Dopamine Tonically Modulates Natriuresis in the Saline-Expanded Dogs

Katsunori Honda, Tomoh Nunokawa, Kenzo Matsuzaki*, and Masahito Nagasaka**

Dopamine (DA) has been shown to be an endogenous catecholamine that promotes natriuresis by activating tubular DA receptors, but its role on natriuresis appears to be equivocal, and the precise mechanisms and signaling pathway of multiple DA's receptor subtypes are not yet clarified. We used low dose of DA intravenously in saline (S) volume-expanded dogs to see the alterations in natriuresis. The results showed that there is a critical dose that induces no enhancement of natriuresis of volume expansion, and that the lower and higher doses of DA produced relatively larger natriuresis. Pretreatment of metoclopramide (MCP) in this settings caused even higher and significant increases of natriuresis. In conclusion, DA seems to determine tonically the level of natriuresis in saline-expanded dogs. DA may exert a dual effect on signal transduction pathways such that one leading to antinatriuresis with high affinity and the other to natriuresis with low affinity signaling cascades for DA. MCP may block the antinatriuretic limb of the signaling pathway. (Hypertens Res 1995; 18 Suppl. I: S147-S150)

Key Words: dopamine (DA), metoclopramide (MCP), natriuresis, saline volume-expansion

DA is widely used in clinical situations where circulatory failure and oliguria exist (1). So, the mechanisms of actions of DA on the systemic and renal hemodynamics and also on the diuresis and natriuresis are extensively explored. However, DA has plural receptor subtypes and their various signal transduction systems in the vasculature and nephron segments in the kidney, and probably there may be more of them which are not yet recognized. And, the relative importance of DA arising from renal and extrarenal origin is equivocal and this makes the analysis once more difficult. Several lines of evidence suggest that endogenously produced renal DA from renal and nonrenal sources may play a physiological role in regulating Na excretion presumably through activation of tubular DA receptors (2). This time, we administered DA in dogs with S intravenously in a dose range which is thought not to affect systemic blood pressure. We observed that the natriuresis is modulated, compared with simple S volume expansion and some relevant parameters determined simultaneously. In one series, we administered DA receptor antagonist, MCP, prior to S infusion concomitant with DA.

Methods

Experimental Protocol
Female mogrel dogs (average body weight about 15 kg) were fed a normal dog-food diet with free access to water except on the day of experiment. Dogs were anesthetized with pentobarbital (25 mg/kg B.W.). Catheter was inserted into the urinary bladder. Then an intravenous (i.v.) infusion of 5% glucose solution at a rate of 1.67 ml/min was started for 1 h before the experiment as the control period. After the control period, physiological saline solution (S) 1,500 ml was drip-infused intravenously for 90 min as the volume expansion in all experiments. The experiments were performed as (1) concomitant drip infusion of DA [designated as (S + DA)] 1.5 mg as the control experiment, (2) 0.75 mg as the half dose of DA, (3) 3.0 mg as the double dose of DA, and (4) pretreatment infusion of MCP 10 mg i.v. (in volus), followed by DA and S as in the protocol (I) (MCP+S+DA).

Each series of 5 dogs experiments were performed. The average body weights of experimental dogs were 15.4 kg, 14.5 kg, 14.3 kg, and 15.1 kg, respectively, and in the group infused with control dose of DA this dose would be equivalent to 1.1 µg/kg/min in the average. DA solutions were prepared from Inovan (R) for injection (Kyowa Hakko Co. Ltd.). MCP was prepared from Primperan (R) for injection (Fujisawa Pharmacol. Industry Co. Ltd.). Blood and urine samples were collected just before the infusion and at each 30 min interval during and after the infusion till 210 min.

Analytical Procedures
Sodium and potassium concentrations in plasma and urine were determined by flame photometry (Japan Spectroscopic Co. Ltd., FLAME-30C). Chloride concentrations of serum and urine were determined

From the First Department of Medicine, Faculty of Medicine, the University of Tokyo, Tokyo, * the Third Department of Medicine, University of Teikyo, Chiba, **Tachikawa Sogo Hospital, Tachikawa, Japan.
Address for Reprints: Katsunori Honda, M.D., First Department of Medicine, Faculty of Medicine, the University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan.

by Chloride Meter (CORNING·EEL 920). Blood total protein (TP) was determined by Serum Protein Refractometer (Tukasa Co. Ltd.). Hematocrit (Ht) was determined by micropipet (Terumo Co. Ltd.) method. Plasma and urine creatinine concentrations were determined by Jaffe's reaction with preadsorption by Lloyd's reagent as modified by Henly. Plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were determined by RIA and the kits were purchased from DINABOT Co. Ltd.

For statistical analysis, t test was used. A statistical significance was considered when \( p < 0.05 \). All data are presented as mean ±SEM.

**Results**

The time courses of average GFR (creatinine clearance) and UV (urinary volume per min) in the experiment of simple S-expanded dogs [designated as (S)], (MCP+S+DA 1.5 mg), (S+DA 0.75 mg), (S+DA 1.5 mg), and (S+DA 3.0 mg) are shown in Fig. 1. Diuresis was nearly the same in (S+DA 1.5 mg) (control) and in (S). Relatively larger increase of diuresis was found in (S+DA 0.75 mg) and (S+DA 3 mg) than in the control. Much larger increase of diuresis was found in (MCP+S+DA 1.5 mg) than in the control, but it was statistically insignificant. No remarkable alterations of GFR were found in all groups.

Time courses of average values of urinary Cl, Na and K excretion rate (ECl, ENa and EK, respectively) in the same groups are shown in Fig. 2. Natriuresis in the control was the same as (S). Larger, but statistically insignificant, increase of natriuresis was found in (S+DA 0.75 mg) and (S+DA 3 mg) than the control, and statistically significant increase of natriuresis was found in (MCP+S+DA 1.5 mg). The same trend was found in ECl alterations, but kaliuresis was small and not different in all groups. PRA and PAC values were depressed during and after the volume expansion in all groups, that is renin and aldosterone system do not play a critical role in enhancement of natriuresis in our experimental conditions. Time courses of PRA and PAC are just the same as in (S+DA) series and did not differ in (MCP+S+DA) group. The trends in time courses of average FENa were the same as in all groups (not shown).

No remarkable alterations of time courses of average values of TP, Ht, plasma Cl, Na and K concentrations (PcCl, PcNa, and PK, respectively), and urinary Cl, Na, and K reabsorption rate (RcCl, RcNa, and RK, respectively) were found through all experiments (data not shown).

**Discussion**

DA has been used clinically in patients with circulatory failure and oliguria to support the blood pressure and maintain urine flow in small doses from 0.5 to 4.0 \( \mu g/\text{kg/min} \) (1). These authors concluded that sufficient data have been amassed to recommend the use of DA in doses of 0.5-2.0 \( \mu g/\text{kg/min} \) for postoperative oliguria when patient’s fluid status is adequately evaluated. Until now, it is well established that DA is a potent natriuretic and renal vasodilator agent in pharmacological usage. The mechanisms of this natriuretic action are considered
to be multiple; DA increases RPF and GFR, and inhibits the tubular transport of Na (3). DA infusion also increases urine cAMP excretion and this effect parallels the decreased reabsorption of Na by the tubules. This is taken by some to suggest that DA may play a regulatory role in renal Na handling (6). However, the data regarding the use of low dose of DA in not-critically ill subjects are incomplete.

Agnoli et al. (1987) reported in low dose (0.1 μg/kg/min DA) infusion experiment in normal women that (1) in hydro-saline retention induced by DOCA, DA produced typical vasodilator and hydro-natriuretic effects, (2) in hydro-saline depletion induced by diuretic treatment and low dietary Na intake, DA lost its vasodilator and natriuretic efficacy, manifesting, conversely, renal Na conserving effects mainly dependent on the increase in distal Na reabsorption and a trend towards glomerular afferent arteriolar vasoconstriction (5). In rat experiments, administered with l-DOPA (as precursor of DA), haloperidol (a blocker of DA receptor) and 6OHD (a potent inhibitor of catecholamine actions), Sato et al. (1987) concluded that locally-formed endogenous DA as well as circulating DA is unlikely to be important in the control of Na and water handling in the kidney (6). On the other hand, DA has been postulated by Jose et al. (1992) to act as an intrarenal natriuretic hormone (4). We used small dose of DA (about 1.1 μg/kg/min as the median) in saline volume-expanded dogs in order not to raise blood pressure and investigated the alterations in natriuresis of volume expansion (about 10% BW). The results showed (1) 1.1 μg/kg/min DA produced no increase of natriuresis in saline-expanded dogs compared with simple saline-expanded dogs, (2) statistically insignificant, but relatively larger, natriuresis was found in dogs with the half and double doses of DA with saline volume expansion compared with the control group, (3) with pretreatment of MCP, dogs with control dose of DA produced significant increase of natriuresis, which suggested that firstly the critical dose with the lowest natriuresis was 1.1 μg/kg/min and more or less doses of DA gave biphasic response in both direction, with enhancement of natriuresis of saline expansion, and secondly DA in lower than the critical dose would act as a antinatriuretic agent in a dose-dependent manner, and above the critical dose it would behave as a natriuretic principle as usually documented. It is considered that DA may have dual signaling pathways in the kidney, the one lead-

![Fig. 2. Time courses of PRA, PAC, and urinary electrolyte excretion rate in (S) (MCP + S + DA 1.5 mg), (S + DA 0.75 mg), (S+ DA 1.5 mg), and (S+ DA 3.0 mg) experiments.](image-url)
Precise mechanisms of these two pathways are presently unclear, but saline expansion might have dissected the existence of such contradictory dual pathways. Using conscious rats injected with MCP under isotonic ECFV expansion, Nati et al. (1994) reported and discussed a role of DA acting via DA2 receptors on renal Na excretion (7). However, our low dose of DA infusion experiment in saline volume-expanded dogs would be explained by a model in which multiple subtypes of DA and multiple second messengers have effects on Na-linked transporters and Na-pump for the modulation of natriuresis. At what step these contradictory bifurcation occurs is to be determined (Fig. 3).

As for the effect of MCP, it may be considered that MCP blocks the antinatriuretic limb of the bifurcating signaling pathway, remaining the activity of the natriuretic limb unopposed. Future investigation will elucidate the precise routes of these interesting dichotomy. In regard to the known effects of MCP on promoting aldosterone secretion, in our experimental settings, saline volume expansion may have offset the often-cited elevation of PAC.

**Fig. 3.** Presumed schema on DA and natriuresis-antinatriuresis systems in our low-dose DA infusion experiments in saline-expanded dogs and dogs with MCP pretreatment systems.

**References**