大韓藥理學會誌 : 第18卷 第1號
Korean J. of Pharmacology
Volume 18, Number 1, 1982

Influence of Intracerebroventricular Isoproterenol on the Renal Function of the Rabbit

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가토신장기능에 미치는 측뇌실내 Isoproterenol의 영향

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중추의 β-adrenoceptor가 신장기능의 조절에 있어서 어떠한 역할을 하고 있는지를 알고자, 가토의 측뇌실내에 isoproterenol 및 propranolol을 투여하여 신장기능의 변동을 관찰하였다.

Isoproterenol은 5~50 μg/kg i.c.v.의 범위에서 항이뇨작용을 나타냈으나 이는 주로 전신혈압하강에 따르는 신혈류 및 사구체여과율의 감소에 기인하며 세뇨관에서의 Na재흡수억제효과는 음폐된 것으로 추론되었다.

Propranolol (500 μg/kg i.c.v.)은 신장기능에 현저한 변동을 초래하지 아니하였으나, propranolol후에 isoproterenol을 투여하면 전신혈압하강은 현저히 약화됨과 동시에, Na, K배설의 증가와 신혈류의 증가, 그리고 뇨량증가경향이 관찰되었다. 즉, prapranolol에 의하여 isoproterenol의 강압작용은 영향을 받으나 신장작용은 영향받지 아니하고 현저하게 표현되었다.

본연구의 결과는, 중추의 β-adrenoceptor도 α-receptor보다는 약하지만 신장기능의 조절에 있어서 어떤 역할을 하고 있음을 시사하였다.

The excretory function of the kidney is under regulatory influence of the central nervous system, either through mediation of humoral agents, such as antidiuretic hormone and natriuretic hormone (De Wardener, 1973), or by way of nerve pathways. Among the nervous influence the sympathetic nerve has been shown to play the most important role (Gottschalk, 1979; Kim *et al*, 1980). In a series of experiments in which attempts were made to modify the central sympathetic tone, by introducing directly into the cerebral ventrical various neurotransmitters and their blocking agents, it has been found that norepinephrine (Lee, A.S., 1974), dopamine (Choi, 1974) and phentolamine (Lee, Y.S., 1974) elicited antidiuresis, while clonidine (Lee, Y.H., 1980) and phenoxybenzamine (Yoo, 1981) induced natriuresis and diuresis, thus indicating that the central α-adrenoceptors are involved in the regulation of the renal function.

Beta-adrenoceptors have been found to exist, along with α-adrenocpetors in the brain tissue, as in the other peripheral tissues and organs (Nahorski, 1978). Stimulating β-adrenoceptors produce effects different from those mediated by α-adrenoceptors in the kidney as in other organs. The α-adrenoceptors effect constriction of renal vessels and enhancement of sodium reabsorption in the tubules (Schrier & Berl, 1973), resulting in antidiuresis and antinatriuresis, whereas β-adrenocep-

tors produce vasodilatation in the renal vasculature (Fenyvesi & Kally, 1970) and also decrements in sodium reabsorption, inducing natriuresis and diuresis (Gill & Casper, 1971). However, little is known as for the physiological roles of β-adrenoceptors in the center, and no report is available, so far, as to the role of the central β-adrenoceptors in the regulation of renal function.

It was therefore attempted in this study to delineate the role of central β-adrenoceptors in the central regulation of renal function, by observing the changes of renal function when isoproterenol, a representative β-adrenergic agonist, was given intracerebroventricularly (i.c.v.) in the rabbit, and the influence of propranolol, a specific β-antagonist, upon the isoproterenol effects.

Methods and Materials

Adult rabbits of either sex, weighing 1.6~2.2 kg, were used. The animals were anesthetized with 1 g/kg urethane, subcutaneously, 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 then kept patent by filling with heparin-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 agents, according to the method of Moon (1964). The parietal bone was exposed by insicing 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 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 agents administered were dissolved in 0.9% NaCl solution and the volume of the 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 collection of two ten-minute samples of control clearance periods were made, and at the end of the control periods the agent was given. After the administration, four or five samples of ten- or twenty-minute clearance periods were collected. At the mid-point of each clearance period a blood sample of 2 ml was collected, immediately centrifuged, and the plasma separated. Together with the urine samples the plasma samples were subjected to chemical analyses. As a measure of glomerular filtration rate, exogenous creatinine clearance was employed as no practical difference has been found between inulin clearance and exogenous creatinine clearance in the rabbit.

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 flamephotemetry, and the osmolality with Advanced Osmometer. Systemic blood pressure was measured by recording from the femoral artery through a pressure transducer on a chart recorder.

Mean changes of each parameter of renal function after administration of the agents were tested for significance using Student's "t" test for paired data, and when comparing two groups of animals "t" test for unpaired data was applied (Snedecor, 1971).

Results

Renal action of i.c.v. isoproterenol

In Table 1 are summarized the changes of renal function after 5 μg/kg isoproterenol i.c.v. in 7 similar experiments. Urine flow rate(Vol) was reduced to about half and remained decreased until 60 min, when the decrease was statistically significant. Excretory rates of both sodium and potassium as well as osmolar clearance decreased, but the reabsorptive rate of osmotically free water (T^cH_2O) showed no significant change. The rate of sodium reabsorption in the tubules (R_{Na}) slightly increased, with no statistical significance. Renal plasma flow (C_{PAH}) decreased significantly for 20 min after administration, while glomerular filtration rate showed only slight tendency of decrease.

The responses to 15 μg/kg isoproterenol i.c.v. were observed in 11 experiments and are shown in Table 2. Urine flow rate decreased gradually to a significant degree after 40 min. However, the decrements of urine flow rate up to 40 min were less marked than with 5 μg/kg. During these periods the sodium excretion and osmolar clearance showed distinct tendency of increment, which might be responsible for the decreased antidiuretic response to a larger dose. Renal hemodynamics also tended to decrease with 15 μg/kg.

The dose administered was increased further to 50 μg/kg i.c.v. in 6 experiments, and the results were summarized in Table 3. Urine flow rate decreased significantly immediately after administration and remained decreased. The renal plasma flow and glomerualr filtration rate also significantly decreased for ten min following administration and then slightly recovered, but remained decreased during the rest of the observation periods. Sodium excretion also decreased significantly immediately following the administration, but it recovered and even overshot above the control levels for 30 min, to decrease again. Potassium excretion also followed the pattern of sodium excretion. Osmolar clearance reflecting the pattern of electrolyte excretion also decreased significantly for 10 min, and recovering somewhat it remained depressed for the rest of the observation periods. The free water reabsorption tended to increase throughout the experiment.

Overall, with 50 μg/kg isoproterenol i.c.v. a marked antidiuresis was observed, which seemed to be related to the decrement of glomerular filtration, and the possible natriuresis appeared to be masked by the prominent hemodynamic changes.

Renal action of i.c.v. propranolol

Next, the renal effects of propranolol i.c.v. were investigated before the influence of β-adrenergic blockade on the isoproterenol action was studied. In Table 4 the results of 6 experiments in which 500 μg/kg propranolol were given i.c.v. were summarized.

Urine flow significantly decreased after 20 min, and the renal plasma flow transiently decreased between 10 and 20 min. However, glomerular filtration rate as well as excretion of both sodium and potassium did not change appreciably. Free water reabsorption tended to increase, though not statistically significant. Thus, propranolol produced no significant effect on the renal hemodynamics and on the electrolyte excretion, but elicited antidiuresis which may be related to increased free water reabsorption in the tubules.

Influence of propranolol pretreatment on the renal action of isoprotereolol

To test the effects of central β-adrenergic blockade on the renal action of i.c.v. isoproterenol, 500 μg/kg propranolol was given i.c.v. twenty minutes prior to isoproterenol administration, and the two ten-minute clearance periods before isoproterenol served as the control periods for 50 μg/kg isoproterenol effects. In Table 5 the results of 6 such experiments were summarized.

Sodium excretion increased significantly imme-

Table 1. Effect of 5 μg/kg isoproterenol i.c.v. on the renal function of the rabbit

	Control	0′~10′	10′~20′	20′~40′	40′~60′	60′~80
Vol(ml/min)	0.17±0.06	−0.05±0.03	−0.09±0.06	−0.09±0.05	−0.07±0.03*	−0.10±0.05
C_{PAH}(ml/min)	12.6 ±2.2	−1.8 ±3.3	+1. 4±2.8	−2. 5±0.9*	−4.0 ±1.2 *	−3.9 ±0.9*
C_{cr}(ml/min)	4.13±0.80	−0.88±0.84	−0.75±0.80	−0.31±0.70	−0.72±1.09	−0.54±0.68
FF(%)	36.8 ±6.2	+2.0 ±3.1	+3.6 ±3.3	+4.3 ±2.9	+7.0 ±3.7	+4.8 ±3.0
$U_{Na}V$(μEq/min)	2.9 ±0.7	−1.5 ±0.5*	−0.9 ±0.6	−0.8 ±0.6	−1.5 ±0.8	−1.9 ±1.0
R_{Na}(%)	99.37±0.17	+0.24±0.10	+0.26±0.12	+0.16±0.14	+0.29±0.19	+0.42±0.21
U_KV(μEq/min)	5.0 ±1.6	−1.9 ±1.1	−1.2 ±1.3	−1.1 ±0.5	−1.4 ±0.5 *	−2.2 ±1.0
C_{osm}(ml/min)	0.25±0.04	−0.10±0.04*	−0.05±0.05	−0.04±0.02	−0.09±0.01**	0.12±0.02
T^CH_2O(ml/min)	0.05±0.05	−0.01±0.02	+0.07±0.05	+0.07±0.05	0±0.03	0±0.05

Mean values and S.E. from 7 experiments. Vol=urine flow rate; C_{PAH} and C_{cr} are clearances of para-amino hippuric acid and creatinine; FF is filtration fraction as obtained by C_{cr}/C_{PAH}; $U_{Na}V$ and U_KV are excreted amounts of sodium and potassium; R_{Na} is fraction of filtered sodium reabsorbed in the tubule; C_{osm} is clearance of osmolar substances; T^CH_2O is reabsorption of osmotically free water. Asterisks are significant differences from control values (*=$p<0.05$, **=$p<0.01$).

Table 2. Effect of 15μ/kg isoproterenol i.c.v. on the renal function of the rabbit.

	Control	0′~10′	10′~20′	20′~40′	40′~60′	60′~80′
Vol(ml/min)	0.21±0.03	−0.01±0.04	−0.04±0.05	−0.06±0.05	−0.09±0.04*	−0.13±0.04*
C_{PAH}(ml/min)	12.6 ±2.0	−0.9 ±1.5	−2.9 ±2.5	−4.6 ±2.5	−5.2 ±3.2	−7.0 ±2.8*
C_{cr}(ml/min)	4.63±3.32	−0.62±0.63	−1.23±3.32	−1.92±1.04	−2.10±1.04	−2.28±1.23
FF(%)	37.7±11.6	−0.6 ±1.5	−1.0 ±3.9	−2.1 ±3.1	+1.5 ±4.7	+4.5 ±5.1
$U_{Na}V$(μEq/min)	5.6 ±1.2	+1.5 ±1.9	+3.3 ±2.7	+0.3 ±2.3	−1.6 ±1.5	−3.6 ±1.3
R_{Na}(%)	98.64±0.40	−0.34±0.33	−0.64±0.58	−0.40±0.58	−0.27±0.53	+0.50±0.46
U_KV(μEq/min)	4.4 ±0.7	−0.7 ±0.8	−0.4 ±1.1	−1.2 ±1.0	−1.6 ±0.9	−2.1 ±1.0
C_{osm}(ml/min)	0.31±0.04	+0.03±0.05	+0.03±0.08	−0.02±0.07	−0.07±0.07	−0.09±0.06
T^CH_2O(ml/min)	0.12±0.04	0±0.02	+0.04±0.05	+0.03±0.04	0±0.05	0±0.05

Mean values and S.E. from 11 experiments. Legends as in Table 1.

diately after isoproterenol administration, and during the next ten-minute period it reached three times of the control value, and the natriuresis lasted for an hour. Potassium excretion also increased following the pattern of sodium excretion. Reflecting these increases in electrolyte excretion the osmolar clearance also increased. However, the free water reabsorption significantly increased, reducing the magnitude of diuresis which would usually parallel with increased electrolyte excretion. The urine flow rate doubled but because of large individual variations no statistical significance was found. The renal plasma flow tended to increase slightly, whereas glomerular filtration increased about 34% during 20 to 40 min after isoproterenol.

In **Fig. 1** the effects of 50 μg/kg isoproterenol i.c.v. were compared with those of the propranolol-

Table 3. Effect of 50 μg/kg isoproterenol i.c.v. on the renal function in the rabbit

	Control	0′~10′	10′~20′	20′~40′	40′~60′	60′~80′
Vol(ml/min)	0.22±0.07	−0.13±0.05*	−0.14±0.08	−0.16±0.07	−0.14±0.09	−0.10±0.16
C_{PAH}(ml/min)	8.9 ±0.7	−4.1 ±1.0**	+0.2 ±1.9	−2.1 ±1.5	−3.2 ±1.1*	+1.0 ±0.4
C_{cr}(ml/min)	3.23±0.43	−1.70±0.38**	−0.50±0.65	−0.74±0.49	−0.92±0.45	+1.43±0.98
FF(%)	36.2 ±2.5	−1.3 ±4.3	−3.1 ±4.3	+3.6 ±3.7	+4.4 ±4.5	+7.6 ±7.0
$U_{Na}V$(μEq/min)	3.9 ±1.7	−2.2 ±0.8*	+0.2 ±1.4	+0.4 ±1.5	−0.6 ±1.7	−2.9 ±1.6
R_{Na}(%)	99.08±0.31	+0.20±0.15	−0.20±0.26	−0.92±0.77	−0.62±0.79	−0.75±0.28
U_KV(μEq/ml)	2.5 ±0.6	−1.3 ±0.4*	+0.5 ±0.9	−0.7 ±0.6	−0.7 ±0.7	−0.7 ±0.9
C_{osm}(ml/min)	0.17±0.03	−0.10±0.04*	−0.02±0.06	−0.07±0.04	−0.07±0.04	−0.03±0.04
T^cH_2O(ml/min)	−0.05±0.05	+0.08±0.07	+0.12±0.06	+0.10±0.06	+0.08±0.07	+0.08±0.12

Mean values and S.E. from 6 experiments. Legends as in Table 1.

Table 4. Effect of propranolol 500 μg/kg i.c.v. on the renal function of the rabbit

	Control	0′~10′	10′~20′	20′~40′	40′~60′	60′~80′
Vol(ml/min)	0.21±0.06	−0.05±0.05	−0.07±0.03	−0.07±0.02*	−0.12±0.04*	−0.15±0.05*
C_{PAH}(ml/min)	12.7 ±1.8	+0.6 ±1.8	−3.2 ±1.1*	−0.4 ±1.4	−1.9 ±1.5	−1.9 ±1.7
C_{cr}(ml/min)	4.35±0.58	0±0.62	−0.77±0.32	−0.54±0.37	−0.47±0.38	−0.84±0.48
FF(%)	35.7 ±3.4	−0.3 ±1.6	+6.7 ±4.5	+1.4 ±6.7	+5.4 ±3.0	+1.0 ±1.4
$U_{Na}V$(μEq/min)	5.0 ±1.9	−0.1 ±1.8	−0.7 ±1.8	+1.8 ±3.0	−1.8 ±2.3	−3.3 ±1.7
R_{Na}(%)	98.82±0.51	+0.12±0.22	−0.11±0.67	−0.27±0.71	+0.55±0.52	+0.75±0.51
U_KV(μEq/min)	4.0 ±0.7	+0.5 ±0.7	+0.1 ±1.1	+1.6 ±2.2	0±1.3	−1.1 ±0.4*
C_{osm}(ml/min)	0.30±0.03	0±0.08	−0.05±0.04	0±0.08	−0.07±0.06	−0.12±0.03*
T^cH_2O(ml/min)	0.09±0.05	+0.06±0.03	+0.03±0.04	+0.07±0.08	+0.05±0.08	+0.03±0.06

Mean values and S.E. from 6 experiments. Legends as in Table 1.

pretreated group. As marked with asterisks, both groups differ significantly in urine flow rate, electrolyte excretion and in renal hemodynamics. However, free water reabsorption was not affected by propranolol pretreatment.

Influence on the systemic blood pressure

Isoproterenol, when given i.c.v., induced transient hypotension, which seemed to be related to the doses administered. Fig. 2A shows a typical response to 50 μg/kg i.c.v. Blood pressure decreased immediately following the administration. Marked hypotension lasted about 10 min, reaching the nadir at about 5 min, and slight hypotension lasted longer than an hour. The mean value of maximal depressor response from 6 experiments was 20.7±2.7 mmHg (S.E.). In Fig. 2B are shown a typical response to 500 μg/kg propranolol i.c.v. and its influence on the isoproterenol action. Blood pressure increased for about 20 min in response to propranolol, attaining the peak values at 5 min after administration. The mean maximal pressor response was 17.5±4.3 mmHg(n=15). After propranolol pretreatment the hypotensive response to

Table 5. Effect of isoproterenol 50 μg/kg i.c.v. on the propranolol(500 μg/kg, i.c.v.)-pretreated rabbit

	Control	0′~10′	10′~20′	20′~40′	40′~60′	60′~80′
Vol(ml/min)	0.12±0.02	+0.06±0.03	+0.12±0.06	+0.10±0.07	+0.01±0.04	−0.02±0.03
C_{PAH}(ml/min)	11.4 ±2.9	+2.7 ±1.5	+2.7 ±1.4	+2.8 ±1.3	−0.5 ±1.2	−1.3 ±1.2
C_{cr}(ml/min)	4.50±0.79	+1.53±0.66	+1.19±0.60	+1.52±0.29**	−0.05±0.46	−0.67±0.57
FF(%)	44.7 ±5.8	+0.9 ±3.0	−2.5 ±3.9	+1.8 ±4.2	+0.1 ±3.9	−1.8 ±2.5
$U_{Na}V$(μEq/min)	3.1 ±0.9	+4.9 ±1.6*	+9.1 ±4.6	+5.9 ±3.7	+0.8 ±1.8	−0.8 ±1.0
R_{Na}(%)	99.43±0.19	−0.48±0.21	−1.14±0.55	−0.78±0.48	−0.15±0.24	+0.04±0.16
U_KV(μEq/min)	2.8 ±0.7	+1.9 ±0.7*	+2.3 ±1.0	+2.0 ±0.8	+0.3 ±0.8	−0.4 ±0.8
C_{osm}(ml/min)	0.25±0.02	+0.16±0.06*	+0.21±0.10	+0.15±0.07	+0.01±0.06	−0.05±0.06
T^cH_2O(ml/min)	0.13±0.03	+0.10±0.04*	+0.10±0.04	+0.05±0.02	−0.01±0.03	−0.03±0.02

Mean values and S.E. from 6 experiments. Legends as in Table 1.

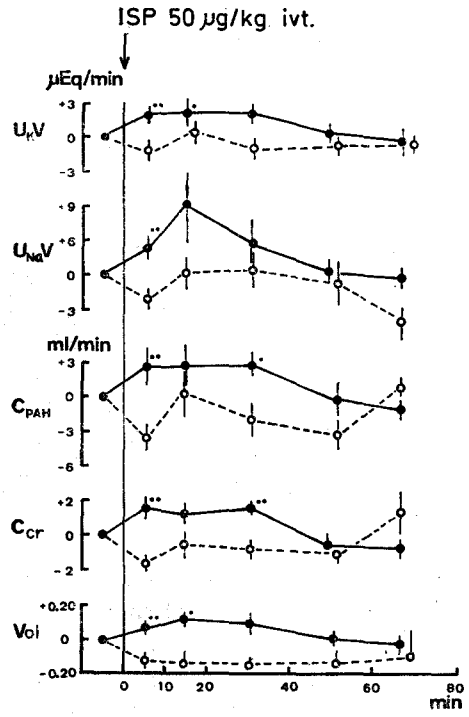

Fig. 1. Influence of propranolol pretreatment on the renal action of intracerebroventricular isoproterenol.
Black dots and drawn lines depict the propranolol(500 μg/kg i.c.v.) pretreated group, whereas open circles and dashed lines represent the isoproterenol(50 μg/kg i.c.v.) group. Propranolol was given 20 min prior to isoproterenol. Asterisks indicate significant differences between two groups (*=p<0.05, **=p<0.01).

isoproterenol was markedly attenuated, and the mean decrease of blood pressure was reduced to 7.3±2.6 mmHg (n=9), significantly differing from the isoproterenol group (p<0.01).

Discussion

Ahlquist's assertion (1948) that the actions of catecholamines are mediated by two different kinds of receptors, alpha and beta, has been repeatedly proven with various techniques and now become firmly established. Recently, however, these receptors were found to be not homogeneous, but consisted of subclasses, slightly differing from each other. The beta-receptors can be divided into β_1 and β_2, the former being abundant in cardiac muscle, while smooth muscles and glands contain mainly the latter (Lands *et al*, 1967a & b). Most tissues contain both types of receptors, but in varying ratios (Minneman, 1979). Alpha-receptors are also known to be consisted of two kinds: α_1 and α_2. The α_1-adrenoceptors exist on the postsynaptic sites of the effector cells of smooth muscles and glands, while α_2-types are located on the nerve endings, and stimulating them leads to the inhibition of norepinephrine release from the nerve endings upon arrival of nerve impulses, thus effecting feedback regulation of

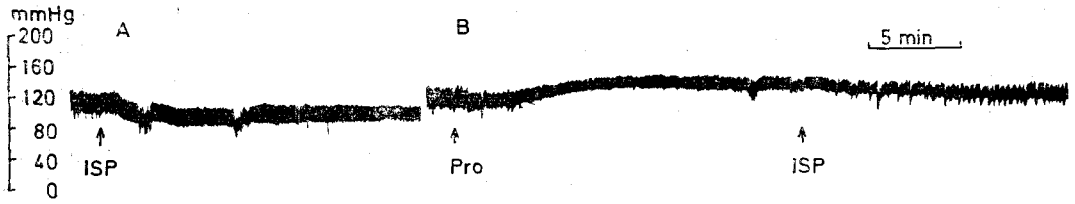

Fig. 2. Response of systemic blood pressure to intracerebroventricular administration of 50 μg/kg isoproterenol(A), and to propranolol, 500 μg/kg, and its influence upon the isoproterenol action(B). ISP=isoproterenol; Pro=propranolol.

transmitter release (Starke, 1977).

Recent studies employing redioactive ligands have revealed that β-adrenoceptors exist in the brain tissue (Farnebo *et al*, 1974), and that only β_2-receptors are found in the rat cerebellum whereas in the cerebral cortex and corpus striatum 65% of the beta-receptors are of β_1-type, and about half is of β_1-type in the limbic forebrain (Farnebo *et al*, 1974; Nahorski, 1981). As to the physiological role of these β-adrenoceptors in the brain little is known so far. The observation that β-agonists augment the release of norepinephrine in the sympathetic nerve endings would not advocate a physiological implication of beta-receptors in the regulation of norepinephrine release, because the magnitude of the effects is far less than that of α-adrenoceptor stimulation (Dixon *et al*, 1979).

In this study it was found that isoproterenol when given directly into a lateral ventricle of the rabbit elicits antidiuresis. But the mechanism involved here seems to be complex, as it was noted that sodium excretion did not go along with increasing doses, while the decrements of urine flow and renal hemodynamics paralleled with the administered doses. With 15 μg/kg i.c.v. sodium excretion increased, though not significant, but with 50 μg/kg it decreased along with decreased renal hemodymics, which, in turn, can be attributed to the severe systemic hypotension. Thus, in larger doses possible natriuretic effect resulting from decreased tubular reabsorption might well have been masked by decreased renal hemodynamics brought about by the depressor action.

The beta-antagonist propranolol, i.c.v., elicited pressor response in the opposite direction to isoproterenol, but on the renal function it induced antidiuresis, though not marked, in the same direction as isoproterenol. However, after pretreatment with propranolol the isoproterenol-induced antidiuresis was reversed to diuresis and natriuresis, along with increasing tendency of renal hemodynamics. Also the systemic hypotension was significantly reduced. These results can be best explained if one assumes a direct tubular action, apart from the hemodynamic one. The possible natriuretic and diuretic effects would not be apparent when severe hypotension diminishes perfusion and filtration in the kidney. But, when the hypotensive response is removed by propranolol, the natriuretic and diuretic effects of isoproterenol can be revealed. However, for this proposition it is required that the natriuretic action of i.c.v. isoproterenol is not affected by propranolol while the depressor action is abolished. If both the renal action and the depressor action of i.c.v. isoproterenol are mediated by the same β-adrenoceptors in the center, it might be expected that both actions are blocked by propranolol.

There are several possibilities to account for the difference in sensitivity of these actions to propranolol. Firstly, β-adrenoceptors may not be involved in the center-mediated renal action of isoproterenol, but other mechanisms such as alpha-adrenergic system may be participated. Secondly, the renal response might be mediated by some different kind of β-receptors which are not sensitive

to the propranolol. Recently, atypical β-receptors not belonging to either β_1 or β_2 were found in turkey red blood cells (Nahorski, 1981). Thirdly, the β-receptors involved in the renal action may differ from those mediate the blood pressure response, as it has been reported that there exist two kinds of beta-receptors, β_1 and β_2, in the brain and their distribution also differ from each other (Minnemann *et al*, 1979; Nahorski, 1981). Also, in binding studies utilizing (^{3}H)-dihydroalprenolol, β_1/β_2 selectivity of ($\pm$) isoproterenol was found to be 30, indicating that isoproterenol binds mainly to β_1-receptors, whereas propranolol binds to both receptors non-selectively (LeClerc, 1981). These findings provide ground for the postulation that both actions are mediated by different kinds of β-adrenoceptors. Further studies employing more specific agonists and antagonists which are known to bind specifically to either one of β-receptors may provide conclusive evidence as to the problem.

As for the mechanism of the center-mediated renal action of isoproterenol, the natriuresis and diuresis observed may be related to the renal hemodynamic action, as the filtration increased, though transiently, in experiments where systemic hypotension had been blocked. But, the natriuresis preceded the increase of glomerular filtration. With 15 μg/kg the sodium excretion tended to increase in spite of decreasing tendency of glomerular filtration, and the reabsorptive rate of sodium in the tubules always tended to decrease. Therefore, a direct tubular action of i.c.v. cannot be ruled out. The fact that the natriuresis is accompanied by kaliuresis renders the distal tubules improbable as the primary site of action, and the increase in free-water reabsorption speaks against the decreased sodium reabsorption in Henle's loop (Suki *et al*, 1965). Thus, the proximal tubules are suggested to be the intratubular site of the possible natriuresis induced by i.c.v. isoproterenol. The increase in free-water reabsorption by the i.c.v. isoproternol was not affected by propranolol pretreatment, but rather became more prominent. This suggest that ADH can be released by i.c.v. isoproterenol, and that this effect is not antagonized by propranolol. Further evidence will be necessary to establish the involvement of ADH, however.

Overall, the above observations suggest that beta-adrenoceptors in the brain are involved in the center-mediated regulation of renal function in the rabbit, though less prominent as with alpha-adrenoceptors.

Summary

In an attempt to delineate the role of beta-adrenoceptors found to be existing in the brain tissue in the central regulation of renal function, isoproterenol, a β-adrenergic agonist, was administered directly into a lateral ventricle of the rabbit brain and the changes of renal function were observed. Also, the effects of propranolol, a specific β-adrenergic blocking agent, and its influence upon the isoproterenol action were studied.

Isoproterenol, in doses ranging from 5 to 50 μg /kg i.c.v., elicited antidiuresis which seemed to be related to the decreased renal hemodynamics brought about by the systemic hypotension. With moderate doses of 15 μg/kg the antidiuresis was less prominent and there was a tendency toward natriuresis, but with higher doses the natriuretic effect became less evident, overrun by the systemic hypotension.

Propranolol, 500 μg/kg i.c..v., produced little effect on the renal function, but it eliminated the antidiuretic action of 50 μg/kg isoproterenol i.c.v. and reversed it to a diuretic and natriuretic one, along with increases in renal plasma flow and glomerular filtration rate. The systemic hypotension also was markedly attenuated by propranolol pretreatment. Thus, it was evident that the renal action of i.c.v. isoproterenol was not blocked by propranolol and became explicit only when the hypotensive action of isoproterenol which seems to be propranolol-sensitive is removed. Various possibilities to account for this disparity in

sensitivity were discussed.

It is suggested from these observations that the central β-adrenoceptors might also be involved in the regulation of renal function along with α-adrenoceptors, though less significant than the latter.

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