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Renal Effects of Intracerebroventricular Bromocriptine in the Rabbit[1]

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ABSTRACT

In view of the facts that dopamine (DA) when given directly into a lateral ventricle (i.c.v.) of the rabbit brain induces antidiuresis and that haloperidol, a non-specific antagonist of DA receptors, produces anti-diuresis in smaller doses and diuresis and natriuresis in larger doses, the present study was undertaken to delineate the roles of various DA receptors involved in the center-mediated regulation of renal function. Bromocriptine (BRC), a relatively specific agonist of D-2 receptors and at the same time a D-1 antagonist, elicited natriuresis and diuresis when given i.c.v. in doses ranging from 20 to 600 μg/kg, roughly in dose-related fashion, while the renal perfusion and glomerular filtration progressively decreased with doses, indicating that the diuretic, natriuretic action resides in the tubules, not related to the hemodynamic effects. These diuresis and natriuresis were most marked with 200 μg/kg, with the fractional sodium excretion reaching about 10%. With 600 μg/kg, however, the diuretic, natriuretic action was preceded by a transient oliguria resulting from severe reduction of renal perfusion, concomitant with marked but transient hypertension.

When given intravenously, however, BRC produced antidiuresis and antinatriuresis along with decreases in renal hemodynamics associated with systemic hypotension, thus indicating that the renal effects produced by i.c.v. BRC is not caused by a direct renal effects of the agent which might have reached the systemic circulation.

In experiments in which DA was given i.c.v. prior to BRC, 150 μg/kg DA did not affect the effects of BRC (200 μg/kg), while 500 μg/kg DA abolished the BRC effects. In rabbits treated with reserpine, 1 mg/kg i.v., 24 h prior to the experiment, i.c.v. BRC could unfold its renal effects not only undiminished but rather exaggerated and more promptly. In preparations in which one kidney is deprived of nervous connection, the denervated kidney responded with marked diuresis and natriuresis, whereas the innervated, control kidney exhibited antidiuresis.

These observations suggest that i.c.v. BRC influences the renal function through release of some humoral natriuretic factor as well as by increasing sympathetic tone, and that various DA receptors might be involved with differential roles in the center-mediated regulation of the renal function.

Key Words: bromocriptine, central dopaminergic system, renal function, central regulation of renal function, natriuretic factor

Abbreviations: DA, dopamine; BRC, bromocriptine

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INTRODUCTION

The central nervous system modulates the excretory function of the kidney in response to momentary needs of the body, either through secretion of humoral agents such as antidiuretic hormone and natriuretic factors (Verney, 1947; De Wardener, 1973), or through nerve pathways. Among the nervous influences, the sympathetic nerve has been shown to play the most important role (Gottschalk *et al*, 1979: Kim *et al*, 1980), and it was found that when norepinephrine was administered into a lateral ventricle (i.c.v.) of the rabbit brain antidiuresis was elicited as a result of decreased renal hemodynamics (Lee, 1972). Also dopamine, the most abundant catecholamine in the brain, elicited antidiuresis when given i.c.v. (Choi,1974), and haloperidol, a dopamine antagonist, was found to produce diuresis and natriuresis when given i.c.v., suggesting a physiological role of central dopaminergic system in the regulation of renal function (Kim *et al*, 1982).

Bromocriptine (BRC) is a derivative of ergot alkaloids which was developed as an effective inhibitor of prolactin release (Flückiger & Wagner, 1968) and was found to stimulate dopamine receptors, and it is employed in treating various disorders related to diminished dopaminergic tone, such as Parkinsonism, hyperprolactinemia, acromegaly, etc. (Thorner *et al*, 1980). Further, it was found that BRC has a potent agonistic action on D-2 receptors in nanomolar concentrations as well as an antagonistic action on D-1 receptors (Kebabian & Calne, 1979). On the renal function no consistent effects were observed when given orally or intraveneously in rats and in dogs (Flückiger, 1976; Mahajan *et al*, 1975, 1976). However, there is no report as to the renal effects of centrally administered BRC. Therefore, present study was undertaken to observe the changes of renal function when BRC is administered directly into a cerebral ventricle in the rabbit and to clarify the mechanism involved in the action.

MATERIALS AND METHODS

Adult rabbits of either sex, weighing 1.6-2.4 kg, were anesthetized with 1 g/kg urethane, s.c.. Free air passage was secured by inserting a T-tube into the trachea. Into an ear-vein infusion of 0.3% NaCl + 3% glucose solution containing 45 mg% of *p*-aminohippuric acid (PAH) and 250 mg% of creatinine (cr) was given at a rate of 0.5 ml/min. Through a small midline incision on the lower abdomen, both ureters were cannulated with PE 50 tubings for the collection of urine samples. For sampling blood a femoral artery was cannulated with a PE tubing, which was then kept patent by filling with heparin-saline (400 U/ml). For the intracerebroventricular (i.c.v.) administration of the agents a lateral ventricle of the cerebrum was cannulated. At a point 1.5 cm rostral to the occiput tubercle and 0.5 cm lateral to the midline, a hole was drilled and a cannula made of PE tubing of 1.5 cm O.D. was introduced and 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 starting the infusion, collection of clearance samples was begun. After collecting two ten-minute samples of control clearance periods, the agents was given, and then four or five samples of ten- or twenty-minute clearance periods were collected, and the blood samples were immediately centrifuged to separate the plasma.

In denervation experiments the kidney was approached through a paravertebral incision and the renal pedicle was isolated from surrounding tissues, and the renal nerve was removed as thoroughly as possible with the aid of a magnifier, and the renal pedicle was wrapped with a cotton swab soaked with 10% phenol.

For reserpinizing animals, 1 mg/kg reserpine was given intravenously 24 hours prior to the experiment, and in anesthetizing these rabbits half the regular dose of urethane was employed.

Quantitative analyses of creatinine were done by the method of Phillips (1944) and PAH by that of

Smith *et al* (1945). Na and K concentrations were determined by flamephotometry, and the osmolality with an "Advanced" osmometer.

Bromocriptine methane sulfonate was obtained from Sigma Co., and a stock solution of 8 mg/ml was prepared in 0.4 N acetic acid and diluted with aqua dest. immediately before the administration. Reserpine was obtained from Fluka Co. The doses administered were calculated as free base.

Statistical significance was tested with Student's paired *t*-test for the changes of renal function from the control period, and when comparing two groups of experiments the unpaired *t*-test was employed (Snedecor & Cochran, 1980).

RESULTS

Effects of i.c.v. bromocriptine on renal function

In five experiments in which 0.2 ug/kg BRC was administered i.c.v. no changes in renal function as well as in systemic blood pressure were noted. With 2 µg/kg only a slight transient decrease of blood pressure was noted. With 20 µg/kg (n = 6) both renal plasma flow (C_{PAH}) and glomerular filtration rate

Table 1: Effects of intracerebroventricular bromocriptine on rabbit renal function

	Control	0 —10	10 —20	20 —40	40 —60 (min)
			60 µg/kg i.c.v. (6)		
Vol	0.34 ± 0.06	0.43 ± 0.07[a]	0.37 ± 0.06	0.26 ± 0.04[a]	0.26 ± 0.04[a]
C_{PAH}	16.2 ± 2.4	16.6 ± 1.7	16.3 ± 2.1	13.8 ± 2.3[a]	12.0 ± 1.5[a]
C_{cr}	6.37 ± 0.77	6.81 ± 0.91	6.36 ± 0.79	5.79 ± 0.83	5.23 ± 0.58[b]
$U_{Na}V$	16.1 ± 5.8	25.0 ± 8.2[a]	22.4 ± 5.9[a]	11.7 ± 4.2	9.1 ± 3.3
FE_{Na}	1.81 ± 0.52	2.81 ± 0.81[a]	2.75 ± 0.67[a]	1.61 ± 0.48	1.40 ± 0.48
			200 µg/kg i.c.v. (6)		
Vol	0.20 ± 0.03	0.38 ± 0.08	0.64 ± 0.12[a]	0.60 ± 0.14[a]	0.43 ± 0.10[a]
C_{PAH}	17.9 ± 4.8	12.2 ± 3.1[a]	13.8 ± 2.7	13.4 ± 2.4	12.5 ± 3.2
C_{cr}	6.22 ± 1.46	4.76 ± 1.06[a]	5.27 ± 0.85	5.00 ± 0.81	4.37 ± 0.76
FF	36.9 ± 2.0	40.6 ± 2.2	40.0 ± 2.9	39.0 ± 2.8	39.4 ± 4.6
$U_{Na}V$	7.4 ± 3.7	29.7 ± 11.7	60.6 ± 17.7[a]	55.6 ± 20.3	36.0 ± 13.0
FE_{Na}	0.94 ± 0.32	4.29 ± 1.36[a]	8.34 ± 1.75[b]	8.09 ± 1.79[a]	6.92 ± 2.02[a]
U_KV	6.2 ± 1.8	10.2 ± 3.6	12.1 ± 3.0[a]	9.2 ± 2.0[a]	6.7 ± 1.1
C_{osm}	0.38 ± 0.07	0.56 ± 0.12	0.81 ± 0.16[b]	0.73 ± 0.18[a]	0.53 ± 0.11
T^cH_2O	0.17 ± 0.05	0.18 ± 0.05	0.17 ± 0.06	0.14 ± 0.06	0.10 ± 0.05
			600 µg/kg i.c.v. (5)		
Vol	0.34 ± 0.07	0.08 ± 0.02[b]	0.53 ± 0.15	0.58 ± 0.10[b]	0.34 ± 0.06
C_{PAH}	15.6 ± 2.2	1.6 ± 0.2[b]	7.7 ± 1.8[a]	11.5 ± 1.2[a]	11.9 ± 2.2[b]
C_{cr}	5.75 ± 0.64	0.84 ± 0.08[b]	3.83 ± 0.91[a]	4.63 ± 0.45[a]	4.45 ± 0.53[b]
$U_{Na}V$	12.7 ± 4.3	3.5 ± 1.3[a]	44.0 ± 14.2[a]	51.4 ± 10.2[b]	27.8 ± 7.5[a]
FE_{Na}	1.71 ± 0.61	2.93 ± 0.99	8.14 ± 1.44[b]	8.22 ± 1.37[b]	4.61 ± 1.24[a]
U_KV	6.0 ± 0.9	1.4 ± 0.2[b]	8.0 ± 1.3[a]	8.3 ± 0.9[a]	5.6 ± 0.6

Mean ± S.E. In parentheses are number of experiments. Vol represents urine flow rate in ml/min; C_{PAH}, C_{cr} and C_{osm} are clearances of *p*-aminohippuric acid, creatinine and osmolar substances, resp., in ml/min; $U_{Na}V$ and U_KV are excretory rates of sodium and potassium, resp., in µEq/min; FF = filtration fraction in percent; FE_{Na} is fractional excretion of sodium in percent; and T^cH_2O = rate of free-water reabsorption in ml/min. Significance of paired difference from control periods were tested with Student's *t*-test. a: $p < 0.05$; b: $p < 0.01$.

(C_{cr}) tended to increase transiently, and excretory rate of sodium also tended to increase, but the fractional excretion of sodium and potassium excretion increased significantly. These effects lasted twenty minutes.

In rabbits which received 60 μg (≒ 90 nmole)/kg i.c.v., marked diuresis and natriuresis as well as kaliuresis were evident as shown in the upper part of Table 1. Renal hemodynamics did not show any increase, but rather it decreased in the later periods.

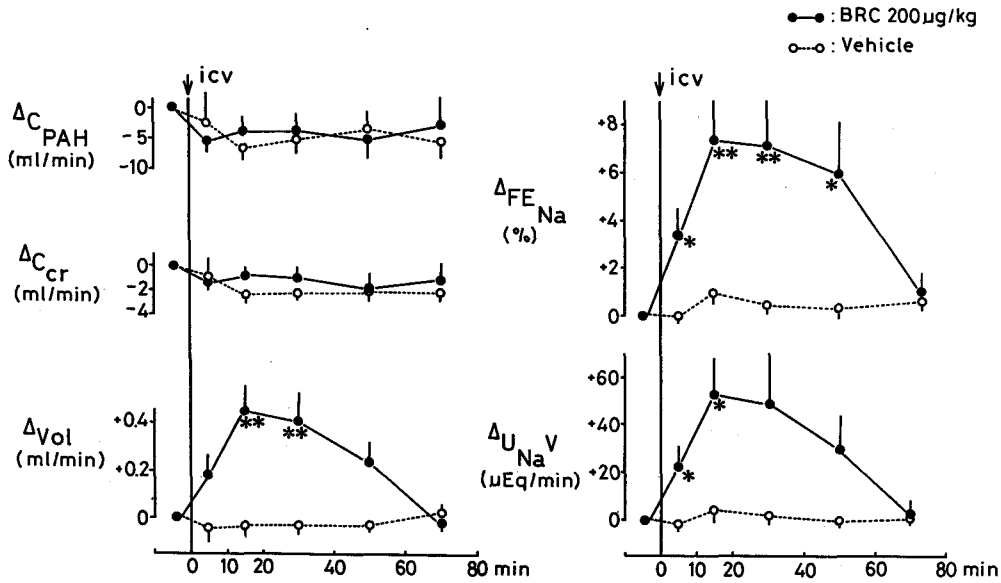

Fig. 1. Effects of intracerebroventricular bromocriptine (200 μg/kg) and vehicle on renal function of the rabbit. Mean differences from the control periods with one standard error are shown. Significant differences from the corresponding values of the vehicle group are marked with asterisks (* $p < 0.05$; ** $p < 0.01$). Other legends are as in Table 1.

Table 2. Changes of systemic arterial pressure after i.c.v. and i.v. administration of bromocriptine

Dose (μg/kg)		No. of exp.	Control (mmHg)	0 —10	10 —20	20 —40	40—60 (min)
0.2	i.c.v.	6	97 ± 4	0 ± 1	5 ± 6	7 ± 7	5 ± 2
2	i.c.v.	5	91 ± 1	−5 ± 3	−4 ± 1[b]	−1 ± 1	−1 ± 2
20	i.c.v.	6	95 ± 8	−8 ± 2[a]	−6 ± 3	−4 ± 3	−2 ± 3
60	i.c.v.	6	87 ± 7	−6 ± 5	−7 ± 2[a]	−6 ± 1[c]	−9 ± 6
200	i.c.v.	6	81 ± 14	49 ± 16[a]	18 ± 10	15 ± 8	5 ± 7
600	i.c.v.	5	88 ± 3	56 ± 4[b]	16 ± 8	2 ± 5	−14 ± 7
Vehicle	i.c.v.	6	86 ± 3	17 ± 13	3 ± 2	2 ± 2	2 ± 1
60	i.v.	6	89 ± 4	−5 ± 0[c]	−3 ± 2	−4 ± 2	−6 ± 4
200	i.v.	6	80 ± 7	−15 ± 6[a]	−16 ± 4[b]	−13 ± 2[b]	−10 ± 3[a]

Mean ± S.E. Significance tested with *t*-test for paired differences from control values.
a: $p < 0.05$, b: $p < 0.01$, c: $p < 0.001$.

With the dose further increased to 200 μg (= 300 nmole)/kg i.c.v., the renal response became more prominent, as presented in the middle part of Table 1. In spite of significant decreases of renal plasma flow and glomerular filtration rate, by 32 and 23%, respectively, sodium excretion nearly quadrupled, with the fractional excretion of sodium significantly increasing already in the first 10-min period. Urine flow rate, osmolar clearance, and K-excretion nearly doubled. In the next ten-minute period these effects reached the peak, with the urine flow more than tripling and sodium excretion more than 8 times the control value. Fractional sodium excretion also increased about 9 times and K-excretion and osmolar clearance nearly doubled. But, the renal hemodynamics remained depressed, and reabsorption of free water did not change at all. These natriuretic and diuretic effects remained sustained in the next 20 minute period and then declined gradually to return to the control levels after 60 min. Systemic blood pressure increased on the average 49 mmHg at the mid-point of the first 10-min period, as shown in Table 2. The vehicle for BRC in amount to deliver 200 ug/kg when given i.c.v. produced no significant changes in urine flow rate and excretory rates of electrolytes, except for the decreases in renal hemodynamics. In Fig. 1 the changes of several parameters of renal function after 200 ug/kg BRC i.c.v. are compared with those of the vehicle. The excretory rates of electrolytes and urine flow rate are significantly different, indicating that the natriuresis is elicited by BRC.

In the lower part of Table 1 are summarized the data from 5 experiments with 600 ug/kg i.c.v.. During the first 10-min period following the administration urine flow nearly ceased, with the perfusion decreased to nearly 1/10 and the filtration to 1/7 of the control level. Excretory rates of both sodium and potassium decreased to about 1/4, but the fractional excretion of sodium increased from 1.71 to 2.93%, indicating that the tubular reabsorption of sodium is depressed. Both osmolar clearance and free-water reabsorption decreased in proportion to the decreases in solute excretions. In the next ten-minute period, however, when the renal hemodynamics recovered to about half the control levels, sodium excretion shot up to 44 uEq/min, more than three times above the control level, and the fractional sodium excretion increased significantly to 8.14%. Potassium excretion and urine flow rate also significantly increased. In the next 20-min period the renal hemodynamics further recovered but is still significantly lower than the control level, and after reaching the plateau during the 20-40 min period, the diuresis and natriuresis declined gradually. Systemic blood pressure increased on the average 56 mmHg immediately after the administration and returned to the control level by 30 minutes (Table 2). Renal vascular resistance as calculated from mean arterial pressure divided by C_{PAH} increased from the control value of 5.6 unit to 90 in the first period after the administration.

Effects of i.v. bromocriptine on renal function

To test the possibility that the intracerebroventricularly administered BRC might have entered the systemic circulation and thus have affected the renal function directly, the effects of intravenous administration were observed. In 6 experiments with 60 μg/kg i.v. no changes of renal function were evident. Only slight and transient decrease of systemic blood pressure was noted, as seen in Table 2. In Table 3 the data from 6 experiments with 200 μg/kg i.v. are summarized. As shown here all the parameters of renal function began to decline immediately after the administration, and from after 10 minutes all the decrements became significant, except for the reabsorption of free-water. Mean arterial pressure also decreased (Table 2). These effects persisted long and did not fully disappear until the end of the observation, i.e. 80 min after the administration. It is thus clear that the effects of i.v. BRC are quite different from those of i.c.v. BRC and that no direct action is involved in the renal action of i.c.v. BRC.

Influence of dopamine on the BRC action

To see whether these diuretic and natriuretic effects of i.c.v. BRC are mediated by central dopamine receptors, the influence of i.c.v. dopamine (DA) on the BRC action was investigated. DA, 150 ug (≒ 1

Table 3: Effects of bromocriptine, 200 μg/kg i.v., on rabbit renal function

	Control	0 —10	10 —20	20 —40	40—60 (min)
Vol	0.27 ± 0.03	0.22 ± 0.05	0.17 ± 0.03[a]	0.16 ± 0.02[b]	0.13 ± 0.01[b]
C_{PAH}	18.2 ± 2.6	12.9 ± 3.3	12.4 ± 2.4[a]	14.5 ± 2.6[b]	12.3 ± 1.6[a]
C_{cr}	6.49 ± 0.77	4.90 ± 1.15	4.82 ± 1.00[a]	5.18 ± 0.87[a]	4.87 ± 0.71[a]
$U_{Na}V$	10.3 ± 2.0	9.1 ± 3.1	5.9 ± 2.1	3.8 ± 1.4[a]	2.2 ± 0.9[a]
U_KV	7.7 ± 1.5	6.2 ± 1.8	4.9 ± 1.1[a]	4.7 ± 1.1[b]	3.9 ± 0.7[a]
T^cH_2O	0.20 ± 0.05	0.17 ± 0.06	0.17 ± 0.05	0.17 ± 0.04	0.15 ± 0.04

Mean ± S.E. from 6 experiments.

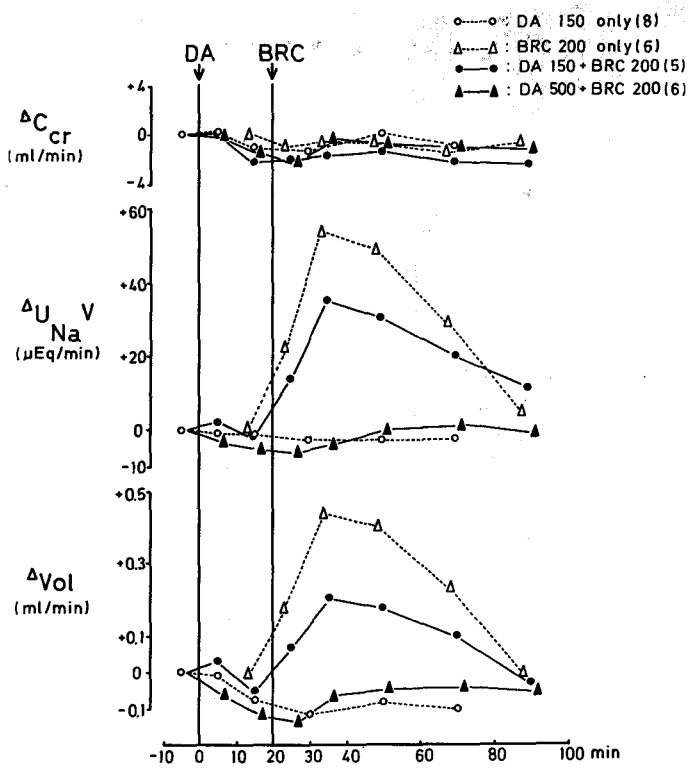

Fig. 2. Influence of i.c.v. dopamine (DA) pretreatment on the renal effects of i.c.v. bromocriptine (BRC). Mean changes from the control periods are shown. Numerals represent the doses in μg/kg and the number of experiments are in parentheses.

μmole)/kg, i.c.v., induced antidiuresis and antinatriuresis, along with decreases in renal perfusion and glomerular filtration, which persisted until the end of the experiment. Fig. 2 depicts mean changes from the control clearance values of several parameters of renal function. As shown here, when BRC was given i.c.v. twenty min after the DA administration, the antidiuresis and antinatriuresis reverted to brisk diuresis and natriuresis though slightly less marked than with BRC alone, whereas renal hemodynamics remained depressed. However, when the dose of DA was increased to 500 μg/kg, i.c.v., no diuresis and natriuresis were observed after BRC.

Effects of i.c.v. BRC in reserpinized rabbits

Reserpinization affects markedly the renal function of the rabbit. In the control period before BRC administration the value of C_{PAH} was 33.5 ± 3.4 ml/min (Mean $\pm$ S.E., $n = 6$), 87% higher than the non-reserpinized group, and C_{cr} was, with 9.94 ± 0.53 ml/min, 60% higher than the control group. Sodium excretion and urine flow rate also tended to be higher in the reserpinized rabbits. These are presumably due to decreased sympathetic influence to the kidney.

In these animals, BRC, 200 ug/kg i.c.v., promptly increased excretory rates of sodium and potassium, along with marked decreases in renal hemodynamics. These natriuresis and diuresis reached peak values during the second ten-minute period after administration, the fractional sodium excretion amounting to 10%, and then the effects rapidly declined. Fig. 3 compares the reserpinized group with the control group in mean changes from control values for the two ten-minutes periods after the BRC administration. It is clearly seen that the diuretic and natriuretic responses to i.c.v. BRC are more prompt and marked in the reserpinized rabbits. Systemic blood pressure responded just the same as in the control animals.

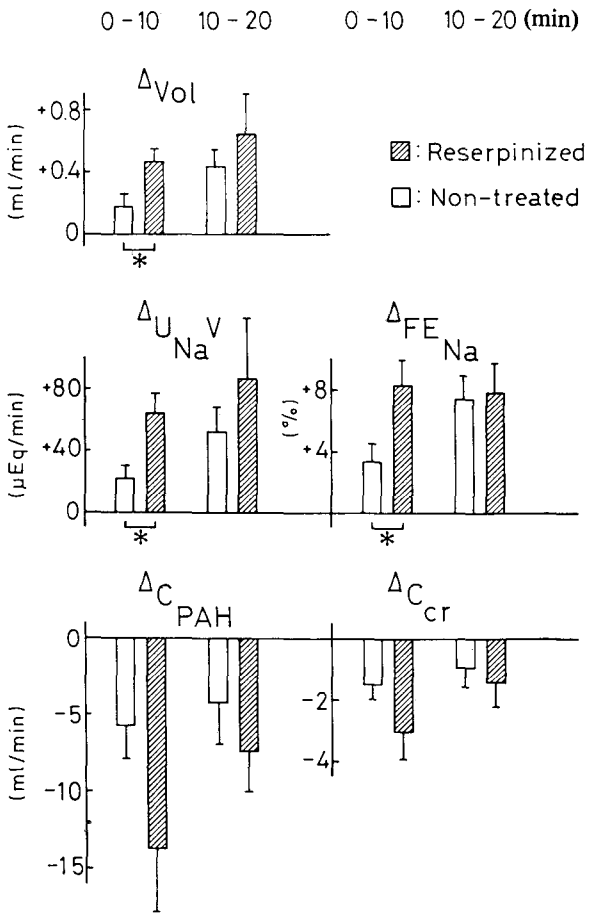

Fig. 3. Influence of reserpinization on the renal effects of i.c.v. BRC (200 μg/kg). Mean changes from control periods for the two ten-minute periods are shown. White columns represent the non-reserpinized control goup, whereas the shaded columns the reserpinized animals. Horizontal bars indicate one S.E. The asterisks denote significant difference between both groups at p-values less than 0.05. Other legends as in Table 1.

Influence of denervation on the BRC action

In Table 4 are shown the data of experiments in which one kidney was denervated and the other was left intact. As seen here, in the pre-administration control periods the denervated kidney has greater perfusion and filtration rate, nearly as much as twice than the contralateral innervated kidney. And the urine flow rate is 11 times and the urinary excretory rate of sodium is 60 times greater in the experimental kidney than in the control kidney, indicating that the denervated kidney is undergoing a prominent "denervation diuresis", whereas the contralateral kidney is subjected to a marked antidiuresis.

In this state, BRC 200 μg/kg i.c.v. promptly increased sodium excretion by nearly 70 μEq/min, with the fractional excretion reaching nearly to 20%, and tripled the urine flow rate, in spite of a dip in renal perfusion in the denervated kidney. In the control side, however, urine flow rate was reduced further, along with marked decreases in renal hemodynamics. Sodium excretion tended to decrease. Osmolar clearance, free-water reabsorption and potassium excretion decreased significantly.

Table 4: Influence of denervation on the renal effects of i.c.v. bromocriptine

		Control	0 —10	10 —20	20 —40 (min)
Vol	D	0.38 ± 0.10	0.96 ± 0.18[b]	0.89 ± 0.15[a]	0.56 ± 0.11[a]
	I	0.04 ± 0.01	0.01 ± 0.01[a]	0.01 ± 0.00[b]	0.02 ± 0.00
C_{PAH}	D	12.9 ± 1.8	9.5 ± 1.4[a]	11.2 ± 1.5	9.0 ± 0.8
	I	7.1 ± 1.4	3.3 ± 1.8[a]	2.8 ± 0.9[b]	4.7 ± 1.3
C_{cr}	D	4.51 ± 0.55	4.10 ± 0.52	4.56 ± 0.68	3.41 ± 0.40[a]
	I	2.73 ± 0.54	1.29 ± 0.62	1.19 ± 0.31[b]	1.61 ± 0.40
$U_{Na}V$	D	42.9 ± 10.7	108.9 ± 19.1[b]	103.0 ± 15.4[a]	67.1 ± 13.8
	I	0.7 ± 0.2	0.2 ± 0.1	0.4 ± 0.2	0.4 ± 0.2
FE_{Na}	D	7.62 ± 2.21	19.45 ± 2.69[c]	17.19 ± 2.44[b]	14.28 ± 2.62[a]
	I	0.22 ± 0.08	0.16 ± 0.06	0.22 ± 0.06	0.17 ± 0.05
U_KV	D	6.7 ± 1.2	10.0 ± 1.5[b]	9.2 ± 1.5[b]	7.0 ± 1.1
	I	2.4 ± 0.4	1.0 ± 0.4[a]	1.0 ± 0.2[a]	1.2 ± 0.2[a]

Mean ± S.E. from 6 experiments. "D" represents the denervated, experimental kidney; "I" stands for the innervated, contralateral kidney. Other legends as in Table 1.

DICUSSION

Bromocriptine (BRC) is a derivative of α-ergocryptine, an ergot alkaloid, in which a hydrogen in 2-position is replaced by a bromine, and it was found to have less α-adrenergic, serotonergic and oxytocic activities than the mother compound (Flückiger, 1976, 1980). Instead, it possesses a potent dopaminomimetic acitivity, especially on the dopaminergic receptors on the hypothalamic neurons and on the prolactin-containing cells of the hypophysis (Nagasawa *et al*, 1973; Flückiger, 1976, 1978). Thus, it is clinically employed in suppressing prolactin secretion in amenorrhea/galactorrhea syndrome and in various clinical disorders related to the diminished activity of central dopaminergic system, such as Parkinsonism, acromegaly, etc. (Calne *et al*, 1974; Chiodini *et al*, 1975).

On the renal action of BRC administered systemically, there are several reports, but they are largely at variance. Flückiger (1968) found no consistent changes in excretory rates of water and electrolytes in

the rat with single oral dose of 10 mg/kg or 1 mg/kg s.c., whereas a decrease (Richardson, 1973; Mahajan *et al*, 1975) and an increase were noted in prolonged treatment (Mahajan *et al*, 1976). Renal perfusion increased without change in glomerular filtration in rats (Stier *et al*, 1982) and no change in filtration was found in the dog (Mahajan *et al*, 1976). In this study we found, when given i.v., an antidiuresis along with decreased renal hemodynamics as well as systemic hypotension in the rabbit. However, there is no report available, so far, as to the renal effects of centrally administered BRC. In the present study BRC was shown to elicit marked natriuresis and diuresis in the rabbit when it was introduced directly into a lateral ventricle (i.c.v.), in spite of decreases in renal hemodynamics. These natriuretic and diuretic action increased with the dose, reaching a maximal effect with 200 ug/kg i.c.v., which increased the fractional excretion of sodium up to more than 8%. Systemic arterial pressure increased only transiently, not contributing to the natriuresis. Renal hemodynamics decreased markedly, indicating that the natriuresis resulted from decreased reabsorption of sodium in the tubules and not from increased filtration. With further increase of dose to 600 μg/kg, the hemodynamic action became so severe that the tubular action could not manifest itself immediately following the administration. But, when the initial hemodynamic depression is amoliorated, the natriuresis became evident. The fact that i.v. BRC did not produce natriuresis or diuresis indicate that the i.c.v. BRC elicits the renal response through central mechanism, not by a direct action on the kidney.

The renal function is under regulatory influence from the center, either through sympathetic nerves or by mediation of humoral factors. Increased sympathetic tone reduces the renal perfusion and increase tubular reabsorption of sodium, thus antidiuresis ensues (Gottschalk *et al*, 1979; Kim *et al*, 1980). The antidiuresis induced by i.c.v. morphine is abolished by denervation of the kidney (Kang, 1978) and inhibited by i.c.v. phenoxybenzamine (Kook *et al*, 1985). Decreasing the central sympathetic tone increases urinary output and sodium excretion, as evidenced by the facts that natriuresis follows after i.c.v. clonidine (Kook *et al*, 1984) or phenoxybenzamine (Kook *et al*, 1985). Also, the natriuresis observed after reserpinization can be accounted for by decreased sympathetic tone. In these reserpinized animals, the i.c.v. BRC could induce natriuresis not only unhindered, but also more promptly and exaggerated, suggesting that the natriuresis is not related to the sympathetic tone, that it is brought about by some humoral mechanism, and that the sympathetic influence is opposed to the natriuretic action. The denervation experiments also show that the natriuresis became more marked on the denervated kidney, whereas the innervated kidney which had been undergoing severe antidiuresis did not respond to the i.c.v. BRC.

Between both kidneys there exists reno-renal reflex (Ueda *et al*, 1967; Aars & Akre, 1970), and stimulating the afferent renal nerve of one kidney decreases the renal nerve activity on the contralateral kidney (Aars & Akre, 1970; Kopp *et al*, 1984). The afferent nerve activity through the chemoreceptors and mechanoreceptors of the kidney integrate at the spinal and supraspinal levels and influence the efferent renal sympathetic nerve activity either on the ipsilateral or contralateral kidney (Recordati *et al*, 1980). And renal nerve activity increases in compensation for the acute denervation of the contralateral kidney (DiBona & Rios, 1980). In the present study, the contralatereal kidney seems to be undergoing a severe antidiuresis as a result of increased efferent sympathetic activity due to the reno-renal reflex. Also, the stress from the operation procedures might have contributed to the increased sympathetic tone. In this state of increased sympathetic tone the natriuretic action of i.c.v. BRC seems to be incapable of unfolding itself. Also, the observation with 600 μg/kg BRC i.c.v., in which transient decrease in renal hemodynamics counteracted the natriuresis, seems to support the postulation.

Since natriuresis was observed when ECF volume was expanded (Milies, 1960; De Wardener *et al*, 1961), many suggested the existence of natriuretic factors (De Wardener, 1973; Kramer & Krück, 1978). Kidney, left auricle, brain, etc. were implicated as the source of the factors (Kramer & Krück, 1978). Lichardus & Ponec (1973) advocated the role of hypophysis, while Mouw group presented evidence that natriuretic factor is released when sodium concentration in cerebrospinal fluid is raised, and that this factor is a hormone not relevant to ADH, renal activity, mean arterial pressure, aldosterone, or to

angiotensin II (Beasley *e al,* 1983; Pierce *et al,* 1983; 1984). As to the nature and origin of the natriuretic factor involved in the i.c.v. BRC action no evidence is at hand as yet. Prolactin was found to produce diuresis and natriuresis in the heart-lung preparation (Lockett, 1965), but its secretion is inhibited by BRC. Corticosteroids and renin induce sodium retention. ADH also can be ruled out, as no change in free-water reabsorption was noted in this experiment. Recently, atrial natriuretic factor (ANF) was purified, its peptide sequence determined and its analogues synthesized. A synthetic peptide composed of 26 amino acids has been found to have the same biological activity (Gutkowska *et al,* 1984; Seymour *et al.* 1984; Burnett *et al,* 1984). However, whether the natriuretic factor involved in the BRC action is related to the ANF awaits further investigation. As for the intrarenal site of the natriuretic action, proximal tubules are suggested from the magnitude of natriuresis and from the facts that it is accompanied by kaliuresis and that free-water reabsorption did not decrease (Suki *et al,* 1965; Pitts, 1974).

The central dopaminergic receptors are not of a single type, and they can be subdivided by various criteria into multiple types (Kebabian & Calne, 1979; Seeman, 1981). Widely accepted is the classification into D-1 and D-2 receptors by the linkage to adenylate cyclase (Kebabian & Calne, 1979). D-1 activates the cyclase, whereas D-2 is independent of it. The former are claimed to be located on the postsynaptic cholinergic interneurons, whereas the latter are found both on the postsynaptic and presynaptic sites as autoreceptors (Carlsson, 1975; Schwarcz *et al,* 1978) and their functional differences are delineated with the aid of various pharmacological agents, as well as by lesioning or binding studies (Minneman *et al,* 1978; Kebabian & Cote, 1981). Stimulating D-2 receptors produces dyskinesia and emesis, and induces delusion and hallucination in schizophrenic patients (Kebabian & Calne, 1979; Calne, 1981). D-2 receptors are also located on the lactotrophs of the pituitary and inhibits prolactin release (Enjalbert & Bockaert, 1983). On the renal vessels are D-1 receptors effecting vasodilatation (Kebabian & Calne, 1979; Goldberg & Kohli, 1983). Bromocriptine is claimed to be an agonist on central D-2 receptors in nanomolar concentrations (Kebabian & Calne, 1979; Sibley & Creese, 1983), and it has dual action on D-1 receptors in that it antagonizes in micromolar concentration while stimulates in nanomolar potencies (Kebabian & Calne, 1979). No evidence is available at present as to which type of DA-receptors are involved in the i.c.v. BRC-induced natriuresis, i.e., whether the natriuresis is resulted from the stimulation of D-2 receptors or from the antagonism to D-1 receptors. The antagonism by dopamine which stimulates both receptors, as observed here, could be interpreted as supporting D-1 antagonism of BRC. But, also possible is the other speculation if one assumes that BRC effects release of natriuretic factor through D-2 stimulation and at the same time it increases the sympathetic tone via D-1 stimulation. Dopamine could then antagonize the natriuresis by overwhelming hemodynamic action of increased sympathetic tone which is produced by D-1 stimulation.

Overall, the present study provides further evidence that the central dopaminergic system is involved in the physiological regulation of renal function in the rabbit.

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=국문초록=

가토에 있어서 측뇌실내 Bromocriptine의 신장작용

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가토 측뇌실내로 dopamine을 투여하면 항이뇨를 일으키고, 도파민 길항제 haloperidol은 소량에서는 항이뇨를, 대량에서는 이뇨와 Na 배설증가를 초래한다는 보고에 비추어, 본 연구에서는 중추를 통한 신장기능 조절에 관여하는 도파민 수용체의 역할을 구명코자, D-2 receptor agonist이고 D-1 antagonist인 bromocriptine(BRC)의 작용을 검토하였다.

측뇌실내로 BRC를 투여하면 20-600 μg/kg의 범위안에서 대략 용량에 비례하여 natriuresis와 이뇨가 나타났으나, 신혈류와 사구체 여과율은 증량에 따라 점차 감소하였다. 따라서 이뇨 및 Na 배설증가는 신세뇨관에서의 Na재흡수 감소에 의한 것임을 알수 있었다. 이러한 Na 배설증가는 200μg/kg에서 가장 현저하여 Na 배설분획은 약 10%에 달하였다. 그러나 600μg/kg 에서는 일시적인 현저한 혈압상승에 따르는 급격한 감소로 인하여 일시적 폐뇨가 선행한 다음 이뇨 작용이 나타났다.

BRC의 정맥내 투여시에는 전신혈압 하강에 따르는 신혈류역학의 감소와 아울러 항이뇨가 나타났으며, 이는 측뇌실내로 투여한 BRC의 작용은 전신순환내로 유입되어 초래될 수도 있는 직접신장작용에 기인한것이 아니고 중추를 통한 것임을 시사하였다.

Dopamine 150 μg/kg을 측뇌실내로 투여한 후에도 BRC 200 μg/kg은 작용을 나타낼 수 있으나, dopamine 500 μg/kg에 의해서는 BRC의 작용이 소실 되었다. 24시간전에 1 mg/kg의 reserpine으로 처리한 가토에서는 200 μg/kg BRC의 작용이 오히려 더 빠르고 강화되었다. 일측신장 신경을 제거한 표본에서는, BRC투여로 대조신은 항이뇨를 나타냈으나 실험신(탈신경측)은 심한 이뇨와 Na배설 증가를 일으켰다.

이상의 실험결과는, 측뇌실내 BRC는 natriuretic factor를 유리시킴과 동시에 교감신경 긴장도를 증가시키는 것을 시사하였으며, 또한 가토 신장기능의 중추 도파민계를 통한 조절에 있어서 여러 도파민 수용체가 각각 다른 기능을 하고 있음을 시사하였다.