	4.3 ± 0.1			
Dopamine	4.2 ± 0.1			

Discussion

Dopamine is one of many hormonal systems involved in the regulation of salt and water metabolism. Infusion of dopamine augments sodium excretion (1), and dopaminergic mediation may be important in the natriuresis induced by volume expansion.

The exact site of dopamine action in the kidney is still in doubt. Multiple reports have shown vasodilating effects of dopamine on the renal circulation (3,12,13). It has been suggested that the sympathetic innervation of the kidney controls postglomerular vascular resistance (13) and that control of this mechanism is achieved through a balance between vasodilating effects of dopamine and vasocontrictive effects of norepinephrine. On the other hand, there is evidence in cats for a diuretic and natriuretic effect of dopamine which is not dependent on its vascular action (14) implying a direct tubular effect. Dopamine receptors were found to be present on proximal tubules (15).

In addition to direct (vascular or tubular) effects of dopamine on the kidney, interactions with other renal systems of volume regulation such as renin, kallikrein-kinin and prostaglandins as well as postulated "natriuretic peptide" (16) have been suggested as additional factors involved in renal effects of dopamine.
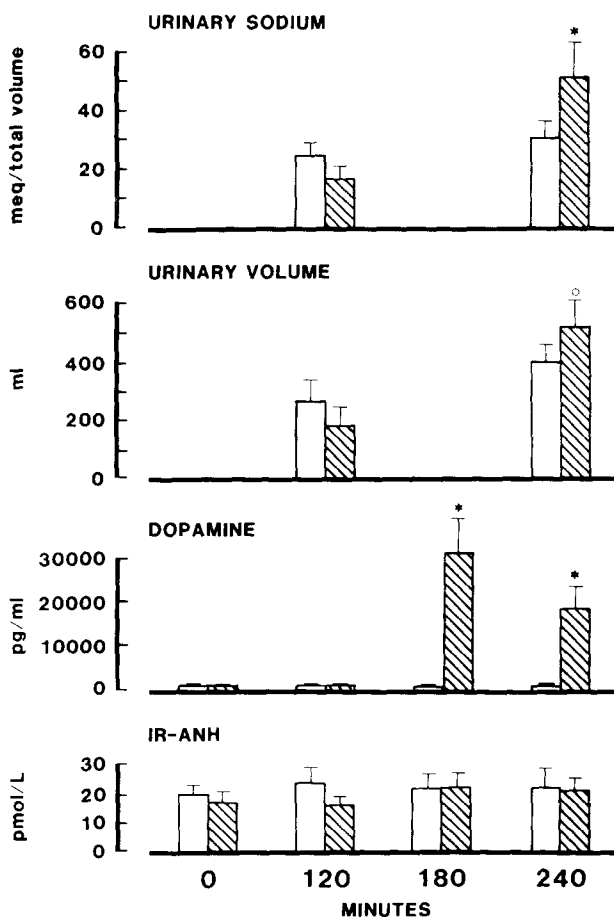
FIG. 1

Urinary sodium and volume, plasma dopamine and IR-ANH levels during placebo (open bars) and dopamine (hatched bars) administration.

Repeated measures ANOVA p <0.025 for urinary data p <0.01 for plasma dopamine.
* Newman-Keuls test α=0.05 compared to all other groups
o Newman-Keuls test α=0.05 compared to corresponding 120' data

The recently described natriuretic peptides collectively known as atrial natriuretic hormone have potent diuretic and natriuretic effects in animals (4,5) and humans (6,7). Conflicting data exist in regard to a possible role for stimulation of D_1 type dopamine receptors in mediating the diuretic and vasodilating actions of ANH. In one report (17) the diuretic response to atrial extract or synthetic ANH in anaesthetized rats was completely blocked by the dopamine receptor antagonists haloperidol and chlorpromazine. On the other hand, the specific D_1 anatagonist SCH 23390 did not block the selective renal vasodilating action of ANH (18). The possibility that increased ANH secretion is partially responsible for the natriuretic effects of dopamine has not been studied before.

In the present study, the infusion of dopamine did not cause any changes in plasma levels of renin activity or aldosterone. These results are similar to other studies reporting the effects of intravenous dopamine in normal man (19,20). Intravenous dopamine infusion caused a significant diuresis and natriuresis when compared to placebo (normal saline) and the plasma levels of dopamine rose dramatically (Figure 1). IR-ANH levels did not change. These results exclude a role for increased secretion of atrial natriuretic hormone in the natriuretic and diuretic effect of dopamine.

The dose of dopamine used in this study was chosen after preliminary studies in two subjects showed that infusion of 2 µg/kg/min was ineffective in producing natriuresis (data not shown). Previous studies have also shown a threshold dose of dopamine for natriuresis to be approximately 4 µg/kg/min (21). This dose of dopamine has been shown to have hemodynamic effects which are limited to renal and mesenteric vasodilation (22).

The only known stimulatory mechanism of ANH secretion in rats and humans is an increase in atrial volume. This has been shown by experiments with volume infusion, administration of vasopressors, water immersion, and chronic overload due to congestive heart failure (23-26). The stimulating effect of atrial distention cannot be blocked by vagotomy or β-blockade (27). Dopaminergic stimulation of atrial myocytes is another possible mechanism linking atrial stretch and secretion of the hormone. Based on the results of this study, however, a role for dopamine as a neurotransmitter involved in stimulation of ANH secretion appears unlikely.

Acknowledgments

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