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Influence of Intracerebroventricular Clonidine on the Rabbit Renal Function

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=국문초록=

가토신장기능에 미치는 측뇌실내 Clonidine의 영향

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신장기능에 대한 중추신경계의 역할을 구명코자. presynaptic α-adrenoceptor의 선택적 작동약인 clonidine을 urethane마취 가토의 측뇌실내로 (*icv*)투여하여 신장기능의 변동을 관찰하였다. 5 μg/kg *icv* 이하의 양으로는 신장기능의 유의한 변동을 볼 수 없었으나, 15μg/kg *icv* 으로는 20분간에 걸쳐 현저한 Na 및 K배설 증가를 볼 수 있었다 이 때 신혈류 및 사구체 여과율은 유의한 변동을 나타내지 아니하였다. 또 이때 Na재흡수율은 유의하게 감소하였으며, Na배설증가 작용이 세뇨관에서의 Na재흡수 억제에 기인함을 알 수 있었다. 전신혈압 변동은 이 작용에 기여하지 아니하였다. Presynaptic α-adrenoceptor에 대한 선택적 길항약인 yohimbine 100 μg/kg을 clonidine투여 20분전에 측뇌실내로 투여하면 clonidine의 신장작용이 완전히 차단되었다. 이 량의 yohimbine은 측뇌실내 투여시 신장기능에 아무런 변동도 초래하지 아니하였다. 15 μg/kg clonidine을 정맥내로 투여하면 투여 직후에 뇨량 감소와 신장기능 감퇴를 초래한 뒤 후기에 약간의 Na배설증가의 경향을 보였으나, clonidine을 *icv*로 투여하였을 때 볼 수 있던 만큼의 Na배설증가는 볼 수 없었다. 따라서 *icv* clonicine의 신장작용에는 신장에 대한 clonidine의 직접작용이 관여하지 않음을 알 수 있었다. 이 연구결과는 가토의 신장기능 조절에 있어서 중추의 교감신경 긴장도가 중요한 역할을 하고 있음을 시사하였다.

INTRODUCTION

The excretory function of the kidney is under the regulatory influence of the central nervous system in response to momentary needs of the body. In addition to the secretion of humoral agents such as antidiuretic hormone (Verney, 1947) and natriuretic factors (Cort *et al.*, 1968; De Wardner, 1973), the CNS modulates the excretory function through nerve pathways, among which the sympathetic nerves have been shown to play the most important role (Smith,

1951; Gill & Casper, 1969). In a series of studies in which attempts were made to modify the central sympathetic tone, it was found that norepinephrine (Lee, 1972) and dopamine(Choi, 1974) influence the renal function when administered directly into a lateral ventricle (*icv*) of the rabbit brain, and that antidiuresis ensued mainly as a result of decreased renal hemodynamics. Also, phentolamine, an α-adrenergic blocking agent, was shown to induce antidiuresis and antinatriuresis when given *icv* (Ko, 1974; Lee, 1974).

Clonidine, presently used widely as an antihypertensive, has been found to be an agonist for presynaptic (α_2—) adrenoceptors (Hoefke & Kobinger, 1966; Kobinger & Walland, 1967). By stimulating the presynaptic adrenoceptor in the CNS, it depresses the central sympathetic tone, and the sympathetic "outflow" in the periphery is diminished (Schmitt, 1970). In this study, clonidine was given *icv*, and the effect of this diminished central sympathetic tone on renal function was investigated. The renal action of yohimbine, a specific presynaptic adrenoceptor antagonist (Drew, 1976; Starke *et al.*, 1975), and its influence on the action of clonidine was investigated also.

METHODS AND MATERIALS

Adult rabbits of either sex, weighing 1.6 — 2.5 kg, were used. The animals were anesthetized with 1g/kg urethane, s.c., fastened to the table in the supine position, and a trachea cannula was inserted to secure free air passage. Into a jugular vein, an infusion 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. Through a small midline incision on the lower abdomen, the urinary bladder was exposed, and both ureters were cannulated with PE 50 tubings for collection of urine. For sampling blood a femoral artery was cannulated with PE tubing which was kept patent by filling with heparinized saline (400 U/ml).

The animal was then changed to the prone position, and a lateral ventricle of the cerebrum was cannulated for administration of the agent. The parietal bone was exposed by incising the scalp along the midline and a hole was drilled at a point 1.5 cm rostral to the occipital tubercle and 0.5 cm lateral to the midline. After piercing through the dura mater a cannula made of PE tubing of 1.5 cm O.D. was introduced obliquely until the cerebrospinal fluid came up in the cannula, and the cannula was then sealed off to prevent leaking. The cannula was kept in place by cementing it to the bone with bond. The agent was dissolved in 0.9% NaCl solution and the volume of administration did not exceed 0.2 ml. At the end of each experiment small amount of a dye solution was injected through the cannula before the animals was sacrificed, the ventricle was opened, and the location of the tip of the cannula was ascertained.

When urine flow gradually increased and became stable several hours after the beginning of infusion, the collection of two or three ten-minute control clearance samples was begun, and after the administration of the agent 4 or 5 more samples of ten- or twenty-min clearance periods were collected. At the mid-point of each clearance period a blood sample was collected, immediately centrifuged, and the plasma separated. Together with the urine samples the plasma samples were subjected to chemical analysis. As a measure of glomerular filtration

Table 1. Effects of intracerebroventricular clonidine on rabbit renal function

	Control	0'-20'	40'-40'	40'-60'	60'-80'
			Vehicle (0.9% NaCl sol.) *icv* (5)		
Vol	0.15±0.02	0.15±0.01	0.20±0.03	0.13±0.03	0.17±0.04
C_{PAH}	11.7 ±1.0	11.4 ±0.5	12.2 ±1.0	12.2 ±0.9	10.3 ±0.9
C_{cr}	5.02±0.45	5.23±0.19	5.67±0.46	5.42±0.52	4.74±0.49
$U_{Na}V$	1.8 ±0.6	1.9 ±0.7	1.8 ±0.5	1.3 ±0.6	1.2 ±0.5
R_{Na}	99.67±0.11	99.67±0.14	99.70±0.10	99.60±0.16	99.78±0.08
U_KV	4.3 ±0.6	4.6 ±0.4	5.1 ±0.4	4.8 ±0.5	4.3 ±0.5
C_{osm}	0.34±0.05	0.36±0.02	0.40±0.04	0.36±0.04	0.33±0.04
			15 μg/kg clonidine *icv* (6)		
Vol	0.17±0.02	0.29±0.09	0.15±0.03	0.11±0.02	0.12±0.03
C_{PAH}	23.1 ±2.6	23.3 ±3.0	24.5 ±3.8	22.9 ±3.6	21.4±3.5
C_{cr}	7.12±0.61	7.27±0.72	6.97±0.88	6.97±0.99	6.77±1.01
FF	31.6 ±1.5	32.0 ±1.8	29.3 ±1.6	31.1 ±1.1	32.1 ±1.5
$U_{Na}V$	7.3 ±4.2	21.9 ±11.5*	8.7 ±4.0	3.8 ±1.8	5.5 ±2.1
R_{Na}	99.32±0.36	97.80±1.22**	99.16±0.40	99.66±0.13	99.47±0.10
U_KV	6.1 ±0.7	8.5 ±1.1*	6.6 ±1.4	5.6 ±1.1	6.1 ±1.3
C_{osm}	0.46±0.05	0.68±0.15	0.47±0.09	0.41±0.08	0.44±0.09
T^cH_2O	0.29±0.04	0.40±0.06	0.32±0.06	0.30±0.06	0.32±0.06

Mean values and standard errors are shown. Vol represents urine flow rate in ml/min; C_{PAH}, C_{cr} and C_{osm} are clearances of p-amino-hippuric 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; R_{Na} is the percentage of filtered sodium reabsorbed in tubules; FF=filtration fraction in percent; T^cH_2O=rate of free water reabsorption in ml/min. Significance of difference from the corresponding values of saline group are shown as *=$p<0.05$, **=$p<0.01$. In parentheses are number of experiments.

rate, exogenous creatinine clearance was utilized as no practical difference has been found between exogenous creatinine clearance and inulin clearance in the rabbit (unpublished observation).

Systemic blood pressure was measured by recording from the femoral artery through a pressure transducer on a recorder. 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 were determined by flamephotometry, and the osmolality with "Advanced" osmometer. Clonidine chloride was obtained from Boehringer Ingelheim and yohimbine HCl from Merck Co.

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

RESULTS

Renal Action of icv Clonidine

First, as a control experiment, the effect of *icv* saline used as vehicle of the agent, on the renal function was examined. In the upper part of Table 1 is the summary of the data from 5 identical experiments in which only 0.2 ml of 0.9% NaCl solution was administered *icv*. There

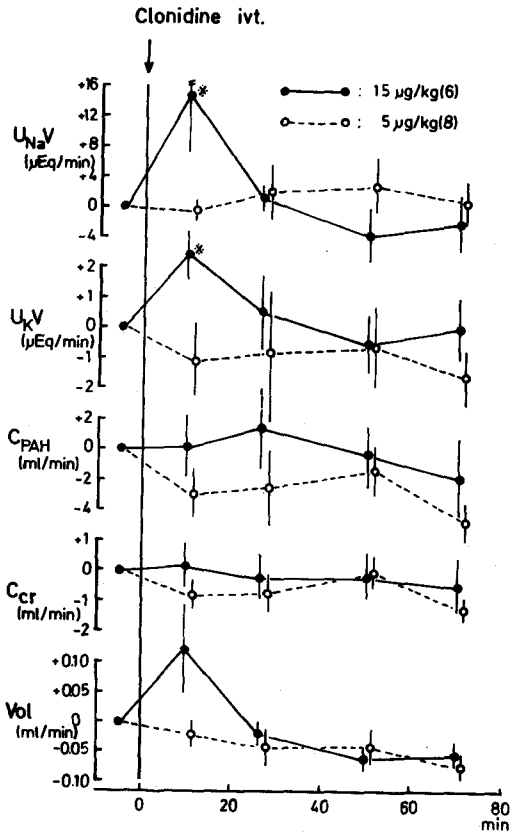

Fig. 1. Influence of intracerebroventricular clonidine on the renal function in the rabbit. Mean changes from the control values and standard errors are depicted. The asterisks indicate significant difference ($p<0.05$) from the corresponding values of the saline control group. Abbreviations are as in the tables. In parentheses are the number of experiments.

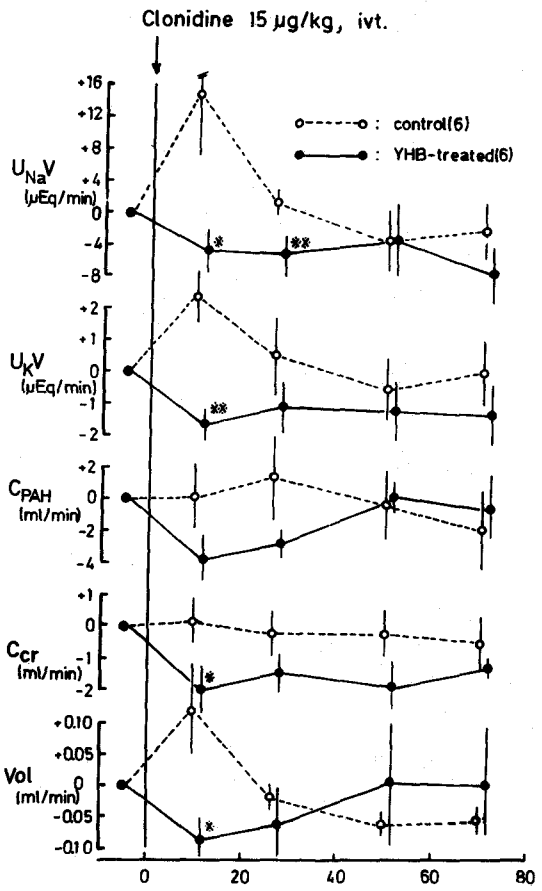

Fig. 2. Influence of yohimbine (YHB) pretreatment on the renal action of *icv* clonidine. "Control" group received 15 μg/kg clonidine *icv* without yohimbine pretreatment, whereas "YHB-treated" group received 100 μg/kg yohimbine *icv* 20 min before clonidine. Significance of differences between both groups are indicated as *=$p<0.05$, **=$p<0.01$.

was only slight fluctuation in various parameters of renal function, and no statistically significant changes were observed.

The data from 8 experiments in which 5μg/kg clonidine was given *icv* are shown in Figure 1. The urine flow rate (Vol) tended to decrease slightly following the administration. The renal plasma flow (C_{PAH}) and glomerular filtration rate (C_{cr}) also tended to decrease for 40 min, so that the filtration fraction tended to increase slightly. Sodium excretion showed a tendency to increase after a slight dip, whereas potassium excretion, osmolar clearance and free water reabsorption tended to decrease. All these values, however, were not significantly different from the control period, nor were they statisti-

Table 2. Effects of yohimbine *icv* on renal function and its influence on the *icv* clonidine action

	Control	0'-20'	20'-40'	40'-60'	60'-80'
		100 μg/kg yohimbine *icv* (6)			
Vol	0.17±0.04	0.16±0.04	0.14±0.01	0.10±0.01	0.08±0.02
C_{PAH}	16.7 ±0.9	12.5 ±1.6	15.3 ±1.2	12.5 ±1.1	10.4 ±2.4
C_{cr}	7.02±0.43	5.81±0.79	6.79±0.54	6.32±0.04	5.36±1.16
$U_{Na}V$	1.9 ±0.8	3.5 ±1.9	4.4 ±2.0	3.5 ±1.9	2.4 ±1.2
$U_{K}V$	5.5 ±0.7	5.0 ±1.0	5.8 ±0.7	5.0 ±0.9	4.1 ±1.1
C_{osm}	0.43±0.08	0.42±0.06	0.51±0.06	0.50±0.07	0.43±0.04
		15 μg/kg clonidine *icv* after yohimbine (6)			
Vol	0.18±0.04	0.11±0.03*	0.13±0.04	0.19±0.11	0.19±0.09
C_{PAH}	14.6 ±1.6	10.2 ±2.1	11.7 ±2.1	14.7 ±4.6	13.9 ±3.8
C_{cr}	6.97±1.09	5.00±1.03*	5.61±1.07	5.20±0.73	5.78±1.18
$U_{Na}V$	9.7 ±4.1	4.9 ±2.3*	4.8 ±2.7**	6.2 ±3.7	2.3 ±1.7
R_{Na}	98.48±0.70	98.28±0.37*	99.21±0.46	99.00±0.53	99.50±0.38
$U_{K}V$	5.1 ±0.4	3.4 ±0.6**	4.0 ±0.8	3.9 ±0.8	3.9 ±0.7
C_{osm}	0.39±0.06	0.31±0.06	0.30±0.03	0.27±0.05	0.28±0.04
$T^{c}H_2O$	0.21±0.03	0.19±0.05	0.15±0.04	0.07±0.07	0.09±0.08

Legends are as in the previous table. Significance of difference from the corresponding values of 15 μg/kg clonidine group (lower part of Table 1) are shown as *=$p<0.05$, **=$p<0.01$.

cally different from the corresponding values of saline control group.

The results of 6 experiments with 15 μg/kg clonidine *icv* are summarized in the lower part of Table 1. The urine flow rate increased about 70% from the control value of 0.17 to 0.29 ml/min during 20 min following the administration, during which no significant changes of either RPF or GFR were observed. The sodium excretion however increased three-fold from 7.3 to 21.9 μEq/min and potassium excretion also increased significantly from 6.1 to 8.5μEq/min. Also, the percent reabsorption of filtered sodium in the tubules significantly decreased from 99.32 to 97.80%. Both osmolar clearance and free water reabsorption tended to increase in accord with the increase in excretion of electrolytes.

In Fig. 1 the renal response after 5 and 15 μg/kg clonidine *icv* are depicted. Here, the changes of renal function after the administration are calculated as the difference from each control clearance values. As shown here, it is clear that 15 μg/kg clonidine *icv* induces marked natriuresis, kaliuresis and diuresis, without any changes of renal hemodynamics.

Systemic blood pressure decreased upon *icv* administration of clonidine. About 1 to 2 min after administration the systemic blood pressure began to decrease, and at 5 to 10 min it reached the lowest values and then it gradually returned to pre-administration levels. With 5 μg/kg *icv* it decreased on the average 21±2.4 mmHg (n=6) and with 15 μg/kg 41±5.0 mmHg

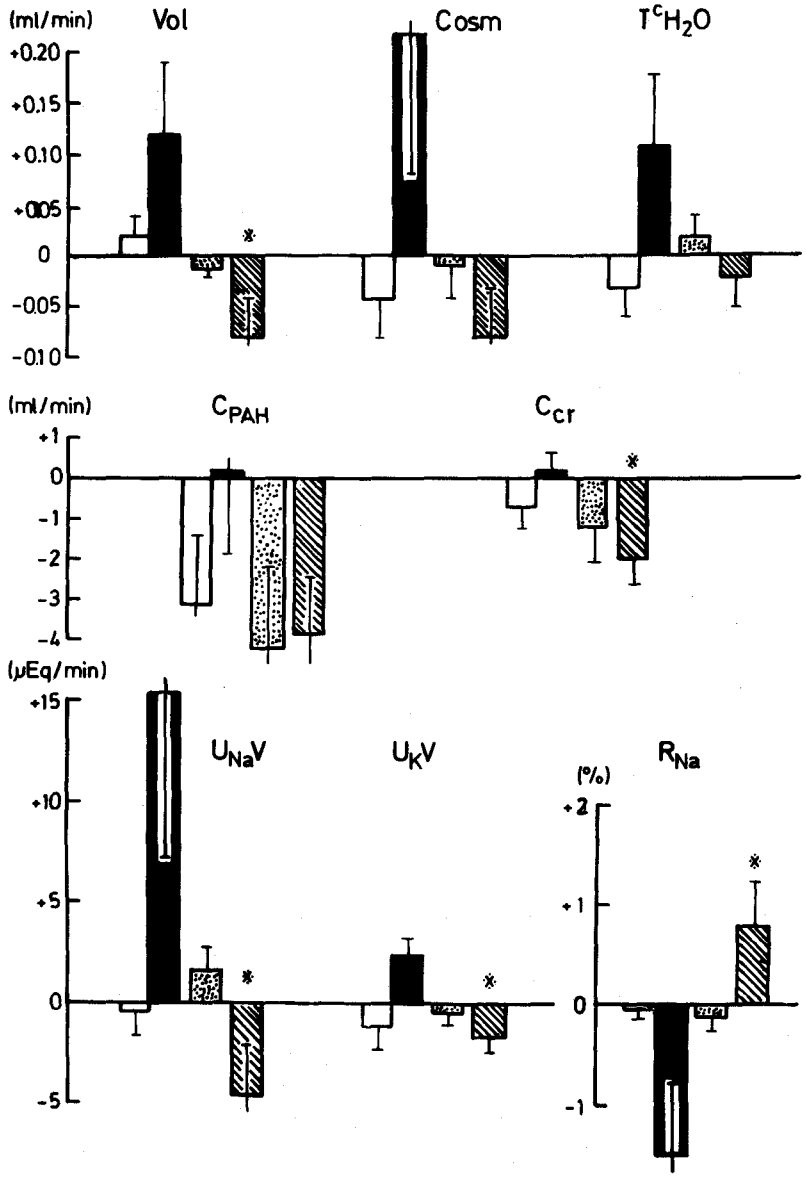

Fig. 3. Comparison among various groups of changes of renal function during 20 min following *icv* administration. White columns represent 5 μg/kg clonidine group, black ones 15 μg/kg clonidine group, stippled columns the 100 μg/kg yohimbine group, and the shaded one the yohimbine + clonidine groups. Mean values with S.E. are shown. Asterisks indicate significant difference ($p<0.05$) between 15 μg/kg clonidine group and the yohimbine + clonidine group.

(n=8) at the peak of the action.

When the dose administered was increased further to 50 μg/kg *icv* the urine output almost ceased, so that no clearance determination could made.

These experiments indicate that 15 μg/kg clonidine *icv* induces natriuresis and kaliuresis which are not related to changes in systemic

blood pressure, nor relevant to the hemodynamic changes of the kidney, and these effects are brought about by depressed tubular reabsorption of sodium.

Influence of icv Yohimbine on the Renal Action of icv Clonidine

Yohimbine is an indolealkylamine alkaloid which has been reported to be a selective presynaptic adrenoceptor antagonist. It can abolish specifically the depressor action of clonidine (Starke *et al.*, 1975). Before investigating the influence of yohimbine pretreatment on the renal effect of clonidine, the renal effect of *icv* yohimbine itself was examined. The upper part of Table 2 is the summary of 6 experiments in which 100 μg/kg of yohimbine *icv* were administered. This dose is sufficient to block the depressor action of clonidine (Kang, 1980).

As shown, urine flow rate tended to decrease, and the RPF decreased more than GFR so that the filtration fraction tended to increase. Urinary excretion of electrolytes and osmolar clearance did not significantly change.

In the lower part of Table 2 are the results of 6 experiments in which yohimbine 100 μg/kg was administered *icv* twenty minutes before clonidine 15 μg/kg icv. The two ten-minute clearance periods following yohimbine administration served as the control of clonidine action in these experiments.

As clearly seen, urinary excretions of water and electrolytes as well as renal hemodynamics tended to decline after clonidine, and there can be observed no natriuresis as seen in experiments without yohimbine pretreatment. In Figure 2 the data from two groups, the clonidine group and the yohimbine-pretreated group are compared. In Figure 3 are shown the changes

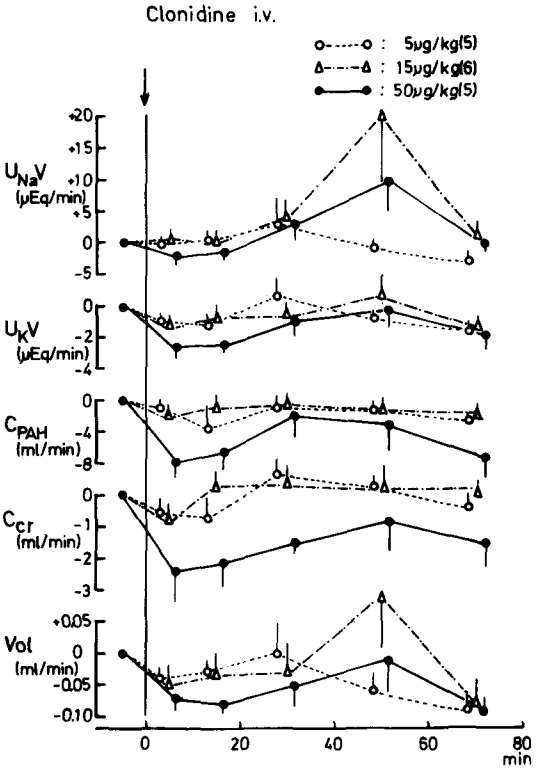

Fig. 4. Effects of intravenous clonidine on the renal function. Mean changes from the control clearance periods and one standard error are shown.

of various parameters of renal function during 20 min after *icv* administration of clonidine.

The systemic blood pressure responded with a slight increase to 100 μg/kg yohimbine *icv*, but after pretreatment with yohimbine, clonidine 15 μg/kg *icv* elicited only slight decrements of 6.0±4.0 mmHg (n=5).

From these observations it is clear that yohimbine pretreatment completely abolished the renal effects, as well as the hypotensive action of clonidine icv.

Renal Action of Intravenous Clonidine

To test the possibility that the *icv* clonidine might have reached the systemic circulation and

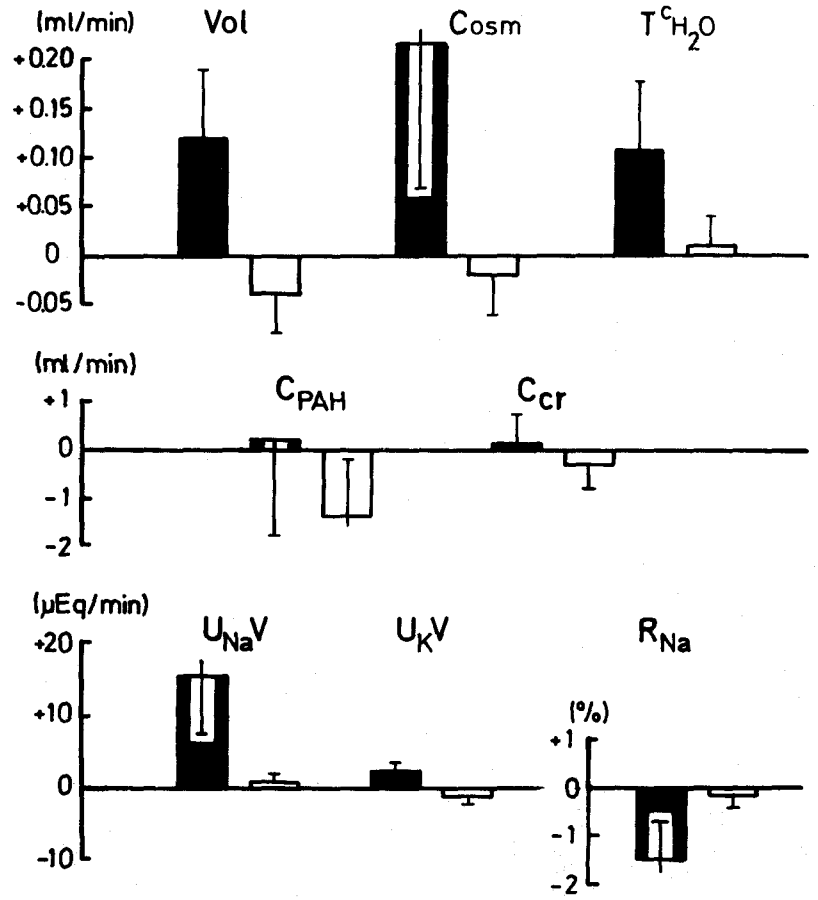

Fig. 5. Comparison of renal effects between groups of *icv* and *iv* clonidine. Black columns represent the *icv* group and the white columns the *iv* group. The dose given was 15 μg/kg. Values from the 20-min period following the administration were compared.

acted directly on the kidney, the renal effects of intravenously given (*iv*) clonidine were examined. Figure 4 depicts the effects of *iv* clonidine on the renal function. With 5 μg/kg *iv* no significant changes were noted except slight and transient tendency of decreased renal function. With 15 μg/kg clonidine *iv* only slight and transient decreases of both renal hemodynamics and urine flow rate were noted immediately following the administration. But the sodium excretion increased about four-fold after 40 min, though statistically not significant. Potassium excretion, osmolar clearance and free water reabsorption also tended to increase about an hour after the administration. The fractional sodium reabsorption in the tubules also decreased from 99.36 to 96.80%. Increasing the doses further to 50μg/kg *iv* enhanced the transient antidiuresis, antinatriuresis and antikaliuresis along with significant decreases in RPF and GFR for 20 min following the administration. But the sodium excretion tended to increase after 20 min,

together with increases in osmolar clearance and free water reabsorption.

In Figure 5 the changes of renal function during 20 min after administration of 15 μg/kg clonidine are compared between the two groups of either *icv* or *iv* administration.

These data indicate that the changes induced by *icv* clonidine are not the result of direct action of clonidine on the kidney, but are brought about indirectly by way of the action on the center.

DISCUSSION

These observations indicate that intracerebroventricularly administered clonidine induces natriuresis and kaliuresis in the rabbit. These actions can be abolished by pretreatment with yohimbine. When given intravenously clonidine produces no such effects, but a transient antidiuresis. It is further evident that these actions are not related to the changes of systemic blood pressure, as no increase in blood pressure was noted which could entail a "pressure diuresis" (Selkurt *et al.*, 1965). Since no changes in renal plasma flow and glomerular filtration rate accompanied the increases of water and electrolyte excretion, and since the fractional sodium reabsorption in the tubules was depressed, it is obvious that the renal effects did not result from hemodynamic changes within the kidney, and that the inhibition of sodium reabsorption in the tubules is the major cause of the effects.

As for the intrarenal site of the action, the proximal tubules are suggested. Present knowledge of renal physiology indicates that if sodium reabsorption is inhibited in the distal tubules potassium excretion decreases (Berliner, 1961), as is the case with "K-sparing diuretics". If sodium transport is inhibited in the Henle's loops, potassium excretion will increase along with sodium, but free water reabsorption, and hence the concentrating ability decreases as the efficiency of the counter-current multiplier system declines (Suki *et al.*, 1965). This is the case with "loop diuretics". An increase of sodium load, however, for the intact Henle's loops and distal tubules would result in increased excretion of potassium along with sodium, and also in increase of free water reabsorption with increased osmolar clearance. These changes are seen in cases of diuretics which either inhibit the proximal sodium reabsorption or increase glomerular filtration. The results obtained in this study with clonidine *icv* can therefore be most plausibly accounted for by the inhibition of proximal sodium reabsorption.

The natriuretic response to *icv* clonidine must have been brought about either by the mediation of humoral agents or by way of nerve pathways to the kidney, as the possibility of direct action on kidney can be ruled out by the *iv* experiments. So far, there is no evidence against the involvement of some humoral agents in the action, but the promptness of the response renders the participation of nerves more likely.

The renal function is greatly influenced by the central nervous system. As is well known, in states of elevated sympathetic tone such as fright, anxiety or stressful states, renal blood flow and also glomerular filtration greatly diminishes and thus antidiuresis ensues (Smith, 1951). Also evidence for hypothalamic control of renal sodium excretion has been presented by many authors (Keeler, 1959; Andersson, 1969; Dorn *et al.*, 1970). Removing the nerve connection to the kidney induces diuresis known as "denervation diuresis" (Bello-Reuss *et al.*,

1975). Though cholinergic nerve fibers have also been reported to exist in the kidney (McKenna & Angelokos, 1968), adrenergic fibers are by far the most abundunt, and they not only innervate the intrarenal vasculature, but also are found near or connected with tubular cells (Muller & Barajas, 1972; DiBona, 1977). The influence of nerve stimulation and neurotransmitters on the renal function have been studied by many workers (DiBona, 1977; Bello-Reuss, 1976; Kim *et al.*, 1980).

Recently, it has been shown that there are two kinds of α-adrenergic receptors (Langer, 1977). In addition to the postsynaptic (α_1 −) receptors on the effector cells, there is another type of receptors on the sympathetic nerve endings which are therefore presynaptic. The latter, which are also called α_2-adrenoceptors, regulate the release of the neurotransmitters, feeding back negatively. Thus stimulation of these receptors result in decreased norepinephrine release from the nerve ending, and the antagonist for the receptors augments the neurotransmitter release. Clonidine has been known to stimulate this receptor specifically (Hoefke & Kobinger, 1966; Kobinger & Walland, 1967) and yohimbine was shown to be the specific antagonist to it (Starke *et al.*, 1975). Phentolamine and phenoxybenzamine have been shown to act on both pre- and post-synaptic α-adrenoccptors (Drew, 1976; Lefkowitz & Hoffman, 1980). These two kinds of α-adrenoceptors have been reported to exist in the brain also (Farnebo & Hamberger, 1971; Wemer *et al.*, 1970; Kang, 1980).

As found in this investigation, clonidine, when given *icv*, induces natriuresis and diuresis as well as hypotension, presumably by stimulating the central presynaptic adrenoceptors. This is in agreement with the finding that norepinephrine *icv* also produces antidiuresis (Lee, 1972), and this can be abolished by intravenous phentolamine (Ko, 1974). Endogenous norepinephrine is able to stimulate both pre- and postsynaptic receptors, so that it enhances the sympathetic outflow at the nerve endings, and only in cases when the neuronal uptake of norepinephrine is fully saturated or inhibited by cocaine, can it inhibit the norepinephrine release from the nerve endings upon nerve stimulation (Dubocovich & Langer, 1974; Starke, 1972). Clonidine however is not taken up in the neurone and therefore it can inhibit, without the aid of cocaine, the release of the neurotransmitter at the nerve endings. Thus the hypotension as well as the diuretic effect can be expected, as the sympathetic tone to the kidney is diminished (Schmitt, 1970), resembling the effects of denervation. Also, the fact that yohimbine is able to abolish the clonidine action supports the premise that clonidine diuresis results from stimulation of central presynaptic α-adrenoceptors.

Karppanen *et al.*(1977) showed that histamine receptors might be involved in the central action of clonidine by showing that H_2-antagonist Metiamide blocked the clonidine hypotension. This hypothesis seems very attractive. However, histamine when introduced directly into a lateral ventricle of rabbit brain induced antidiuresis (Shin, 1974). Also the finding that histamine does not share the hypotensive action with clonidine when given *icv* (Shin, 1974), and that (^{3}H)-clonidine binding to cerebral H_2-receptors are negligible (Karppanen, 1981), make this hypothesis less tenable.

In contrast to the paucity of reports on the renal action of *icv* clonidine, there are many papers on the effect of *iv* clonidine on renal function. However, they are largely at variance

with each other, and there seems to be a great species difference. Hoefke *et al.* (1966) reported diuresis and antidiuresis in rats but "nondiuretic" in the dog. Biollaz *et al.* (1979) reported diuresis and natriuresis in unanesthetized rats, but the same effects were not apparent under pentobarbital anesthesia. Roman *et al.* (1979) observed natriuresis and diuresis due to decreased ADH secretion on *iv* infusion in the rat. Humphrey *et al.* (1975) also reported diuresis induced by suppression of ADH secretion in the dog. In disagreement with these reports, antidiuresis and sodium retention were reported in the dog and in man (Marchand *et al.*, 1971; Davidov *et al.*, 1967). In the rabbit, a transient antidiuresis and antinatriuresis, followed by a tendency toward a natriuresis were observed in this study. The antidiuresis and antinatriuresis increased with increasing doses but the secondary natriuresis seemed to be greater with 15 μg/kg than with 50 μg/kg, which can be accounted for by the fact that with larger doses the renal hemodynamic derangements were more prominent and long-lasting. The secondary natriuresis with *iv* clonidine suggests the involvement of a central action, especially when large doses were given intravenously. In support of this premise is the observation that in inhibiting the pressor response to increased intracranial pressure in the rabbit 75 μg/kg clonidine *iv* is as effective as 30 μg clonidine *icv*, while 15 and 30 μg/kg *iv* were not effective (Kim *et al.*, 1980).

The fact that *icv* clonidine induces diuresis and natriuresis by decreasing sympathetic outflow to the kidney indicate that the sympathetic center plays an import role in the physiological regulation of renal function in the rabbit.

SUMMARY

To explore the regulatory roles of CNS on the renal function, clonidine, a specific presynaptic α-adrenoceptor agonist, was administered into a lateral ventricle of the brain (*icv*) and the changes of renal function were studies in urethane-anesthetized rabbits. 5μg/kg *icv* elicited no significant changes in renal function. However, 15 μg/kg induced marked natriuresis and kaliuresis for 20 min. Neither RPF nor GFR changed significantly. The fractional sodium reabsorption was significantly reduced, indicating that the renal action was of the tubular origin. Changes of systemic blood pressure were not contributory to the renal action. Yohimbine, a specific antagonist for presynaptic α-adrenoceptor, when given *icv* in doses of 100 μg/kg 20 min prior to clonidine, completely abolished the renal action of *icv* clonidine. Yohimbine *icv* did not produce any significant changes in renal function. Intravenous clonidine, 15 μg/kg, elicited antidiuresis and decrement of renal function immediately after administration, followed by a slight tendency toward natriuresis, but no natriuresis corresponding to those seen after the *icv* clonidine were observed, indicating that in the renal action of *icv* clonidine no direct action is involved. These observations indicate that the central sympathetic tone plays a role in the regulation of renal function in the rabbit.

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