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Influence of Yohimbine on the Central Dopaminergic Regulation of Renal Function

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ABSTRACT

Recently it has been shown that central dopaminergic system regulates the renal function and that intracerebroventricularly (icv) administered dopamine (DA) produces antidiuresis and antinaturiuresis, resembling icv norepinephrine, and evidence has been accumulated which would suggest the involvement of adrenergic system in the DA effects. It was attempted therefore in this study to see whether the DA effect is influenced by pretreatment of yohimbine which is known as a specific α_2-adrenoceptor antagonist.

Yohimbine produced, when given icv in doses of 100 μg/kg, marked antidiuresis and antinatriuresis along with decreases in renal perfusion and glomerular filtration. DA, in doses of 15 μg/kg, also produced antidiuresis and antinaturiuresis. However, after yohimbine-pretreatment DA 15 μg/kg improved renal hemodynamics, and electrolyte excretion and urine flow rate transiently increased. With 150 μg/kg DA, the antidiuresis was more marked in the control group. But the yohimbine-pretreated animals responded with marked diuresis and natriuresis, sodium excretion increasing more than three-fold, which lasted for 20 minutes. K^+-excretion, osmolar clearance as well as free-water reabsorption increased. Renal hemodynamics improved partly.

Apomorphine, a DA agonist, when given icv in doses of 150 μg/kg, produced diuresis and naturiuresis, concomitant with increased renal hemodynamics. Yohimbine-pretreatment however did not abolish the apomorphine-induced diuresis and naturiuresis. Antidiuresis and antinatriuresis elicited by norepinephrine, 10 μg/kg, was not affected by yohimbine-pretreatment.

These results indicate that the renal effects of icv DA is not so simple as those of norepinephrine, and the diuretic natriuretic effect which had been masked by the hemodynamic effect becomes manifest only when the decreases in hemodynamics were removed by the pretreatment of yohimbine. It was further suggested that those DA receptors which mediate the natriuretic response to icv DA is not affected by yohimbine, whereas those receptors involved in the decrease in renal hemodynamics are blocked by yohimbine. And the possibility of involvement of adrenergic system in the DA action is not substantiated.

Key Words: Central DA system, Renal function, Yohimbine, Natriuresis, Diuresis
Abbreviations: DA, dopamine; Yo, yohimbine; NE, norepinephrine; icv, intracerebroventricular

INTRODUCTION

Renal function is under constant regulation of CNS either via humoral agents or through nerve pathways, among which the adrenergic system plays the most important roles (Andersson *et al.*, 1969; Gottschalk, 1979; Kim *et al.*, 1980; Kook, 1975; Kook *et al.*, 1984). Recently, it has been shown that dopamine, the most abundant catecholamine in the brain, and its receptors also participate in the central modulation of the renal function (Choi, 1974; Moore and Bloom, 1978). Dopamine (DA), when administered directly into a lateral ventricle (icv) of rabbit brain, produces antidiuresis and decreases in renal hemodynamics in a dose-dependent manner (Choi,

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1974; Kim *et al.*, 1982), and these effects are blocked by icv administration of DA antagonists, indicating that central DA-receptors are involved in the effect (Kim *et al.*, 1982; Kim, 1984). Haloperidol, a DA antagonist, elicits diuresis and natriuresis when given icv in rabbit (Kim *et al.*, 1982), and certain agonists of DA receptors were found to induce natriuresis and diuresis when administered icv (Cho, 1983; Kook *et al.*, 1985a). All these observations strongly suggest that central dopaminergic system also plays a role in the regulation of renal function.

Recently, however, it was reported that DA agonists produce presynaptic inhibition of noradrenergic transmission in the rabbit hypothalamus (Galzin *et al.*, 1982), and the norepinephrine release in rabbit hippocampus is modulated not only by alpha-2 adrenoceptors but also by presynaptic D_2-receptors (Jackisch *et al.*, 1984; Jackisch *et al.*, 1985). Also, there are several lines of evidence indicating that DA receptors are located on the central noradrenergic neurons. Thus, it is possible that adrenergic system may be involved in the manifestation of renal effects of central DA system.

Yohimbine is known as a specific blocking agent of the presynaptic alpha-2 adrenoceptors (Goldberg and Robertson, 1983), and it augments norepinephrine release from peripheral nerve endings (Starke *et al.*, 1975) as well as from brain tissue (Dietl *et al.*, 1981; Goldberg and Robertson, 1983). Thus, by increasing the sympathetic tone to the kidney, it can produce antidiuresis and antinatriuresis along with decreases in renal perfusion and glomerular filtration when administered icv in rabbits (Kook *et al.*, 1985b). And these effects of icv yohimbine was abolished by pretreating the rabbits with reserpine.

The present study was undertaken therefore to clarify the interrelationship between both system in central regulation of renal function, by observing the influence of blocking the central α_2-adrenoceptors upon the renal effects of various DA agonists and norepinephrine administered icv in the rabbits.

METHODS

Adult rabbits of either sex, weighing 1.7-2.3 kg, were anesthetized with 1 g/kg urethane s.c. Free air passage secured by a T-tube in trachea. Infusion of 0.3% NaCl and 3% glucose solution containing 45 mg% of para-aminohippuric acid (PAH) and 250 mg% of creatinine (cr) was given at a rate of 0.5 ml/min into an ear vein. Through a small midline incision close to symphysis, both ureters were cannulated with PE tubings for urine collection, and for obtaining blood samples a femoral artery was cannulated with PE tubing filled with heparin-saline (400 U/ml). For the intracerebroventricular (*icv*) administration of the agents a lateral ventricle of the cerebrum was cannulated. After fastening the animal in prone position, a hole was drilled on the skull at a point 1.5 cm rostral to the occiput tubercle and 0.5 cm lateral to the midline, and a cannula made of PE tubing of 1.5 mm O.D. was introduced obliquely until the clear cerebrospinal fluid appeared in the cannula, and then it was kept in place by cementing to the bone. The volume administered did not exceed 0.15 ml. At the end of each experiment the location of the cannula was checked.

When urine flow rate became stable several hours after initiation of infusion, collection of the clearance samples was begun. After two ten-minute clearance periods, the agents was given and then four or five clearance samples of 10-min or 20-min periods were collected. The blood samples were immediately centrifuged to separate the plasma.

Quantitative analyses of creatinine were done by the method of Phillips (1944) and PAH by the methods of Smith *et al.*, (1945). Na^+ and K^+ concentrations were determined by flamephotometry, and the osmolality with "Advanced" osmometer. Statistical significance was assessed with Student's paried *t*-test for the changes of renal function from the control period, and when comparing two groups of animals the unpaired *t*-test was employed (Snedecor & Cochran, 1980). For multiple group comparison an analysis of variance followed by Bonferroni's adjustment was applied (Wallenstein *et al.*, 1980).

Yohimbine hydrochloride, dopamine hydrochloride, apomorphine hydrochloride and norepinephrine bitartrate were obtained from Sigma Co. The doses administered were calculated as bases and dissolved in 0.9% NaCl solution immediately before the administration.

RESULTS

I. Influence of Yohimbine on the Dopamine Action

Yohimbine when given intracerebroventricularly (icv) elicits antidiuresis and antinatriuresis along with decreases in renal hemodynamics in doses ranging from 10 to 100 μg/kg. Table 1 shows the effects of 100 μg/kg icv yohimbine, as summarized

Table 1. Effect of yohimbine 100 μg/kg icv on the rabbit renal function

	Control	0′-10′	10′-20′	20′-40′	40′-60′	60′-80′
Vol (ml/min)	0.332±0.064	0.099±0.024*	0.076±0.027*	0.139±0.015*	0.227±0.045	0.223±0.053
C_{PAH} (ml/min)	16.29±3.87	3.94 ±1.75**	4.50 ±2.71*	9.11 ±2.33*	10.77±2.42	9.45 ±2.47*
C_{cr} (ml/min)	6.12±1.14	1.74±0.55**	1.71 ±0.86**	3.74 ±0.97*	4.39±1.13*	4.13 ±1.22*
$U_{Na}V$ (μEq/min)	11.0 ±2.1	3.6 ±1.1*	2.8 ±1.2*	5.4 ±1.3*	9.7 ±1.7	9.1 ±1.7
FE_{Na} (%)	1.57±0.49	1.85 ±0.57	1.66 ±0.45	1.46 ±0.45	2.24 ±0.59	2.83 ±0.65
U_KV (μEq/min)	3.7 ± ±0.4	1.3 ±0.4***	1.4 ±0.7**	2.7 ±0.5*	3.5 ±0.8	3.3 ±0.8

Mean ± S.E. from 5 experiments. Abbreviations: Vol, rate of urine flow; C_{PAH} and C_{cr} are clearance of PAH and creatinine, resp.; $U_{Na}V$ and U_KV are excretory rates of sodium and potassium, resp.; FE_{Na} is fractional excretion of filtered sodium. Significance of paired differences from control periods were tested with Student's *t* test. *p<0.05; ** p<0.01; ***p<0.001.

Table 2. Effect of dopamine 150 μg/kg icv on the rabbit renal function

	Control	0′-10′	10′-20′	20′-40′	40′-60′	60′-80′
Vol (ml/min)	0.236±0.029	0.245±0.034	0.167±0.025*	0.131±0.033**	0.170±0.061	0.179±0.068
C_{PAH}(ml/min)	15.94±1.91	15.59±1.95	12.21±1.84*	9.63 ±1.62**	11.25±1.28**	8.36 ±1.20**
C_{cr} (ml/min)	5.95±0.56	5.68±0.52	4.52±0.57*	3.82±0.61**	4.76±0.69	3.65 ±0.58***
$U_{Na}V$(μEq/min)	3.29±0.75	3.37±0.86	2.47 ±0.73	1.11 ±0.34***	0.96 ±0.31**	1.13 ±0.37*
FE_{Na} (%)	0.48±0.13	0.46 ±0.13	0.43 ±0.12	0.21 ±0.05**	0.14 ±0.04**	0.22 ±0.06
U_KV (μEq/min)	5.16±0.90	5.04 ±0.97	4.03 ±0.86	2.61 ±0.59**	2.54 ±0.55**	2.46 ±0.68**

Mean ± S.E. from 14 experiments. Legends as in Table 1.

Table 3. Influence of yohimbine pretreatment on the renal function of dopamine

	Control	0′-10′	10′-20′	20′-30′	30′-40′	40′-60′	60′-80′	80′-100′
Vol (ml/min)	0.284±0.029	0.100±0.016**	0.131±0.022**	0.387±0.066	0.414±0.112	0.273±0.050	0.146±0.031*	0.185±0.037
C_{PAH}(ml/min)	18.95±4.09	6.59±2.41**	9.08±3.04**	18.54±3.76	16.52±3.98	13.74±2.41	11.79±2.58*	10.78±2.30*
C_{cr} (ml/min)	7.01±1.15	3.25 ± ±1.13**	4.38 ±1.37*	6.25±1.43	6.03±1.25	4.98±0.91**	5.40±1.17	5.10±1.03
FF (%)	39.9 ±2.9	50.7 ±1.8**	50.1 ±2.2**	33.2 ±2.8	38.6 ±3.5	36.6 ±2.9	46.2 ±2.5	48.0 ±2.8
$U_{Na}V$ (μEq/min)	7.2 ±0.8	2.7 ±0.9*	4.1 ±1.4	21.7 ±5.8*	23.5 ±9.6	12.6 ±4.3	2.9 ±1.3**	2.8 ±1.7*
FE_{Na}(%)	0.91 ±0.3	0.85±0.34	0.93±0.35	3.26±1.04*	3.11±1.02	2.10±0.60	0.55±0.25*	0.52±0.27
U_KV (μEq/min)	8.1 ±1.1	3.2 ±1.0***	3.8 ±1.1***	9.0 ±1.4	8.6 ±2.4	6.4 ±1.7	3.3 ±0.8***	3.0 ±0.7***
C_{osm} (ml/min)	0.458±0.023	0.180±0.037***	0.224±0.044**	0.543±0.070	0.549±0.109	0.394±0.050	0.239±0.036	0.235±0.040
T^cH_2O (ml/min)	0.174±0.041	0.080±0.026*	0.093±0.024*	0.156±0.030	0.135±0.028	0.121±0.023	0.092±0.017	0.051±0.016*

Mean ± S.E. from 6 experiments. Yohimbine 100 μg/kg icv was given at 0′ and dopamine 150 μg/kg icv at 20′. FF is filtration fraction; C_{osm} denotes clearance of osmotically active substances; T^cH_2O is reabsorption of free water.

from 5 experiments. All the parameters of renal function promptly decreased immediately following the administration, to reach to one quarter to one half of the control values for twenty minutes, and then these effects gradually receded toward the preinjection levels.

Table 2 shows the effects of 150 μg/kg dopamine (DA) icv, maximal effective dose, on the renal function from 14 rabbits. The renal hemodynamics declined from 10 minutes after the administration to reach the minimum values after 20 minutes. Urine flow rate and excretory rates of electrolytes also decreased significantly after 20 minutes. These effects lasted long and did not recover until the end

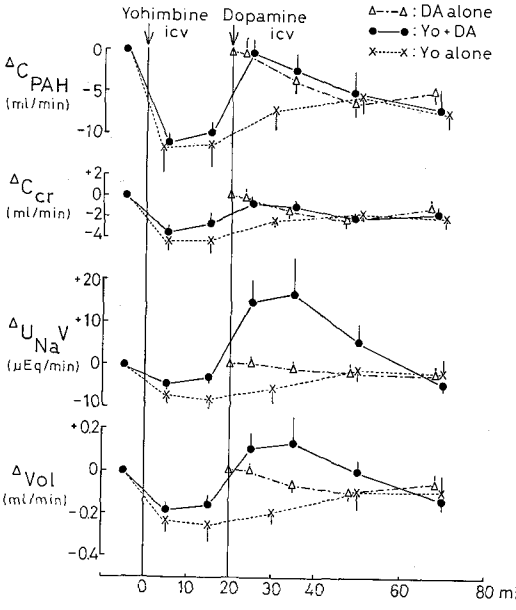

Fig. 1. Influence of pretreatment with yohimbine on renal effects of icv dopamine. Yo: Yohimbine 100 μg/kg icv, DA: Dopamine 150 μg/kg icv. Mean differences and one S.E. are depicted.

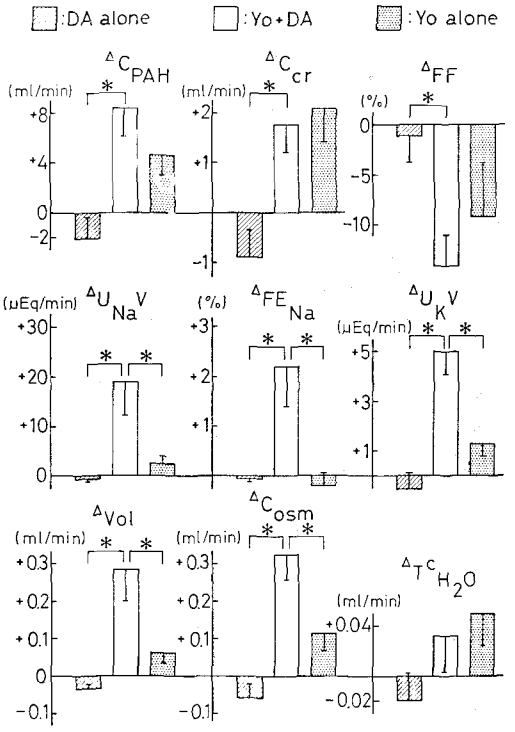

Fig. 2. Comparison of changes of renal function induced by dopamine (DA) alone, yohimbine (Yo) alone and dopamine after pretreatment of yohimbine (Yo + DA). Differences between the value during 20 minutes after the administration and the value of 10 min period before the administration were calculated from Table 1, 2 and 3 and mean differences and one S. E. are depicted. Asterisks indicate significant difference between groups.

of experiments.

The data from 6 experiments in which dopamine 150μg/kg was given icv 20 minutes after the yohimbine administration are summarized in Table 3. As clearly seen here typical antidiuresis and antinatriuresis as well as decreases in renal hemodynamics followed the yohimbine administration. However, dopamine produced, contrary to the control experiment without yohimbine pretreatment, remarkable natriuresis which amounted to three-fold of pre-yohimbine values and lasted for 20 minutes, and increases of K^+ excretion and urine flow rate. Renal plasma flow and glomerular filtration transiently recovered but did not exceed the pre-yohimbine levels.

Fig. 1. depicts the changes of several parameters of renal function from the control values, comparing three groups. It seems clear that after yohimbine pretreatment dopamine produces natriuresis, as contrasted to the antinatriuresis and antidiuresis elicited by dopamine alone. However, the renal function begins to recover from 20 min after the yohimbine administration, when dopamine was given after yohimbine. Therefore, in comparing the dopamine effects between both the yohimbine-pretreated and the non-treated groups, changes in "Yo alone" group was taken as control. Fig. 2 compares three groups, in which the values for "Yo + DA" group were calculated as the differences between the after-DA value (mean of the 20′-30′ value and the 30′-40′) and the before-DA value (the 10′-20′ value), and the values for "Yo alone" were the difference between the 20′-40′ value and the 10′-20′. It is clear that in all parameters except for T^cH_2O the yohimbine-pretreated group ("Yo + DA") significantly differed from the nontreated group ("DA alone"), whereas it was not significantly different from "Yo alone" group in changes of renal hemodynamics.

Reducing the doses of dopamine to 15 μg/kg icv elicited less prominent but still significant antinatriuresis and antidiuresis. However, after yohimbine pretreatment it produced increases in renal hemodynamics as well as in electrolyte excretion, as

shown in Table 4. All parameters except for filtration fraction differed significantly between both groups. The changes in the "Yo+DA15" group were, however, not significantly different from those of the yohimbine-alone group shown in Table 1, indicating that smaller doses of dopamine can produce antinatriuresis and antidiuresis which is abolished by yohimbine, but are not potent enough to elicit marked natiuresis and diuresis, which can be unfolded under the influence of icv yohimbine.

II. Influence of Yohimbine on the Apomorphine Action

Apomorphine 150 μg/kg icv produced marked diuresis and natriuresis which lasted for 40 minutes, along with a transient increase in filtration rate, as summarized in Table 5. The fractional excretion of sodium increased from 1.48% to 5.28%. The influence of yohimbine-pretreatment on the apomorphine effects were observed in 6 rabbits and summarized in Table 6. As seen here, the decreases in renal function induced by yohimbine were

Table 4. Changes of renal function induced by 15 μg/kg dopamine with and without pretreatment of yohimbine

	DA 15	Yo + DA 15
Vol (ml/min)	−0.031 ± 0.014	+0.079 ± 0.031**
C_{PAH} (ml/min)	+0.40 ± 0.17	+5.90 ± 2.43*
C_{cr} (ml/min)	+0.183 ± 0.051	+2.27 ± 0.41*
FF (%)	+0.16 ± 0.74	−6.31 ± 3.82
$U_{Na}V$(μEq/min)	−2.33 ± 1.27	+3.14 ± 0.89**
FE_{Na} (%)	−0.578 ± 0.216	+0.034 ± 0.071*
U_KV (μEq/min)	−0.18 ± 0.14	+2.12 ± 0.54**
C_{osm} (ml/min)	−0.017 ± 0.022	+0.122 ± 0.035**
T^cH_2O (ml/min)	+0.009 ± 0.006	+0.055 ± 0.014*

Mean ± S.E. from 6 experiments, each. Data are the differences between the values of 20 min period following dopamine (DA 15 μg/kg icv) administration and the values before DA administration. Yo: Yohimbine 100 μg/kg icv. Significant differences between both groups are marked with asterisks (*$p<0.05$ and **$p<0.01$).

Table 5. Effect of apomorphine 150 μg/kg icv on the rabbit renal function

	Control	0′-10′	10′-20′	20′-40′	40′-60′	60′-80′
Vol (ml/min)	0.41 ± 0.10	0.98 ± 0.24*	0.75 ± 0.20*	0.61 ± 0.12*	0.36 ± 0.10	0.30 ± 0.10*
C_{PAH} (ml/min)	23.3 ± 2.7	34.8 ± 7.0	22.7 ± 3.6	20.4 ± 2.5	15.9 ± 1.9*	13.4 ± 1.4*
C_{cr} (ml/min)	7.71 ± 0.71	9.75 ± 1.11*	7.52 ± 0.96	7.13 ± 0.65	6.52 ± 0.56	5.61 ± 0.55*
$U_{Na}V$ (μEq/min)	18.3 ± 5.2	62.5 ± 18.8*	53.5 ± 14.1**	37.2 ± 9.6**	14.7 ± 4.5	10.2 ± 2.6
FE_{Na} (%)	1.48 ± 0.39	4.39 ± 1.14*	5.28 ± 1.50*	3.80 ± 1.19*	1.62 ± 0.47	1.28 ± 0.34
U_KV (μEq/min)	7.3 ± 1.3	11.2 ± 2.0*	9.3 ± 1.4	8.4 ± 0.9	7.0 ± 0.6	6.0 ± 0.6
C_{osm} (ml/min)	0.43 ± 0.05	0.88 ± 0.15**	0.73 ± 0.10**	0.57 ± 0.07*	0.39 ± 0.07	0.30 ± 0.03*
T^cH_2O (ml/min)	0.02 ± 0.08	−0.10 ± 0.13	−0.02 ± 0.12	−0.02 ± 0.08	0.03 ± 0.08	0.00 ± 0.09

Mean ± S.E. from 7 experiments.

Table 6. Influence of yohimbine pretreatment on the renal function of apomorphine

	Control	0′-10′	10′-20′	20′-30′	30′-40′	40′-60′	60′-80′
Vol (ml/min)	0.341 ± 0.043	0.187 ± 0.032*	0.209 ± 0.033*	0.494 ± 0.091	0.456 ± 0.083	0.297 ± 0.059	0.219 ± 0.040**
C_{PAH}(ml/min)	17.09 ± 1.47	8.69 ± 1.51**	12.08 ± 1.15*	19.01 ± 1.86	15.70 ± 1.02	13.59 ± 1.48*	13.33 ± 1.30
C_{cr} (ml/min)	6.17 ± 0.61	3.42 ± 0.57*	4.80 ± 0.59*	7.20 ± 0.53	6.19 ± 0.42	5.23 ± 0.66	5.09 ± 0.53
$U_{Na}V$(μEq/min)	10.7 ± 2.0	5.0 ± 1.5**	4.6 ± 1.1*	30.2 ± 9.2	30.5 ± 9.2	13.8 ± 3.1	4.7 ± 1.6
FE_{Na} (%)	1.36 ± 0.28	1.13 ± 0.25	0.69 ± 0.15	3.35 ± 1.07	3.88 ± 1.15	2.14 ± 0.50	0.69 ± 0.22
U_KV (μEq/min)	7.7 ± 1.4	4.3 ± 1.0**	4.8 ± 1.1	9.3 ± 2.0	7.9 ± 1.2	5.3 ± 0.8	4.0 ± 0.7*
C_{osm} (ml/min)	0.487 ± 0.073	0.271 ± 0.049*	0.345 ± 0.061	0.730 ± 0.118	0.668 ± 0.090	0.460 ± 0.071	0.361 ± 0.060*
T^cH_2O (ml/min)	0.147 ± 0.049	0.084 ± 0.034	0.136 ± 0.031	0.236 ± 0.045*	0.213 ± 0.043	0.164 ± 0.052	0.141 ± 0.043

Mean ± S.E. from 6 experiments. Yohimbine, 100 μg/kg icv was gien at 0′ and apomorphine 150 μg/kg icv was given at 20′

Table 7. Changes of renal function induced by apomorphine with or without yohimbine-pretreatment

	Apo	Yo + Apo
Vol (ml/min)	+0.457±0.012	+0.267±0.081†
C_{PAH} (ml/min)	+5.43 ±2.98	+5.28 ±5.26
C_{cr} (ml/min)	+0.92 ±0.41	+1.89 ±0.23
FF (%)	−1.85 ±1.71	+0.00 ±2.9
$U_{Na}V$ (μEq/min)	+39.7 ±9.9	+25.8 ±8.4†
FE_{Na} (%)	+3.56 ±0.99	+3.01 ±1.05†
U_KV (μEq/min)	+3.0 ±0.4	+3.8 ±0.5‡
C_{osm} (ml/min)	+0.383±0.066	+0.355±0.069†
T^cH_2O (ml/min)	−0.075±0.05	+0.088±0.018*

Mean±S.E. from 6 experiments, each. Differences between the 20 min values after Apo (apomorphine 150 μg/kg icv) and the value before Apo were taken as the changes induced by Apo. *: Significantly different ($p<0.05$) between both groups. Significant differences from the yohimbine (Yo)-only group (Table 1) are marked with † ($p<0.05$) and ‡ ($p<0.01$). For the "Yo alone" group, difference between values at the 10'-20' period and the mean values of (20'-30') + (30'-40') period were taken.

Table 8. Changes of renal function by norepinephrine (10μg/kg icv) with and without pretreatment of yohimbine (100 μg/kg icv)

	NE	Yo + NE
Vol (ml/min)	−0.077±0.037	+0.018±0.021*
C_{PAH} (ml/min)	−3.50 ±1.31	+2.89 ±0.83**
C_{cr} (ml/min)	−1.35 ±0.76	+0.64 ±0.31**
FF (%)	+0.95 ±2.06	−10.0 ±3.3*
$U_{Na}V$ (μEq/min)	−4.4 ±2.2	+0.4 ±1.1
FE_{Na} (%)	−0.03±0.38	−0.05 ±0.18
U_KV (μEq/min)	+1.7 ±0.5	+0.6 ±0.6
C_{osm} (ml/min)	−1.2 ±0.04	+0.030±0.029**
T^cH_2O (ml/min)	−0.05 ±0.02	+0.021±0.008**

Mean±S.E. from 6 experiments, each. Data are differences between the 20 min values after NE and the 10 min values before NE. Significant differences from the NE group are marked with * $p<0.05$ and ** $p<0.01$. No significant differences from yohimbine alone group are noted.

promptly abolished by apomorphine, and sodium excretion increased three-fold above the control levels for twenty minutes while renal perfusion and glomerular filtration only slightly and transiently increased.

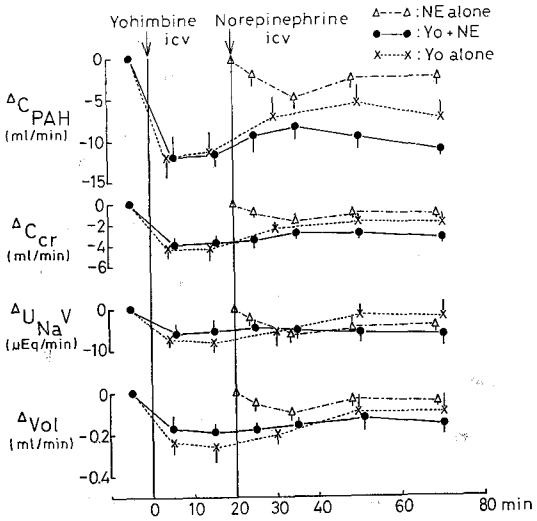

Fig. 3. Influence of pretreatment with yohimbine on renal effects of icv norepinephrine. Yo: Yohimbine 100 μg/kg icv, NE: Norepinephrine 10 μg/kg icv. Mean differences and one S.E. are depicted.

In Table 7 the changes brought about by apomorphine are compared between both the yohimbine-pretreated and the non-treated groups. As clearly seen here, no significant differences between both groups were found except for the free-water reabsorption. Also, the values of "Yo + Apo" group were not significantly different from those of apomorphine-alone group, indicating that icv yohimbine could not influence the effects of icv apomorphine.

III. Influence of Yohimbine on the Norepinephrine Action

Norepinephrine, 10 μg/kg icv, produced significant decreases in renal hemodynamics and urine flow rate, reaching the minimum values at the second ten-minute period, and the excretion of electrolytes as well as osmolar clearance also decreased to about 2/3 of the control level, as shown in Fig. 3. However, even after yohimbine-pretreatment the norepinephrine effects were not reverted to a diuretic one, and the antidiuresis was sustained as clearly seen from Fig. 3. Table 8 compares changes induced by norepinephrine between both the yohimbine-pretreated and the non-treated groups. In most parameters both groups differed significantly, but the changes in "Yo-NE" group did not differ from

those of yohimbine-alone group, indicating that the changes in the former group were brought abrout entirely by yohimbine. It is thus suggested that under the influence of yohimbine, norepinephrine cannot unfold its antidiuretic effect and that no diuretic, natriuretic component is comprised in the effect of norepinephrine.

DISCUSSION

The present study clearly shows that the icv DA-induced antidiuresis and antinatriuresis can be abolished by icv yohimbine (Yo) which can also produce antidiuresis and antinatriuresis and that under the influence of Yo, large doses of DA can elicit marked natriuresis and diuresis. It is further noted that the natriuresis and diuresis induced by icv apomorphine (Apo) was not abolished by Yo-pretreatment and that the antidiuretic effects of norepinephrine (NE) was not affected by Yo.

The sympatho-adrenal system has been shown to influence the renal function, mainly through changes in renal hemodynamics (Bello-Reuss *et al.*, 1976; Gottschalk *et al.*, 1979), although tubular transport mechanisms may also be affected directly (Gill and Casper, 1972; Kim *et al.*, 1980). When NE was administered icv in rabbits, antidiuresis followed, presumably through increased sympathetic tone to the kidney (Lee, 1972), and phenoxybenzamine icv produced natriuresis (Kook *et al.*, 1985c), suggesting that the central sympathetic system had been exerting an inhibitory influence upon the renal function. Furthermore, clonidine, an α_2-adrenoceptor agonist, which inhibits the sympathetic outflow in the periphery, was reported to induce natriuresis when given icv in rabbits (Kook *et al.*, 1984). On the other hand, Yo, a specific α_2-adrenoceptor antagonist, was found to elicit antidiuresis when given icv (Kook *et al.*, 1985b), most likely by increased sympathetic tone. Based on these factors, the present observation on the NE effect may be plausibly accounted for, that is, because NE release had been already fully enhanced by blockade of α_2-adrenoceptors with Yo, NE administered could no longer elicit any discernible effect of its own and the antidiuresis tended to last longer.

Dopamine administered icv also produces antidiuresis, presumably by decreasing renal hemodynamics, likewise as with NE (Choi, 1974). However, the DA effects seem not to be as simple as those of NE. Haloperidol, an unspecific DA antagonist, icv produced diuresis (Kim *et al.*, 1982). However, after metoclopramide-pretreatment, DA produced transient natriuresis, suggesting that certain natriuretic diuretic component may be participating in the DA effect (Kim, 1984). The present observation also indicates that the renal effects of icv DA are complex, as the diuresis and natriuresis were revealed by Yo-pretreatment. It has been shown that there exist DA receptors on the central adrenergic neurons which regulate NE release, likewise as α_2-adrenoceptors (Dietl *et al.*, 1981). If DA would have stimulated these receptors, the sympathetic tone might have been decreased, resulting in diuresis, contrary to our observations. If, however, one assumes that DA would antagonize those DA receptors on the adrenergic neurons, the antidiuresis observed in our study might be possibly explained. But, no evidence is at hand suggesting an antagonistic action of DA on those receptors. Thus, it seems unlikely that sympathetic component is involved in the icv DA effects.

It has been repeatedly shown from various lines of evidence that Yo exerts its action mainly by blocking α_2-adrenoceptors in the center as well as in the peripheral tissues (Starke *et al.*, 1975; Charney *et al.*, 1982; Goldberg and Robertson, 1983). In addition, it has also been reported that Yo influences not only on the serotonergic system (Sanghvi and Gershon, 1970), but also on the DA system (Tayo, 1979; Goldberg *et al.*, 1983). Yo blocks DA receptors as well as adrenoceptors (Scatton *et al.*, 1980) and the DA receptors affected by Yo were suggested to be of D-2 type (Jackisch *et al.*, 1985). Our present observations may be best accounted for if one assumes that Yo antagonizes DA receptors and that only those receptor subtypes which are involved in reduction of renal hemodynamics may be blocked, whereas those which mediate natriuresis may not be affected by Yo. In rabbits without Yo-pretreatment DA would stimulate both types of DA receptors, but the hemodynamic effects mediated by the former pathway may predominate and overwhelm the natriuretic effect mediated by the latter. And only when the former are blocked by Yo, the natriuretic effects can be disclosed fully. Further observations in our laboratory showing that the natriuresis induced by DA after Yo-pretreatment may be reduced by haloperidol and that it is transferrable to rats (in preparation) also support the presumption that certain subtypes of DA receptors are involved in the natriuretic effects and further suggest that natriuretic factor may be involved in the diuresis.

Apomorphine (Apo) was reported to be a dual agonist of DA system, stimulating DA receptors in smaller doses, whereas in larger doses it can

antagonize the receptors (Kebabian and Calne, 1979), and was found to elicit natriuresis and diuresis in rabbits when given icv (Cho, 1983). Also in the present sutdy icv Apo produced natriuresis and diuresis which were not abolished by Yo-pretreatment, and it did not elicit decreases in renal hemodynamics. Thus, one can speculate that Apo, differing from DA, might affect the DA system differentially, that is, either by blocking those DA receptors effecting reduction of renal hemodynamics or by stimulating those involved in mediating natriuresis. Whether the natriuresis elicited by icv Apo shares the mechanism responsible for the natriuresis by DA is one of the questions to be answered in further investigation.

Overall, the present study suggests that the renal regulation via central DA system is dual in nature, that the antidiuretic effects resulting from decreased renal hemodynamics predominate the natriuresis possibly mediated by humoral factor, and that yohimbine may block the former pathway, thus under its influence DA could unravel the natriuretic effect.

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=국문초록=

신장기능의 중추 Dopamine성 조절에 미치는 Yohimbine의 영향

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중추 dopamine(DA)계가 신장기능 조절에 관여하고 있으며 뇌실내로 DA를 투여하면 norepinephrine(NE)처럼 항이뇨와 항Na 배설을 초래함이 보고된 바 있고, 중추 DA작용에 있어서 adrenergic system이 관여한다는 많은 시사가 있다. 따라서 본 연구에서는 alpha-2 adrenoceptor 차단제인 yohimbine이 측뇌실내 DA의 신장작용에 어떠한 영향을 미치는가를 관찰하였다.

Yohimbine 100μg/kg을 가토측뇌실내로 투여시(icv) 신혈류 및 사구체 여과율의 감소와 함께 현저한 항이뇨 및 Na 배설감소를 초래하였으며, DA 15μg/kg icv 역시 항이뇨를 초래하였으나 yohimbine 전 처치후에는 뇨량 및 Na배설의 증가를 초래하였다. 양을 더올려 150μg/kg의 DA를 yohimbine 전처치 가토에 투여하면 3배 이상의 Na배설 증가와 함께 현저한 이뇨작용이 나타났으며 이 작용은 약 20분간 지속되었다. 이때 신혈류 역학은 일부 개선되었다.

다른 DA agonist인 apomorphine은 150μg/kg icv로 현저한 이뇨와 Na 배설증가를 나타내며 신혈류역학도 개선하였으나, yohimbine은 이같은 apomorphine작용을 차단하지 못하였다. NE 10μg/kg icv도 항이뇨 작용을 나타냈으나 yohimbine 전처치에 의하여 차단되지 아니하였다.

이 연구결과로, 중추 DA의 신장작용은 NE처럼 단순하지 않고, 이뇨작용은 신혈류역학의 감퇴에 기인한 항이뇨작용에 의해 은폐되어 있으며, yohimbine은 DA의 항이뇨작용은 차단하나 이뇨작용에는 영향을 미치지 못하며, DA의 항이뇨작용이 지양될때에만 이뇨작용이 발현됨을 알 수 있었다. 또한 중추를 통한 DA의 신장작용에는 adrenergic system이 관여하지 않은 것으로 보인다.