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# Influence of Intracerebroventricular Haloperidol on the Renal Function of the Rabbit

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## 가토신장기능에 미치는 측뇌실내 Haloperidol의 영향

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신장기능 조절에 있어서 중추의 dopaminergic system의 역할을 구명하고자 dopamine의 선택적 길항제인 haloperidol을 가토의 측뇌실내로 투여하여 신장기능의 변동을 관찰하였다.

Haloperidol 15와 50 μg/kg투여시 항이뇨작용을 나타냈으며, 15 μg/kg의 경우는 주로 세뇨관에서 Na 재흡수의 촉진에 의하였으며, 50 μg/kg의 경우에는 주로 세뇨관에서의 수분재흡수가 뚜렷하였다. 그러나 150 μg/kg의 경우에서는 뚜렷한 이뇨작용을 볼 수 있었으며 이때 신혈류 및 사구체 여과율에는 유의한 변동을 볼 수 없었으나 세뇨관에서 Na재흡수가 현저히 억제되어 natriuresis 및 kaliuresis가 출현되었다.

한편 dopamine은 5, 15, 50, 150 μg/kg의 양을 측뇌실내로 투여하였을때 투여량에 대체로 비례하는 항이뇨효과를 관찰할 수 있었다. 여기에서 5, 15 μg/kg의 소량에 의하여는 그 항이뇨작용이 주로 신세뇨관에 있어서 Na재흡수의 촉진에 기인하였으나 50 μg/kg이상의 양에서는 그외에도 신혈류 및 사구체 여과율의 감소가 더욱 뚜렷하여짐을 볼 수 있었다.

Haloperidol 150 μg/kg투여후에 dopamine을 투여하였을때 15 μg/kg dopamine의 효과는 감퇴되었으나 50, 150 μg/kg dopamine의 항이뇨 효과는 차단되지 아니하였으며 dopamine양의 증가에 따라 haloperidol의 이뇨작용이 소실됨을 볼 수 있었다.

이상의 실험결과는 대량의 haloperidol은 중추의 dopamine receptor에 대한 상경적 길항에 의하여 이뇨작용을 나타낸 것으로 해석되며, 소량의 haloperidol은 dopaminergic neurone에 있는 autoreceptor의 차단작용의 결과 항이뇨 작용이 나타난 것으로 추측되었다.

The excretory function of the kidney, particularly of electrolytes and water, is subtly regulated from moment to moment to ensure the constancy of the volume as well as osmotic pressure of the body fluids. The renal excretion of electrolytes and water are regulated primarily by alterations of intrarenal reabsorptive mechanisms, such as changes of renal hemodynamics or redistribution of intrarenal blood flow (Rothe *et al*, 1972; Stein *et al*, 1973). As an extrarenal factor of regulating renal excretions, stimulation of renin-angiotensin system resulting in increased aldosterone secretion (Young & Guyton, 1977; Schwarz & Burg, 1978) may be considered first. But, no less important is the integrative regulatory

influence upon the renal function exerted by the central nervous system (Andersson *et al*, 1969; Schrier, 1970). The CNS influences the renal excretory function not only through release of antidiuretic hormone or secretion of putative "natriuretic hormones" (De Wardener, 1973; Weber *et al*, 1974; Epstein *et al*, 1978; Hays & Levine, 1981) but also directly through nerve connections to the kideny, among which the sympathetic nerve plays the most important role (Gottschalk *et al*, 1979; Kim *et al*, 1980).

On the functional interrelationship between CNS and the kidney many studies have been done, but the knowledge accumulated so far is far from complete. Recently, in a series of experiments on rabbits, we attempted to modify the function of the CNS by directly introducing into a lateral cerebral ventrcle various endogenous substances especially of neurotransmitters and observed the changes of renal function (Lee, A.S., 1972; Choi, 1974; Kook, 1975; Lee, Y.H., 1980). Among others, dopamine, given intracerebroventricularly (i.c.v.), induced antidiuresis and antinatriuresis along with decreases in renal perfusion and glomerular filtration (Choi, 1974).

Dopamine, being the most abundant catecholamine in the brain, has been implicated to play various roles, not only as a precursor of norepinephrine and epinephrine, but also as a neurotransmitter by its own right, in maintaining the functional intergrity of CNS, and various pathologic states are ascribed to the decrement of it (Bunney *et al*, 1973; Baldessarini, 1977; Moore & Bloom, 1978; Carlsson, 1978). However, little is known as to the physiological roles of cerebral dopamine in regulating renal function. Therefore, in order to provide evidence as to the physiological role of the brain dopamine in regulating renal function and to obtain further insight into the mechanism of dopamine action, we investigated in this study the effects of haloperidol, a dopamine antagonist, given i.c.v., on the renal function and the influence of haloperidol pretreatment on the dopamine action.

## METHODS AND METERIALS

Adult rabbits of either sex, weighing 1.6~2.2 kg, were used. Anesthesia was done with 1 g/kg urethane, s.c. Free air passage was secured by inserting a T-tube into the trachea. Into a jugular vein, an infuion of 0.3% NaCl +3% glucose solution containing 45 mg% of p-aminohippuric acid (PAH) and 250 mg% of creatinine(cr) was instituted at a rate of 0.5 ml/min. Both ureters were cannulated with PE 50 tubings for the collectin of urine samples, and for sampling blood a femoral artery was cannulated with a PE tubing, which was then kept patent by filling with heparin-saline. For the administration of agents a lateral ventricle of the cerebrum was cannulated according to the method of Moon (1964). After exposing the parietal bone a hole was drilled at a point 1.5 cm rostral to the occipital tubercle and 0.5 cm lateral to the midline. A cannula made of PE tubing of 1.5 mm O.D. was introduced until the cerebrospinal fluid came up in the cannula, and the cannula was sealed to prevent leaking, and it was kept in place by cementing to the bone with bond. The volume of administration did not exceed 0.2 ml. At the end of each experiment the location of the cannula was checked.

When urine flow gradually increased and became stable several hours after the beginning of infusion, the clearance experiment was started. After collecting two ten-minute samples of control clearance periods, the

agents were given, and four or five samples of ten- or twenty-minute clearance samples were collected, immediately centrifuged to separate the plasma.

Quantitative analyses of creatinine were done by the method of Phillips (1944) and PAH by the method of Smith *et al*, (1945). Na and K concentrations were determined by flamephotometry, and the osmolality with Advanced Osmometer. Systemic blood pressure was measured by recording from the femoral artery through a pressure transducer either on Gould blood pressure monitor or Narco physiograph.

Dopamine was obtained from Sigma Co. as hydrochloride. The doses administered were calulated as free base and diluted with physiological saline immediately before administration. Haloperidol used was Haldol Injection, 5 mg/ml, of McNeil Co., which contains 0.5 mg methylparaben and 0.05 mg propylparaben per ml and was adjusted to pH 3.4±0.02 with lactic acid.

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 animals unpaired t-test was employed (Snedecor, 1971).

## RESULTS

### Action of Haloperidol

Before testing the renal action of i.c.v. haloperidol (HA), the effect of the vehicle employed to dissolve HA was observed. In 6 experiments 0.06ml of the vehicle, a necessary amount to deliver 150 μg/kg of HA, was diluted to 0.2 ml with saline and given i.c.v. No significant change of renal function was observed after the vehicle administration.

Next, the data from 6 experiments in which 15 μg/kg HA i.c.v. were given are summarized in Table 1. Urine flow tended to decrease after 40 min, but the renal plasma flow ($C_{PAH}$) and glomerular filtration rate ($C_{cr}$) did not change. However, the excretory rates of sodium and potassium as well as the fractional Na excretion decreased signficantly after 40 min, indicating that reabsorption of sodium in the tubules is increased. Reflecting the decrease

Table 1. Effect of 15 μg/kg haloperidolicv on the renal function of the rabbit

| | Control | 0′~10′ | 10′~20′ | 20′~40′ | 40′~60′ | 60′~80′ |
|---|---|---|---|---|---|---|
| Vol(ml/min) | 0.37±0.13 | 0.37±0.15 | 0.33±0.15 | 0.35±0.13 | 0.24±0.08 | 0.15±0.03 |
| $C_{PAH}$(ml/min) | 12.8 ±2.3 | 14.5 ±3.0 | 12.9 ±2.6 | 13.1 ±2.4 | 12.9 ±2.5 | 11.3 ±1.4 |
| $C_{cr}$(ml/min) | 6.00±1.16 | 6.27±1.45 | 5.79±1.31 | 6.08±1.20 | 5.66±1.09 | 5.19±0.78 |
| FF(%) | 47.0 ±5.3 | 43.9 ±4.3 | 44.7 ±4.0 | 46.3 ±3.9 | 44.3 ±3.5 | 45.7 ±3.6 |
| $U_{Na}V$(μEq/min) | 15.8 ±5.8 | 14.4 ±4.4 | 12.7 ±4.8 | 13.2 ±5.7 | 9.5 ±4.4 * | 8.5 ±4.5 * |
| $FE_{Na}$(%) | 2.02±0.58 | 2.08±0.63 | 1.61±0.48 | 1.55±0.60 | 1.26±0.58* | 1.11±0.55 |
| $U_KV$(μEq/min) | 5.1 ±0.8 | 4.8 ±0.4 | 4.4 ±0.9 | 4.2 ±0.9 | 3.8 ±0.8 * | 3.7 ±0.9* |
| $C_{osm}$(ml/min) | 0.35±0.06 | 0.35±0.05 | 0.30±0.06 | 0.33±0.05 | 0.29±0.05* | 0.26±0.05* |
| $T^cH_2O$(ml/min) | −0.22±0.13 | −0.04±0.12 | −0.03±0.11 | −0.02±0.11 | 0.05±0.07 | 0.11±0.03 |

Mean±S.E. from 6 experiments. Abbreviations: Vol=rate of urine flow; $C_{PAH}$ and $C_{cr}$ are clearances of PAH and creatinine, resp.; FF is filtration fraction, as calculated from $C_{cr}/C_{PAH}$; $U_{Na}V$ and $U_KV$ are excretory rate of sodium and potasium, resp.; $FE_{Na}$ is fractional excretion of filtered sodium, as calculated from $U_{Na}V/(P_{Na}\times C_{cr})\times 100$; $C_{osm}$ is clearance of osmotically active substances and $T^cH_2O$ represents reabsorption of osmotically free water. Significance of paired differences from the control periods were tested with Student's t-test. *=$p<0.05$.

Table 2. Effect of 50 μg/kg haloperidol icv on the renal function of the rabbit

| | Control | 0′~10′ | 10′~20′ | 20′~40′ | 40′~60′ | 60′~80′ |
|---|---|---|---|---|---|---|
| Vol(ml/min) | 0.30±0.06 | 0.21±0.05* | 0.18±0.05* | 0.14±0.03** | 0.15±0.03* | 0.15±0.03* |
| $C_{PAH}$(ml/min) | 15.3 ±1.4 | 12.5 ±1.5 | 13.8 ±2.1 | 16.4 ±2.4 | 15.2 ±1.9 | 14.5 ±1.4 |
| $C_{cr}$(ml/min) | 6.06±1.40 | 5.01±0.59 | 5.55±0.79 | 6.44±0.97 | 5.86±0.60 | 5.64±0.60 |
| FF(%) | 40.5 ±2.9 | 41.2 ±2.7 | 41.0 ±2.1 | 39.4 ±2.4 | 39.7 ±2.7 | 39.7 ±3.9 |
| $U_{Na}V$(μEq/min) | 11.5 ±5.9 | 8.3 ±3.7 | 9.6 ±4.3 | 6.7 ±3.3 | 5.7 ±2.9 | 4.9 ±2.6 |
| $FE_{Na}$(%) | 1.40±0.71 | 1.08±0.45 | 1.21±0.53 | 0.88±0.42 | 0.71±0.37 | 0.90±0.61* |
| $U_KV$(μEq/min) | 6.9 ±2.4 | 5.6 ±1.9 | 5.7 ±2.1 | 5.4 ±1.8 | 5.3 ±1.9 | 4.8 ±1.7 * |
| $C_{osm}$(ml/min) | 0.38±0.09 | 0.30±0.07 | 0.32±0.09 | 0.32±0.06 | 0.30±0.06 | 0.29±0.05 |
| $T_cH_2O$(ml/min) | 0.08±0.07 | 0.80±0.05 | 0.15±0.06** | 0.18±0.04* | 0.15±0.05 | 0.13±0.04 |

Mean±S.E. from 6 experiment. *$p<0.05$. **$p<0.01$.

Table 3. Effects of 150 μg/kg haloperidol icv on the renal function of the rabbit

| | Control | 0′~10′ | 10′~20′ | 20′~40′ | 40′~60′ | 60′~80′ |
|---|---|---|---|---|---|---|
| Vol(ml/min) | 0.30±0.10 | 0.30±0.13 | 0.46±0.15 | 0.52±0.10** | 0.38±0.11 | 0.30±0.10 |
| $C_{PAH}$(ml/min) | 17.9 ±2.6 | 14.8 ±3.0 | 18.1 ±2.2 | 16.9 ±2.4 | 14.5 ±1.6 | 15.7 ±2.3 |
| $C_{cr}$(ml/min) | 6.61±0.97 | 5.73±1.20 | 7.76±1.04 | 6.86±0.98 | 5.83±0.64 | 6.66±0.86 |
| FF(%) | 37.0 ±1.2 | 38.2 ±1.7 | 42.6 ±1.3* | 40.8 ±1.2 * | 40.1 ±0.8 * | 43.3 ±2.2 ** |
| $U_{Na}V$(μEq/min) | 11.2 ±6.2 | 12.7 ±7.7 | 22.7 ±9.8* | 27.3 ±8.6 * | 14.1 ±7.6 | 9.4 ±5.9 |
| $FE_{Na}$(%) | 2.03±1.41 | 2.05±1.39 | 3.14±1.73* | 3.91±1.54* | 2.30±1.43* | 1.73±1.31 |
| $U_KV$(μEq/min) | 3.3 ±0.5 | 3.1 ±0.9 | 5.4 ±0.8* | 5.7 ±0.8 * | 3.8 ±0.3 * | 3.3 ±0.40 |
| $C_{osm}$(ml/min) | 0.25±0.06 | 0.24±0.08 | 0.40±0.09* | 0.46±0.08** | 0.32±0.08 | 0.27±0.06 |
| $T^cH_2O$(ml/min) | −0.05±0.05 | −0.06±0.05 | −0.05±0.07 | −0.05±0.07 | −0.05±0.06 | −0.03±0.04 |

Mean±S.E. from 6 experiments.

of elecetrolyte excretion, the osmolar clearance decreased significantly, but the reabsorption of free-water only tended to increase.

Table 2 shows the effects of 50 μg/kg HA i.c.v. In this group, the animals responded with significant antidiuresis immediately after the administration, to reach one half the control level, and the antidiuresis until the end of the observation. However, there were no sigificant changes in renal hemodynamics, and also no significant decrease in sodium excretion was noted. Only the fractional sodium excretion and potassium excretion showed significant decrease after 60 min, so that no significant change of osmolar clearance was observed. Free-water reabsorption, however, increased significantly. It is thus clear that the antidiuresis inuced by 50 μg/kg HA i.c.v. was resulted from increased water reabsorption by the tubules.

The response to 150 μg/kg i.c.v. was entirely different from those of the smaller doses (Table 3). The urine flow markedly increased from the control level of 0.30 ml/min to 0.52 ml/min during the 20 to 40 min period and returned to the pre-administration level thereafter. Renal perfusion and glomerular filtration did not change significantly, but the filtration fraction increased. Sodium excretion more than doubled during 10~40 min, and also

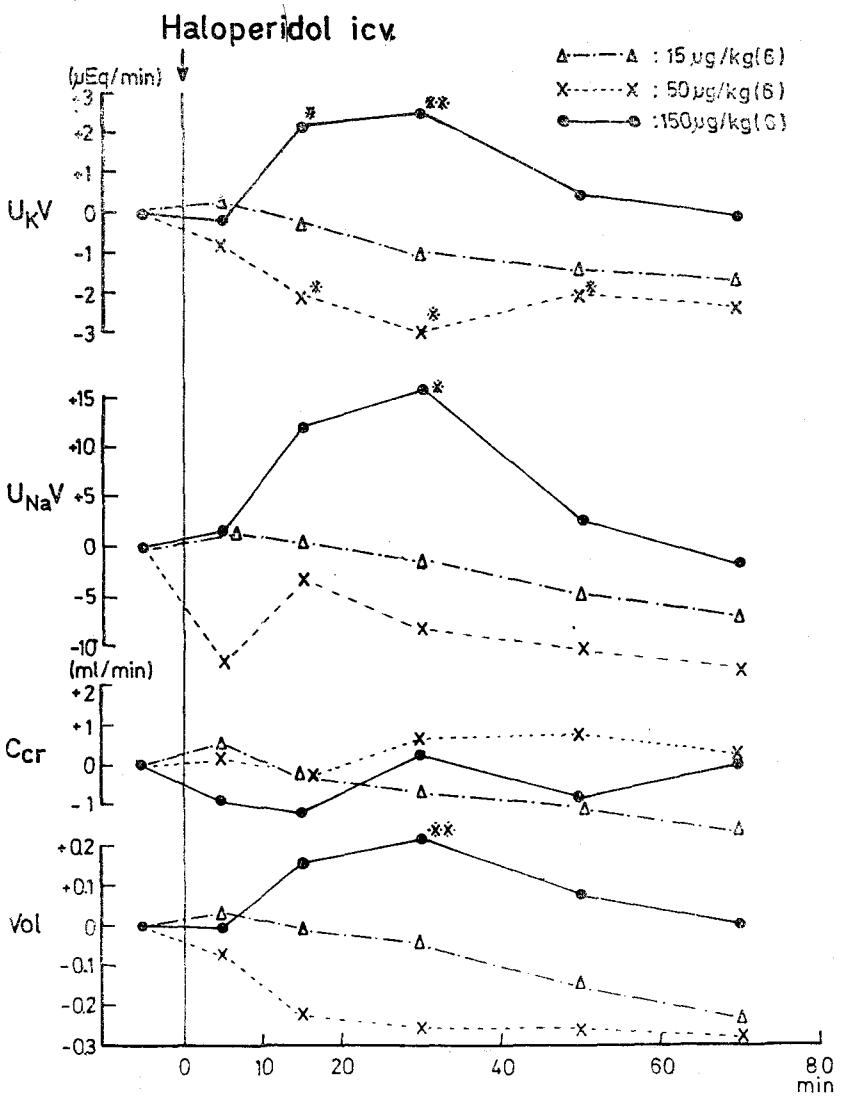


**Fig. 1.** Effects of haloperidol i.c.v. on the rabbit renal function. HA was given at O time. △.....△, 15 μg/kg; x.....x, 50 μg/kg; ●——●, 150 μg/kg. Mean difference from the control clearance are shown. *=p<0.05, **=p<0.01, as tested by Student's paired t-test. Other legends are in the tables.

the fractional excretion significantly increased, showing that the sodium reabsorption in the tubules is diminished. Excretion of potassium as well as osmolar clearance increased in parallel with sodium excretion, but the free-water reabsorption was not affected. Thus, contrary to the responses to smaller doses, natriuresis and diuresis were marked with a dose of 150 μg/kg i.c.v. On the systemic blood pressure no marked changes were observed

with these doses of HA i.c.v.

When the doses were increased further to 500 μg/kg i.c.v., the animals immediately fell into distress with severe dyspnea, hypotension and convulsion, and death ensued within 20 min in all 5 rabbits.

In Fig. 1 the changes of some of the parameters of renal function after i.c.v. HA were depicted. Here, the deviations from the control clearance values are shown.

### Action of dopamine

Before studying the influence of HA-pretreatment on the renal action of i.c.v. dopmaine (DA), the DA action was observed in this section.

The Tables 4-7 show the renal action of 5, 15, 50 and 150 μg/kg, resp. of DA i.c.v. As seen here, 5 μg/kg DA induced only slight decrease in sodium excretion at the end of the experiment, but no signigicant changes were observable with urine flow, renal perfusion and glomerular filtration (Table. 4). With 15 μg/kg, though, the renal perfusion and glomerular filtration increased transiently, but sodium excretion, along with urine flow rate, decreased markedly, indicating that antidiuresis was resulted from increased tubular sodium reabsorption (Table. 5). With 50 μg/kg, marked antidiuresis and natriuresis were evident, and also the free-water reabsorption tended to increase. However, renal perfusion and glomerular filtration also decreased, so that the renal response elicited by 50 μg/kg i.c.v. is caused by both hemodynamic and tubular action (Table.6). Further increasing the dose to 150 μg/kg resulted in severe antidiuresis and more prominent increases of tubular sodium reabsorption and hemodynamic changes (Table. 7).

### Influence of haloperidol on the dopamine action

In Table 8, data from 6 experiments in which 15 μg/kg DA i.c.v. was given 3 min after 150 μg/kg HA i.c.v. As seen here, sodium excretion increased fivefold and the fractional sodium excretion also increased, but because of great individual variation, the increases were not statistically significant. However, as shwon in Fig. 2, the fractional sodium excretion ($FE_{Na}$) of this group (stippled column) differed significantly from that of 15 μg/kg DA alone (white column), and did not differ significantly from that of HA (black column). Thus, it is inferred that the renal

Table 4. Effects of 5 μg/kg dopamine icv on the renal function of the rabbit

| | Control | 0′~10′ | 10′~20′ | 20′~40′ | 40′~60′ | 60′~80′ |
|---|---|---|---|---|---|---|
| Vol(ml/min) | 0.33±0.04 | 0.31±0.10 | 0.33±0.12 | 0.27±0.09 | 0.23±0.06 | 0.19±0.06 |
| $C_{PAH}$(ml/mni) | 18.6 ±2.6 | 19.7 ±2.6 | 19.4 ±3.2 | 16.9 ±3.1 | 16.8 ±2.4* | 14.2 ±1.9 * |
| $C_{cr}$(ml/min) | 7.56±1.05 | 8.10±1.19 | 7.99±1.33 | 7.60±1.20 | 7.19±0.86 | 6.09±0.68 |
| FF(%) | 41.0 ±1.6 | 41.3 ±2.0 | 41.9 ±2.0 | 44.6 ±2.0 | 44.5 ±2.5 | 44.2 ±2.5 |
| $U_{Na}V$(μEq/min) | 8.0 ±2.8 | 7.7 ±2.7 | 7.2 ±2.5 | 5.7 ±2.4 | 4.9 ±2.1 ** | 4.3 ±2.1 * |
| $FE_{Na}$(%) | 0.92±0.36 | 0.86±0.33 | 0.76±0.29 | 0.69±0.34* | 0.57±0.28 | 0.57±0.30* |
| $U_KV$(μEq/min) | 5.7 ±0.5 | 5.7 ±0.5 | 6.1 ±0.7 | 4.8 ±0.6 | 4.5 ±0.5 | 4.2 ±0.5 |
| $C_{osm}$(ml/min) | 0.40±0.07 | 0.42±0.08 | 0.39±0.09 | 0.35±0.07 | 0.33±0.09 | 0.30±0.09 |
| $T^cH_2O$(ml/min) | 0.08±0.12 | 0.11±0.11 | 0.06±0.12 | 0.08±0.10 | 0.11±0.05 | 0.11±0.03 |

Mean±S.E. from 7 experiments.

**Table 5.** Effects of 15 μg/kg dopamine icv on the renal function of the rabbit

| | Control | 0′~10′ | 10′~20′ | 20′~40′ | 40′~60′ | 60′~80′ |
|---|---|---|---|---|---|---|
| Vol(ml/min) | 0.32±0.03 | 0.30±0.03 | 0.28±0.03 | 0.25±0.03* | 0.21±0.04 * | 0.19±0.03** |
| $C_{PAH}$(ml/min) | 11.5 ±1.6 | 11.7 ±1.6 | 12.1 ±1.7 ** | 11.1 ±1.6 | 10.7 ±1.5 | 11.1 ±1.7 |
| $C_{cr}$(ml/min) | 4.89±0.73 | 4.99±0.76 | 5.16±0.77** | 4.71±0.77 | 4.54±0.69 * | 4.49±0.74 |
| FF(%) | 42.0 ±1.7 | 42.1 ±1.7 | 42.3 ±1.5 | 42.1 ±2.4 | 42.6 ±2.8 | 40.2 ±2.2 |
| $U_{Na}V$(μEq/min) | 12.0 ±2.4 | 10.4 ±1.5 | 9.0 ±1.5 | 7.4 ±2.4 *** | 4.9 ±1.5 *** | 4.0 ±1.4 ** |
| $FE_{Na}$(%) | 2.17±0.41 | 1.77±0.29 | 1.42±0.19* | 1.30±0.31** | 0.93±0.25*** | 0.81±0.25*** |
| $U_KV$(μEq/min) | 5.70±1.20 | 5.60±1.20 | 5.50±1.10 | 5.00±1.10 | 4.60±1.10 | 4.60±0.90 |
| $C_{osm}$(ml/min) | 0.47±0.06 | 0.46±0.06 | 0.44±0.06 | 0.39±0.05 | 0.33±0.04* | 0.31±0.03* |
| $T^cH_2O$(ml/min) | 0.15±0.07 | 0.16±0.07 | 0.16±0.07 | 0.14±0.06 | 0.12±0.11** | 0.12±0.05 |

Mean±S.E. from 6 experiments. ***=$p<0.001$

**Table 6.** Effects of 50 μg/kg dopamine icv on the renal function of the rabbit

| | Control | 0′~10′ | 10′~20′ | 20′~40′ | 40′~60′ | 60′~80′ |
|---|---|---|---|---|---|---|
| Vol(ml/min) | 0.28±0.04 | 0.29±0.07 | 0.18±0.05* | 0.14±0.04* | 0.12±0.03* | 0.13±0.04 |
| $C_{PAH}$(ml/min) | 12.3 ±1.9 | 12.0 ±1.9 | 9.4 ±1.7* | 9.6 ±1.3 | 9.2 ±1.2 | 8.7 ±0.9 |
| $C_{cr}$(ml/min) | 4.66±0.47 | 4.71±0.58 | 3.86±0.56 | 4.23±0.59 | 3.92±0.59 | 3.95±0.43* |
| FF(%) | 39.5 ±2.6 | 40.1 ±2.04 | 43.3 ±3.8 ** | 43.9 ±1.2 * | 43.9 ±2.0 | 45.6 ±2.6 |
| $U_{Na}V$(μEq/min) | 5.3 ±1.6 | 5.0 ±50.13 | 3.0 ±1.0 | 1.7 ±0.6 * | 1.2 ±0.3 * | 1.0 ±0.2 * |
| $FE_{Na}$(%) | 0.85±0.25 | 0.94±0.34 | 0.55±0.18 | 0.31±0.12* | 0.25±0.09* | 0.19±0.05* |
| $U_KV$(μEq/min) | 3.3 ±0.7 | 3.4 ±0.7 | 2.6 ±0.8 | 2.0 ±0.4 | 1.8 ±0.3 | 2.0 ±0.5 |
| $C_{osm}$(ml/min) | 0.26±0.04 | 0.27±0.04 | 0.20±0.05* | 0.18±0.04* | 0.17±0.04** | 0.17±0.03** |
| $T^cH_2O$(ml/min) | −0.03±0.05 | −0.03±0.06 | 0.02±0.03 | 0.05±0.02 | 0.05±0.03 | 0.03±0.03 |

Mean±S.E. from 6 experiments.

**Table 7.** Effects of 150 μg/kg dopamine icv on the renal function of the rabbit

| | Control | 0′~10′ | 10′~20′ | 20′~40′ | 40′~60′ | 60′~80′ |
|---|---|---|---|---|---|---|
| Vol(ml/min) | 0.22±0.04 | 0.21±0.05 | 0.14±0.03* | 0.10±0.03** | 0.13±0.06* | 0.11±0.05** |
| $C_{PAH}$(ml/min) | 11.8 ±1.1 | 11.8 ±1.3 | 8.9 ±1.1 | 8.0 ±1.7 * | 9.2 ±1.8 | 7.7 ±1.4 |
| $C_{cr}$(ml/min) | 5.21±0.71 | 5.27±0.66 | 3.88±0.44 | 3.62±0.81* | 4.89±1.05 | 3.68±0.78* |
| FF(%) | 43.6 ±2.2 | 44.7 ±2.8 | 44.8 ±2.1 | 45.5 ±1.7 | 52.5 ±3.0 ** | 47.6 ±2.3 * |
| $U_{Na}V$(μEq/min) | 4.5 ±1.0 | 3.6 ±1.0 | 3.0 ±0.8 | 1.6 ±0.5 ** | 1.3 ±0.5 ** | 1.0 ±0.3 ** |
| $FE_{Na}$(%) | 0.71±0.18 | 0.51±0.14 | 0.58±0.15 | 0.32±0.08* | 0.19±0.05** | 0.21±0.05* |
| $U_KV$(μEq/min) | 3.0 ±0.6 | 2.6 ±0.4 | 2.2 ±0.40 | 1.5 ±0.4 * | 1.7 ±0.40* | 1.4 ±0.4 ** |
| $C_{osm}$(ml/min) | 0.23±0.05 | 0.19±0.03 | 0.15±0.02 | 0.12±0.03** | 0.14±0.03* | 0.11±0.03** |
| $T^cH_2O$(ml/min) | 0.1 ±0.06 | −0.01±0.05 | 0.01±0.03 | 0.01±0.03 | 0.02±0.04 | 0.01±0.04 |

Mean±S.E. from 8 experiments.

action of 15 μg/kg DA i.c.v. is blocked by the pretreatment with 150 μg/kg HA i.c.v.

Next, 50 μg/kg DA i.c.v. was administered ten minutes after HA i.c.v. (Table. 9). For ten min following administration the typical natriuretic action of HA was still evident, but after 10 min it began to decrease and reached values lower than pre-administration control

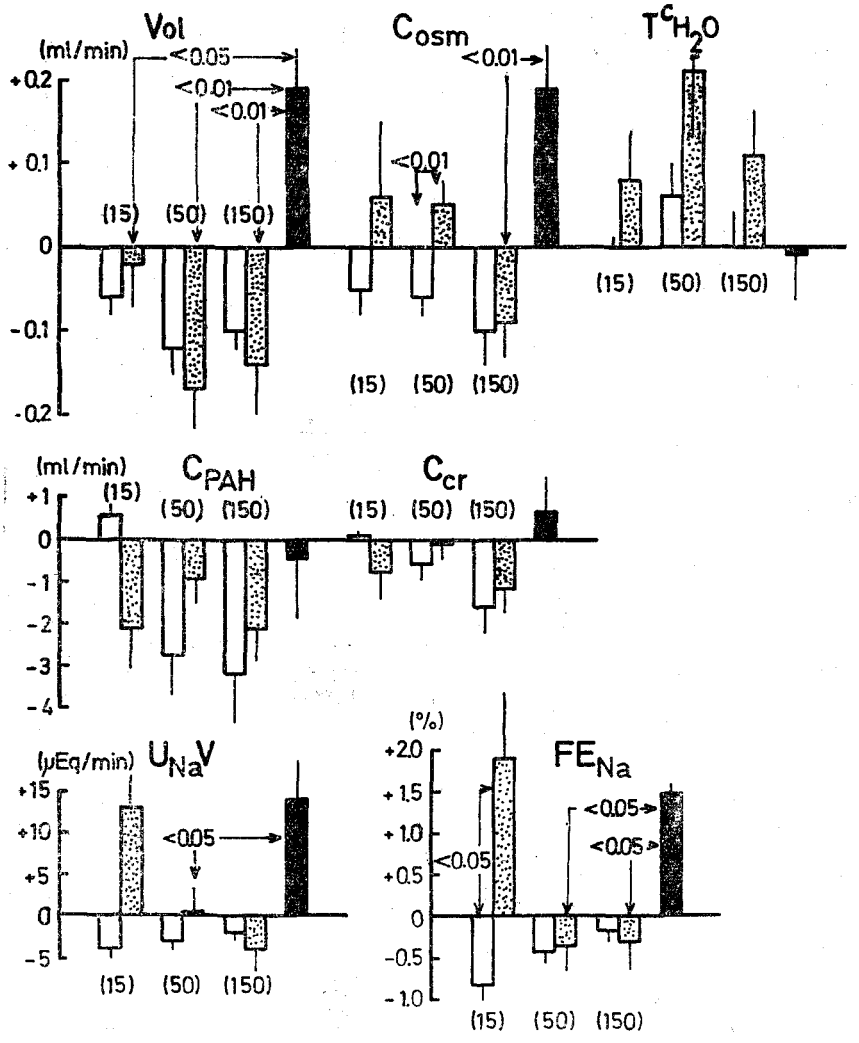


**Fig. 2.** Influence of haloperidol pretreatment on the dopamine effects. Mean changes with S.E. from the control values of the two periods(10′~20′ and 20′~40′) after dopamine administration are shown. The white columns indicate dopamine group, the stippled represent haloperidol-pretreated group, and the black columns stand for the haloperidol group. The dose of haloperidol was 150 μg/kg. Dopamine was given 3 to 10 min after haloperidol, and the doses of dopamine in μg/kg are indicated in the parentheses. Significance of difference between groups were tested with unpaired t-test and p-values of significant differences are shown.

Table 8. Influence of haloperidol(150 μg/kg icv) pretreatment on the renal effects of 15 μg/kg dopamine icv

| | Control | 0′～10′ | 10′～20′ | 20′～40′ | 40′～60′ | 60′～80′ |
|---|---|---|---|---|---|---|
| Vol(ml/min) | 0.25±0.05 | 0.33±0.14 | 0.30±0.12 | 0.16±0.05 | 0.17±0.04* | 0.16±0.05* |
| $C_{PAH}$(ml/min) | 12.6 ±1.9 | 13.5 ±2.2 | 10.4 ±1.5 | 10.4 ±1.7 | 11.2 ±2.5 | 9.3 ±1.80** |
| $C_{cr}$(ml/min) | 5.67±0.87 | 6.16±0.08 | 5.05±0.69 | 4.62±0.50 | 4.84±0.76 | 3.97±0.60 |
| FF(%) | 46.6 ±4.8 | 48.4 ±5.8 | 50.9 ±5.2 * | 48.1 ±5.8 | 47.1 ±5.2 | 46.3 ±5.3 |
| $U_{Na}V$(μEq/min) | 5.7 ±1.6 | 21.2 ±1.21 | 27.7 ±13.5 | 9.7 ±4.8 | 5.9 ±2.5 | 3.7 ±1.9 |
| $FE_{Na}$(%) | 0.69±0.89 | 2.19±1.08 | 3.78±1.70 | 1.37±0.61 | 0.89±0.37 | 0.55±0.24 |
| $U_KV$(μEq/min) | 3.7 ±0.7 | 5.1 ±0.8 | 5.3 ±0.7 | 4.4 ±0.7 | 3.4 ±0.6 | 2.3 ±0.4 |
| $C_{osm}$(ml/min) | 0.31±0.70 | 0.47±0.11 | 0.46±0.12 | 0.29±0.06 | 0.25±0.04 | 0.19±0.04 |
| $T^cH_2O$(ml/min) | 0.07±0.08 | 0.08±0.05 | 0.16±0.04 | 0.14±0.02 | 0.08±0.03 | 0.03±0.03 |

Mean±S.E. from 6 experiments. Haloperidol was given 3 min prior to dopamine.

Table 9. Influence of haloperidol(150 μg/kg icv) pretreatment on the renal effects of 50 μg/kg dopamine icv

| | Control | Haloperidol | after dopamine 0′～10′ | 10′～20′ | 20′～40′ | 40′～60′ | 60′～80′ |
|---|---|---|---|---|---|---|---|
| Vol(ml/min) | 0.35±0.10 | 0.38±0.10 | 0.33±0.07 | 0.19±0.06 | 0.17±0.04 | 0.22±0.11 | 0.28±0.13 |
| $C_{PAH}$(ml/min) | 11.5 ±1.9 | 10.1 ±1.5 | 11.8 ±1.1 | 10.3 ±0.8 | 10.9 ±1.1 | 10.8 ±1.5 | 11.5 ±2.2 |
| $C_{cr}$(ml/min) | 4.33±0.58 | 3.99±0.66 | 4.80±0.63 | 4.12±0.57 | 4.42±0.52 | 4.38±0.49 | 4.99±0.92 |
| FF(%) | 40.5 ±4.5 | 40.3 ±4.2 | 40.7 ±4.1 | 30.4 ±3.9 | 41.0 ±3.4 | 42.0 ±3.80 | 45.10±4.60 |
| $U_{Na}V$(μEq/min) | 10.5 ±4.4 | 14.6 ±5.1 | 21.4 ±5.5* | 14.0 ±3.9 | 7.4 ±2.1 | 6.2 ±3.1 | 7.6 ±3.3 |
| $FE_{Na}$(%) | 1.40±0.49 | 2.25±0.67 | 3.52±0.77** | 2.38±0.41 | 1.20±0.29 | 0.96±0.01 | 1.00±0.38 |
| $U_KV$(μEq/min) | 2.4 ±0.6 | 2.7 ±0.7 | 3.6 ±0.4 | 3.4 ±0.6 | 3.3 ±0.5* | 2.8 ±0.5 | 3.3 ±0.8 |
| $C_{osm}$(ml/min) | 0.27±0.07 | 0.31±0.08 | 0.40±0.08* | 0.33±0.09 | 0.29±0.05 | 0.25±0.03 | 0.26±0.04 |
| $T^cH_2O$(ml/min) | −0.08±0.08 | −0.07±0.07 | 0.08±0.06* | 0.14±0.51* | 0.12±0.06* | 0.03±0.10 | −0.02±0.11 |

Mean±S.E. from 6 experiments. Haloperidol was given 10 min prior to dopamine.

Table 10. Influence of haloperidol(150 μg/kg icv) pretreatment on the renal effects of 150 μg/kg dopamine icv

| | Control | Haloperidol | after dopamine 0′～10′ | 10′～20′ | 20′～40′ | 40′～60′ | 60′～80′ |
|---|---|---|---|---|---|---|---|
| Vol(ml/min) | 0.31±0.07 | 0.36±0.09 | 0.20±0.08 | 0.15±0.08* | 0.17±0.09 | 0.21±0.10 | 0.19±0.09* |
| $C_{PAH}$(ml/min) | 11.0 ±0.7 | 13.3 ±2.8 | 6.3 ±1.5* | 7.5 ±2.3 | 8.1 ±1.8 | 12.3 ±2.4 | 11.4 ±1.6 |
| $C_{cr}$(ml/min) | 4.51±0.41 | 5.35±0.62 | 2.96±0.83 | 3.20±0.95 | 3.39±0.77 | 4.64±0.70 | 4.72±0.84 |
| FF(%) | 41.5 ±2.4 | 45.3 ±3.7 | 44.7 ±3.4 | 43.1 ±4.3 | 42.4 ±2.3 | 40.1 ±4.4 | 41.0 ±4.0 |
| $U_{Na}V$(μEq/min) | 9.4 ±2.7 | 16.6 ±6.3 | 10.5 ±2.2 | 6.2 ±1.5 | 4.8 ±1.8 | 4.9 ±1.9 | 5.3 ±2.2 |
| $FE_{Na}$(%) | 1.49±0.41 | 2.11±0.77 | 3.66±1.26 | 1.52±0.36 | 0.89±0.19 | 0.66±0.20 | 0.77±0.26 |
| $U_{Na}V$(μEq/min) | 2.6 ±0.5 | 3.5 ±0.9 | 2.8 ±0.9 | 2.2 ±0.6 | 2.3 ±0.6 | 2.5 ±0.6 | 2.6 ±0.60 |
| $C_{osm}$(ml/min) | 0.27±0.05 | 0.37±0.10 | 0.22±0.06 | 0.18±0.05 | 0.18±0.05* | 0.21±0.05 | 0.19±0.06 |
| $T^cH_2O$(ml/min) | −0.04±0.04 | 0.01±0.04 | 0.02±0.03 | 0.02±0.03 | 0.02±0.04 | −0.01±0.06 | 0±0.04 |

Mean±S.E. from 6 experiments.

levels after 20 min. But, when compared with 50 μg/kg DA alone group (white column) the decrements were less marked. Free-water reabsorption decreased significantly in this group, while no significant changes were observed in renal perfusion and glomerular filtration rate. As shown in Fig. 2, only $C_{osm}$ differed significantly from 50 μg/kg DA group (white column), but sodium excretion (also the fractional excretion) and urine flowe rate differed siginificantly from the HA group (black column).

When 150 μg/kg DA i.c.v. was given after HA (Table 10), antidiuresis and antinatriuresis as well as decreases in renal plasma flow and glomerular filtration rate immediately followed the DA administration, so that, as shown in Fig. 2, no difference from the group of 150 μg/kg DA alone (white column) was found, whereas the difference from the HA group (black column) became significant in most parameters.

It is clear from these observations that HA could abolish the renal actions of 15 μg/kg DA i.c.v., but not those of the higher doses.

The systemic blood pressure was transiently depressed by 9 to 12 mmHg with 50 and 150 μg/kg of DA i.c.v. HA pretreatment did not abolish the hypotensive action of i.c.v. DA, but tended to augment the hypotension slightly. With 150 μg/kg of HA given *intravenously* in 6 experiments, no significant change in renal function was observed.

## DISCUSSION

Dopamine (DA) is the most abundant catecholamine in the brain and plays important roles, not only as the immediate precursor of norepinephrine in the biosynthetic pathway, but also as a neurotransmitter (Moore & Bloom, 1978). Differing from the distribution of norepinephrine, DA is located abundantly in basal ganglia, especially in caudate nucleus, and in other parts, such as in nucleus accumbens, olfactory tubercle, median eminence, and in frontal cortex, and plays vital roles in the function of extrapyramidal pathways and in the limbic system, particularly of the hypothalamus (Carlsson & Lindqvist, 1963; Hokfelt, 1978). However, little is known on the role of this central dopaminergic system on the regulation of body fluids and on the renal function. Only, Choi (1974) observed antidiuresis when DA was injected directly into a cerebral ventricle, suggesting a role of DA upon renal function. Our observations confirm that when introduced into a lateral ventricle of a rabbit brain DA induces antidiuresis in dose-related fashion. However, the mechanism involved is not simple in that in small doses (15 μg/kg) the antidiuresis resulted mainly by the enhanced tubular sodium reabsorption rather than by hemodynamic action, but in higher doses the hemodynamic action became more marked, and also the increased free-water reabsorption seemed to participate.

These observations, however, does not substantiate the physiological role of DA system in the brain in regulating renal function. It might as well be only an expression of the pharmacological action. Therefore, to obtain an evidence as to the physiological role, we tried to examine the renal response to the blockade of the central dopamine-receptors. The rationale is that a diuretic response would be expected, if DA in the brain had been exerting via the DA-receptors in the center an antidiuretic influence upon the kidney.

Haloperidol (HA) is a representative memb-

er of butyrophenones developed in Belgium in 1956 and is now widely employed as "neuroleptic" or major tranquilizer in the practice of psychiatry and anesthesia (Carlsson, 1978). In addition to an action on the alpha-adrenergic receptors, it is well documented that HA produces specific blockade on the DA-receptors in the limbic system and basal ganglia (Clement-Cormier *et al*, 1974), and that parkinsonism can be induced, when a large dose of HA is given, by blocking the dopaminergic system in the extrapyramidal pathway, especially in nigro-striatal tract (Baldessarini, 1979; 1980).

Though pharmacology of HA has been extensively studied, little is known on the renal action, and no report is at hand on the influence of i.c.v. HA on the renal function. In this study it was found that HA i.c.v. elicits antidiuresis in smaller doses, but diuresis and natriuresis in a large dose of 150 μg/kg. 15 μg/kg i.c.v. of HA brought about decrease in urine flow as a result of enhanced tubular sodium reabsorption and free-water, resembling the responses to small doses of DA. But, a moderate dose (50 μg/kg) elicited antidiuresis resulting from increased free-water reabsorption with no changes in renal perfusion and filtration as well as in Na reabsorption. With the large dose of 150 μg/kg the renal response reversed to a diuresis and natriuresis as a consequence of depressed tubular sodium reabsorption. It may be reasonable, therefore, to assume that in the response to the moderate dose the antidiuretic and natriuretic action evident with the small doses might have been cancelled out or covered by the natriuretic and diuretic action seen with the large dose.

It is not an easy task to adequately account for the contradictory responses to different doses of HA, as observed in this study. First of all, it is conceivable that HA might influence, beside the dopaminergic system, other systems such as adrenergic system, especially when large doses are administered. However, this possibility seems unlikely because the HA action could be overcome by increasing doses of DA, and also because an agonistic action of HA on the DA-receptors must be proven, especially with smaller doses. Secondly, differing sensitivity to both DA-receptors and alpha-adrenergic receptors in the center may be inferred. For this premise to be tenable, however, the postulation is necessary that smaller doses of HA stimulate rather than block those receptors, for which no evidence is available so far. Rather, it seems to be more plausibly explained, if one takes into consideration that there exists many types of DA-receptors in the brain with differing sensitivity to various agonists (Carlsson, 1975; Kebabian, 1973; Beart, 1982). According to Carlsson (1975) there are two kinds of DA-receptors, the first being located at the postsynaptic site and related to activation of adenyl cyclase, and the second type being the presynaptic receptors situated on the soma or dendrites of dopaminergic neurones (autoreceptors). Stimulation of the latter diminishes the release of DA whereas stimulating the former augments the DA release. Thus, the agents which stimulate the postsynaptic receptors in the striatum is effective in treating Parkinsonism (Woodruff, 1982; Nilsson & Carlsson, 1982). And as it was shown that the autoreceptors (presynaptic) are more sensitive to agonists than the postsynaptic receptors (Nilsson & Carlsson), it may be assumed that small doses of HA blocks the autoreceptors first, resulting in increased DA release, which in turn brings about antidiuretic responses resembling the small doses of

DA. However, when the dose administered were increased, HA blocks the postsynaptic receptors also, which then leads to depressed "tonic" influence of DA, so that a diuretic and natriuretic response is produced.

In support for this explanation are the observations that diuretic and natriuretic action of a large dose of HA was not affected by small dose (15 μg/kg) of DA, whereas they were completely overcome by larger doses of DA. This indicates that HA competes with DA for dopaminergic receptors, exhibiting a competitive, surmountable antagonism. The fact that HA-induced diuresis was reversed by DA also suggests that the HA-diuresis is indeed brought about through DA-receptors, not by certain unknown mechanism.

The free-water reabsorption is enhanced by the presence of ADH. It increases the water permeability of the collecting tubules, resulting in increased osmotic water flow into the hypertonic milieu of inner medulla, produced by the countercurrent multiplier system. Therefore, the level of free-water reabsorption is an indirect indicator of plasma ADH level (Pitts, 1974). With large dose of DA the free-water reabsorption only tended to increase, so that increased ADH could not be supported. But, the distinct increase of free-water reabsorption with 50 μg/kg HA which has become obscure with 150 μg/kg HA because of marked natriuresis, did appear again when 50 μg/kg of DA was added. This suggests that DA-receptors are involved also in the release of ADH, and it may be presumed that moderate doses of HA block the more sensitive autoreceptors resulting in increased ADH release, while with a large dose the postsynaptic DA-receptors also are blocked, abolishing the increased ADH release.

On the intrarenal location of the natriuresis induced by a large dose of HA, the distal nephron can be ruled out, as potassium excretion paralleled with increase in sodium excretion. Almost all the potassium excreted in the urine derived from the distal tubules exchange for reabsorbed sodium, so that inhibition of sodium reabsorption in the distal nephron is accompanied by decreased potassium excretion (Pitts, 1974; Giebish, 1981). Judging from the magnitude, and considering that reabsorption of salt in the proximal tubles is directly affected by renal innervation (Burg, 1981), the proximal tubules seem to be the most likely site of action, though more evidence is necessary.

When 150 μg/kg HA was administered *intravenously* no change was observed on the renal function. Therefore, it is clear that the HA-induced natriuresis and diuresis are enitrely of central origin. On the systemic blood pressure HA did not have any influence, but DA produced depressor response which was not affected by HA pretreatment, suggesting that the DAreceptors involved in the regulation of renal function is not identical with those engaged in blood pressure regulation.

## SUMMARY

In an effort to provide evidence as to the regulatory role of the central dopaminergic system on the renal function, the effects of centrally administered dopamine and its specific antagonist haloperidol were investigated.

Haloperidol (HA) given intracerebroventricularly (i.c.v.) induced antidiuresis in doses of 15 and 50 μg/kg. With 15 μg/kg sodium reabsorption in the tubules was increased, while with 50 μg/kg free-water reabsorption was increased. However, a marked diuresis

with increased sodium and potassium was observed with 150 μg/kg. Hemodynamic changes were not evident, indicating that the diuresis is of tubular origin.

Dopamine (DA), on the other hand, produced antidiuresis when given i.c.v. in a dose-related fashion. With smaller doses of 5 and 15 μg/kg the antidiuresis was related to increased reabsorption of sodium in the tubules, but higher doses of 50 and 150 μg/kg the decreases in renal blood flow and glomerular filtration rate were evident in addition to the tubular action.

After pretreatment with 150 μg/kg HA, the effects of 15 μg/kg DA was abolished, but the antidiuretic actions of 50 and 150 μg/kg were not blocked, and the natriuretic diuretic action of HA was overcome and became inconspicuous.

These observations indicate that the central dopaminergic system influences the renal function by producing antidiuresis, and HA elicits diuresis and natriuresis by competitively antagonizing DA specifically on the central dopaminegic receptors. The antidiuresis observed with smaller doses of HA can be best explained by the facts that there are more than two types of DA-receptors in the brain and that the presynaptic autoreceptors on the dopaminergic neurones which affect the dopamine release at the synapse are more sensitive than the postsynaptic receptors.

Overall, these data provide an evidence indicating that the central dopaminergic system plays a role in the regulation of renal function in the rabbit.

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