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Influence of Intracerebroventricular Ketanserin on Rabbit Renal Function

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ABSTRACT

5-Hydroxytryptamine (5-HT) was reported to elicit natriuresis and diuresis when given intracerebroventricularly (icv) and these effects were shown to be abolished by icv methysergide, 5-HT_1 antagonist, thus suggesting that central tryptaminergic system may also participate in the regulation of renal function. We tried in this study to elucidate the role of 5-HT_2 receptors in the central tryptaminergic regulation of renal function, observing the effects of icv ketanserin, a specific 5-HT_2 antagonist.

Ketanserin (KET) icv in doses of 120 μg (= 0.3 μmoles)/kg produced significant natriuresis without affecting renal hemodynamics, indicating that it resulted from decreased tubular Na reabsorption. Systemic blood pressure decreased slightly but significantly. When given iv, no significant effect was observed. 5-HT, 200 μg/kg icv, produced mild but significant natriuresis and diuresis. However, after KET, 40 μg/kg icv, a dose which minimally affects renal function, the natriuresis and diuresis by 5-HT was greatly augmented, with the fractional excretion of filtered sodium reaching 9.3%. The renal effects of other biogenic amines administered icv, such as norepinephrine, dopamine and histamine, were not significantly affected by the KET pretreatment.

These observations suggest that central tryptaminergic system influences renal function in dual ways, i.e., natriuretic and diuretic influence via 5-HT_1 receptors, whereas 5-HT_2 subtypes mediate the antinatriuretic and antidiuretic effects, and that the central tryptaminergic system plays a role in the regulation of rabbit renal function.

Key Words: Ketanserin, Renal function, Central 5-HT receptors.

Abbreviations: UFR, urine flow rate; RPF, renal plasma flow; GFR, glomerular filtration rate; icv, intracerebroventricular; 5-HT, 5-hydroxytryptamine; NE, norepinephrine; DA, dopamine

INTRODUCTION

The central nervous system (CNS) regulates the excretory function of the kidney either through secretion of humoral agents (Verney, 1947; DeWardener, 1973) or via neural pathways, in which the sympathoadrenal system plays the most important roles (Gottschalk, 1979; Kim *et al.*, 1980; Kook *et al.*, 1984; Beers *et al.*, 1986). The tryptaminergic system in the CNS has also been shown to have a role in the regulation of renal function (Park, 1972). 5-Hydroxytryptamine (5-HT), when administered directly into a lateral ventricle (icv) of rabbit brain, elicits diuresis and natriuresis unrelated to the changes in renal hemodynamics. Recently, Kook *et al.* (1988) confirmed the renal effects of icv 5-HT and further presented evidence that tubular reabsorption of sodium is inhibited, suggesting the involvement of certain natriuretic factor in the effects. They observed furthermore that methysergide, a 5-HT_1 receptor blocker, produced antidiuresis when given icv, and that after pretreatment with methysergide the icv 5-HT_1 effects were completely abolished, thus suggesting that 5-HT_1 subtype of tryptaminergic receptors may mediate the natriuretic effects of icv 5-HT.

In this study we attempted to define the role of the 5-HT_2 receptors in the central tryptaminergic regulation of renal function, by observing the renal effects of icv ketanserin, a specific antagonist of the 5-HT_2 receptors and its interaction with the icv 5-HT, and by clarifying the mechanism involved in the effect.

METHODS

Adult rabbits of either sex, weighing 1.8-2.3kg, were anesthetized with 1 g/kg urethane s.c. A T-tube inserted into the trachea secured the free airway. A 0.3% NaCl solution containing 3% glucose, 45 mg% para-amino-hippuric acid (PAH) and 250 mg% creatinine (cr) was infused into an ear vein at a rate of 0.5 ml/min. Through a small midline incision close to the symphysis, both ureters were cannulated with PE tubings for the collection of urine samples and a femoral artery for obtaining blood samples with a PE tubing filled with heparin-saline (400 U/ml). For intracerebroventricular (icv) administration of the agents a lateral ventricle was cannulated. A hole was drilled on the skull at a point 1.5cm rostral to the occiput tubercle and 0.5cm lateral to the midline, and a PE cannula of 1.5mm O.D. was inserted obliquely until clear cerebrospinal fluid appeared in the cannula, and then it was plugged and kept in place by cementing to the bone. The volume administered did not exceed 0.15ml. At the end of each experiment the location of the cannula tip was checked by dissection.

When urine flow rate (UFR) became stable several hours after the infusion began, the collection of clearance samples were started. After two or three 10-min clearance periods the agent was administered, and then two 10-min and three 20-min clearance samples were collected. At midpoint of each clearance period blood sample was obtained from the femoral artery and immediately centrifuged to separate the plasma.

Creatinine was analyzed 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 by osmometry. Statistical significance was assessed by ANOVA with repeated measures on time (Winer, 1971). If significant differences were detected, further analysis as required were done to determine which of the groups differed from the appropriated controls. For multiple group comparison Bonferroni's modified t-test was applied (Wallenstein *et al.*, 1980).

Ketanserin tartrate was obtained from Research Biochemicals Inc., and 5-hydroxytryptamine creatinine sulfate, norepinephrine bitartrate, dopamine and histamine hydrochloride were from Sigma Co. All were dissolved in 0.9% NaCl solution immediately before use. Doses were calculated as the base.

RESULTS

Renal effects of intracerebroventricular ketanserin

Ketanserin (KET) when administered into a lateral ventricle (icv) of rabbit brain elicited natriuretic responses. 12 μg/kg icv induced only slight and transient increases in UFR and sodium excretory rates. As shown in Table 1, 40 μg (=0.1 μmoles)/kg elicited about 30% increases in Na excretion and 10% increase in UFR, while systemic blood pressure significantly decreased by about 4-6 mmHg. With further increase of the dose up to 120 μg/kg icv, Na excretion highly significantly increased, more than tripling to 28.5 μEq/min from 8.7, in the second 10-min period after the administration. The fractional Na excretion also increased more than 3 times up to 2.84%. UFR, K excretion as well as renal plasma flow (RPF) ($=C_{PAH}$) and glomerular filtration rate (GFR) ($=C_{cr}$) tended transiently to increase in the first 10-min period. Reflecting the increased Na excretion, osmolar clearance increased, but the free water reabsorption only tended to increase slightly. Systemic blood pressure decreased by 5-7 mmHg. Fig. 1 depicts the changes of several parameters of renal function induced by 120 μg/kg KET icv. It is clearly seen that the natriuresis is not related to the hemodynamic changes.

Renal effects of intravenous ketanserin

To test the possibility that the icv administered KET might have reached into the general circulation from the site of administration and exerted its effect directly on the kidney, KET was administered intravenously. When 40 μg/kg was given iv, no significant changes in renal function as well as in blood pressure were noted, except for the decreasing tendency of RPF with resultant increase in filtration fraction. Table 2 shows the effects of 120 μg/kg KET iv. Unlike the prominent natriuresis it produced when given icv, the same dose of KET given iv did not elicit any significant changes in renal function, except for increased filtration fraction. Systemic blood pressure decreased by about the same degree as with icv ad-

Table 1. Effects of ketanserin *icv* on rabbit renal function

	Control	0'-10'	10'-20'	20'-40'	40'-60'	60'-80'
			40 μg/kg icv (n = 6)			
Vol (ml/min)	0.283 ± 0.039	0.309 ± 0.043	0.276 ± 0.032	0.274 ± 0.034	0.250 ± 0.046	0.226 ± 0.037
C_{PAH} (ml/min)	14.86 ± 2.92	15.21 ± 2.98	13.95 ± 3.22	13.63 ± 2.94	12.04 ± 3.32**	11.34 ± 3.03**
C_{cr} (ml/min)	6.05 ± 1.29	5.97 ± 1.28	5.63 ± 1.33	5.67 ± 1.15	5.23 ± 1.16**	5.08 ± 1.25**
$U_{Na}V$ (μEq/min)	5.13 ± 2.00	6.56 ± 1.87	6.63 ± 1.94	6.14 ± 1.77	5.44 ± 1.56	4.70 ± 1.52
U_KV (μEq/min)	6.33 ± 1.01	6.36 ± 0.94	5.44 ± 0.83	5.11 ± 0.85*	4.43 ± 0.81**	4.16 ± 0.80**
MAP (mmHg)	81 ± 5	75 ± 5**	77 ± 5*	79 ± 6	80 ± 5	79 ± 5
			120 μg/kg icv (n = 6)			
Vol (ml/min)	0.388 ± 0.055	0.527 ± 0.124	0.512 ± 0.110	0.363 ± 0.094	0.231 ± 0.044	0.223 ± 0.042
C_{PAH} (ml/min)	14.84 ± 1.20	17.98 ± 2.21	15.79 ± 1.20	13.21 ± 1.76	10.64 ± 1.94*	10.73 ± 1.72*
C_{cr} (ml/min)	6.66 ± 0.68	7.47 ± 1.04	6.86 ± 0.61	6.01 ± 0.76	5.36 ± 0.72**	5.55 ± 0.72*
$U_{Na}V$ (μEq/min)	8.72 ± 2.67	18.72 ± 6.55	28.47 ± 9.08**	15.35 ± 5.43	6.55 ± 2.57	5.95 ± 2.45
FE_{Na} (%)	0.933 ± 0.245	1.837 ± 0.644	2.843 ± 0.946**	1.696 ± 0.518	0.739 ± 0.248	0.633 ± 0.208
U_KV (μEq/min)	6.46 ± 0.59	7.79 ± 1.13	7.14 ± 1.01	4.83 ± 0.72*	3.80 ± 0.78**	4.06 ± 0.79**
C_{osm} (ml/min)	0.471 ± 0.052	0.609 ± 0.081	0.656 ± 0.098*	0.476 ± 0.069*	0.356 ± 0.060	0.351 ± 0.053
T^cH_2O (ml/min)	0.084 ± 0.065	0.082 ± 0.091	0.144 ± 0.058	0.114 ± 0.067	0.125 ± 0.033	0.128 ± 0.036
MAP (mmHg)	90 ± 7	85 ± 7*	83 ± 7**	86 ± 6	87 ± 6	87 ± 7

Mean ± S.E. Abbreviations: Vol, rate of urine flow; C_{PAH} and C_{cr} are clearances of PAH and creatinine, resp.; $U_{Na}V$ and U_KV, excretory rates of sodium and potassium, resp.; FE_{Na}, fractional excretion of filtered sodium; C_{osm}, clearance of osmotically active substances; T^cH_2O, reabsorption of osmotically free water; and MAP denotes mean arterial pressure. Significance of difference from control values were calculated by one-way ANOVA for repeated measures on time and subsequent Duncan multiple range test using the mean square error from two-way analysis. * $p<0.05$, ** $p<0.01$.

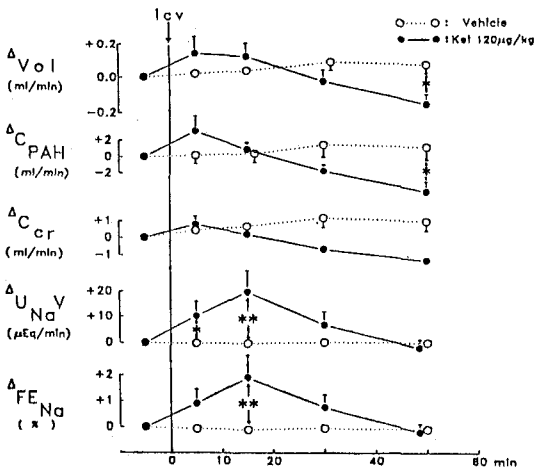

Fig. 1. Effects of ketanserin icv on rabbit renal function. Mean differences from control values with one S.E. (n = 6, each group) are shown. Significant differences from the corresponding values of the vehicle group as tested with ANOVA and Newman-Keuls test are marked with asterisks. * $p<0.05$; ** $p<0.01$. Abbreviations as in Table 1.

ministration. Thus it is likely that the natriuresis of icv KET might be of central origin.

Influence of ketanserin on the 5-HT effects

5-HT, 200μg (1 μmole)/kg icv, produced in the second 10-min period 50% increase in UFR, four-fold increase in Na excretion, 3.7-fold increase in fractional Na excretion, and 60% increase in K excretion, along with significant increases in C_{osm} and T^cH_2O. The RPF increased by 18%, while GFR did not change significantly. The mean changes of several parameters of renal function after the 5-HT administration were shown in Fig. 2, which also shows the influence of ketanserin pretreatment on the 5-HT effects. In these experiments the KET dose of 40 μg/kg, a dose which by itself elicits no significant effects was chosen, and it was given icv 3 min prior to icv 5-HT. As clearly seen in Fig. 2, from the first 10-min period after the administration, UFR, excretory rates of Na and K as well as RPF significantly increased. In the next 10-min period, these effects became more prominent, i.e., UFR increased by 2.5 fold, Na excretion by 6.2 fold up to 93 μEq/min, and

Table 2. Effects of ketansein 120 μg/kg *iv* on rabbit renal function

	Control	0'-10'	10'-20'	20'-40'	40'-60'	60'-80'
Vol (ml/min)	0.308 ± 0.029	0.324 ± 0.040	0.288 ± 0.027	0.277 ± 0.023	0.269 ± 0.035	0.255 ± 0.047
C_{PAH} (ml/min)	19.90 ± 2.08	18.17 ± 2.06	17.29 ± 1.67	16.56 ± 1.92	15.30 ± 1.76*	14.50 ± 2.25**
C_{cr} (ml/min)	7.68 ± 0.82	7.37 ± 0.86	7.30 ± 0.73	6.88 ± 0.82	6.36 ± 0.75	6.21 ± 0.98
FF (%)	38.6 ± 1.5	40.4 ± 1.4	42.2 ± 1.2**	41.7 ± 1.9*	41.6 ± 1.7*	42.8 ± 1.7**
$U_{Na}V$ (μEq/min)	12.54 ± 1.96	15.26 ± 2.90	11.59 ± 1.87	10.72 ± 2.12	8.67 ± 2.10	6.96 ± 2.07**
FE_{Na} (%)	1.248 ± 0.231	1.580 ± 0.314	1.215 ± 0.244	1.164 ± 0.223	1.006 ± 0.229	0.827 ± 0.209*
U_KV (μEq/min)	5.73 ± 0.43	5.67 ± 0.42	5.17 ± 0.38	4.99 ± 0.49	4.64 ± 0.62*	4.34 ± 0.68**
MAP (mmHg)	90.0 ± 3.6	82.2 ± 3.9**	84.8 ± 3.8**	88.0 ± 3.6	90.2 ± 4.2	91.3 ± 3.9

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

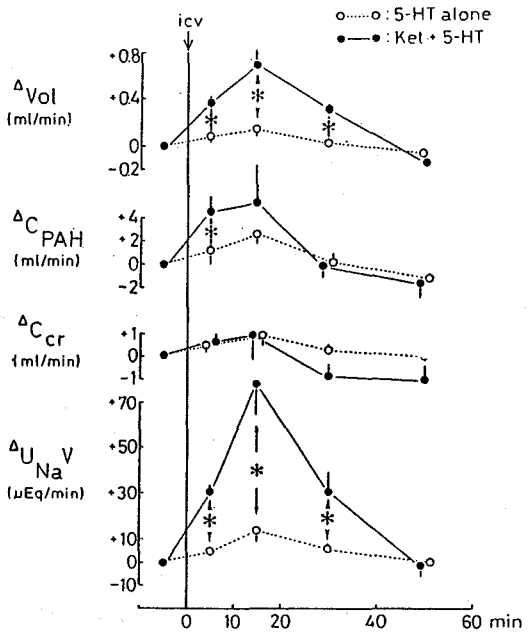

Fig. 2. Influence of icv ketanserin on the renal effects of icv 5-HT. Mean changes from the control values with one S.E. are shown (n = 6, each group). Significant difference between corresponding values of both groups are marked with asterisks. Other legends as in Fig. 1.

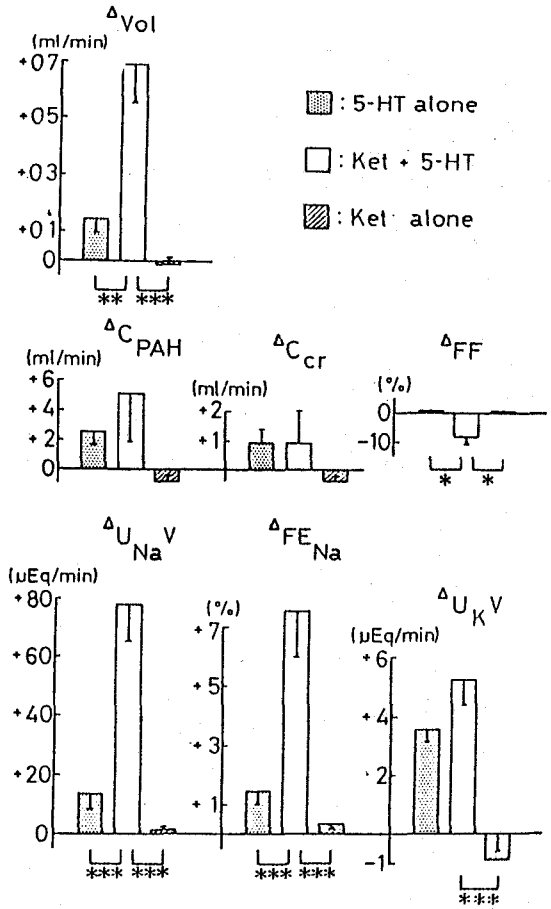

Fig. 3. Comparisons of changes of various parameters of renal function induced by icv 5-HT, ketanserin, and ketanserin + 5-HT. Mean changes from the control values at the 10'-20' clearance periods are compared. Significant changes between groups are marked with asterisks.
* $p<0.05$; ** $p<0.01$; and *** $p<0.001$.

K excretion by two-fold. Reflecting the increased electrolyte excretion, C_{osm} increased 2.3-fold with no significant increase in T^cH_2O. Both RPF and GFR tended to increase slightly. In the next 20-min period, even though both RPF and GFR declined below the pre-administration levels, the diuretic and natriuretic effects persisted, and finally after 40 min all the ef-

fects subsided. As seen in Fig. 2, the diuretic and natriuretic effects of 5-HT was significantly augmented by the pretreatment with KET. Fig. 3 compares the three groups, namely the 5-HT alone, the KET alone and the KET + 5-HT, with respect to the changes of renal function at the second 10-min periods when peak changes take place. As clearly seen here, the changes in GFR and RPF did not significantly differ among the three groups, whereas the KET + 5-HT group showed highly significant increase over other two groups.

Influence of icv ketanserin on the icv effects of norepinephrine, dopamine and histamine

Next, to ascertain the specificity of the ketanserin action, its influence on the renal effects of various biogenic amines known to be involved in the central regulation of renal function were investigated. NE when given icv in doses of 10 μg/kg produced significant decreases in RPF and GFR, and significant decreases in systemic blood pressure by about 5 to 10 mmHg, along with decreasing tendency of urine flow and electrolyte excretion, confirming the observation by Lee (1972). Pretreatment with KET, 40 μg/kg icv, did not influence the icv NE effects on renal function, even though the systemic hypotensive action of icv NE was significantly augmented, with the magnitude increasing up to 17 mmHg.

DA given icv in doses of 150 μg/kg decreased excretory rates of sodium and potassium, along with decreasing tendency of UFR and renal hemodynamics, as already been shown by Choi (1974). Systemic blood pressure markedly decreased by more than 20 mmHg. Neither did KET pretreatment affect these effects of DA, both the renal and the hypotensive.

Histamine elicits antidiuresis when given icv in doses of 100 μg/kg, as shown by Shin (1974). After transient increase of by about 10 mmHg, systemic blood pressure remained unchanged. However, all the parameters of renal function significantly decreased after 10 min, reaching the nadir at the 20-40 min period and then recovering gradually. These effects were not affected by the pretreatment of KET. The transient elevation of systemic blood pressure, antidiuresis, antinatriuresis as well as decreased renal hemodynamics manifested itself unaltered by KET.

DISCUSSION

The contractile response of guinea-pig ileum to 5-HT may be divided into two parts: one being the direct stimulatory action on the smooth muscle, and the other mediated by acetylcholine released from the cholinergic nerves. The former can be abolished by dibenzyline, whereas the latter is blocked by morphine. These facts led Gaddum and Picarelli (1957) to the postulation that all the 5-HT receptors are not of the same type, but they can be divided into D- and M-receptors. Their classical dichotomy of 5-HT receptors is still precise and valid, but the blocking agents they employed in their study were of crude type with low selectivity and meager efficacy. About two decades later Peroutka and Snyder (1979), employing tritiated 5-HT and spiperone, also found that there exist two different types of binding sites for 5-HT on the membrane of cerebral cortex. They designated the one to which 5-HT binds as 5-HT_1 and the other as 5-HT_2, and they further characterized the former as related to adenylate cyclase activity whereas the latter being involved in the center-mediated behavioral effects in rats (Peroutka *et al.*, 1981). Recently, with the advent of many new agonists and antagonists with diverse specificity and efficacy it became clear that 5-HT_2 sites are identical with D-receptors and that stimulation of these receptors leads to the excitement which may be specifically blocked by ketanserin (Leysen *et al.*, 1981; Leysen *et al.*, 1983). The 5-HT_1 sites are blocked by methiothepin, methysergide, etc., but they have low selectivity (Janssen, 1983). Furthermore, 5-HT_1 sites may be subdivided into 5-HT_{1A} 5-HT_{1B} 5-HT_{1C} etc. (Pedigo *et al.*, 1981; Middlemiss, 1986). Bradley *et al.* (1986) asserted that the M-receptors do not identify either with 5-HT_1 or 5-HT_2 and designated them as 5-HT_3, and found that they are widely distributed in peripheral nerve but their physiological functions are not well characterized.

Ketanserin is a quinazoline derivative known as potent and specific antagonist of 5-HT_2 receptors (Leysen *et al.*, 1981; Van Nueten *et al.*, 1981). It binds to 5-HT_2 receptors with a Ki value of 2.1 nM, while it possesses no affinity to 5-HT_1 subtypes (Janssen, 1983). On the contrary, methysergide has Ki values of 99 nM to 5-HT_1 and 12 nM to 5-HT_2. Thus, the 5-HT_1/5-HT_2 ratio being 8.3, it has relative selectivity to 5-HT_1. Cyproheptadine has a ratio of 108, while LSD has with the ratio of 2.4 almost equal affinity to both types.

In the present study ketanserin, 120 μg (0.3 μmoles)/kg icv, produced natriuresis and diuresis, which are not related to the changes in renal hemodynamics or in systemic blood pressure, suggesting the mediation of certain humoral factor in

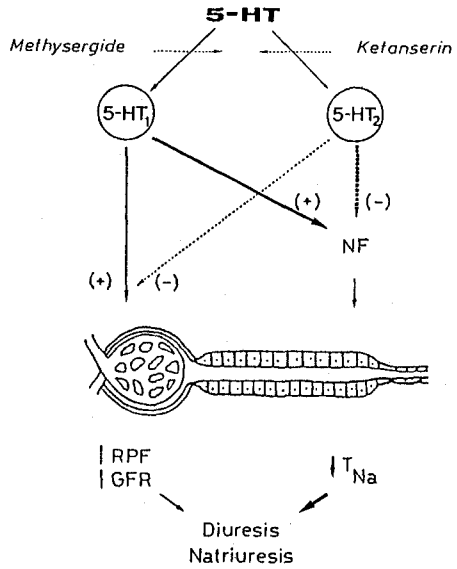

Fig. 4. A working hypothesis on the mechanism of central tryptaminergic regualtion of renal function. Drawn lines indicate stimulatory influence, while broken lines depict inhibitory ones.

the effects. The fact that it elicits, on the contrary, antidiuresis and antinatriuresis when given intravenously may indicate that the effects are of the central origin. It is further shown that the icv KET effects are not related to other receptors such as histamine, dopamine or adrenergic receptors and that they are indeed brought about by the specific blockade of 5-HT_2 receptors. Furthermore, it was observed that under the blockade of 5-HT_2 by ketanserin, icv 5-HT produced more prominent natriuresis and diuresis. These facts indicate that icv 5-HT elicits the natriuresis through mediation of 5-HT_1 receptors and therefore the 5-HT_1-mediated natriuretic effects can manifest itself undiminished when the 5-HT_2 receptors are selectively blocked by ketanserin. It may be further deduced that the 5-HT_2 subtypes had been exerting antidiuretic influence to the kidney, counteracting to the 5-HT_1-mediated natriuretic effects. Kook *et al.* (1988) observed that icv methysergide, 5-HT_1 antagonist, produced antidiuresis and antinatriuresis, and that under the pretreatment of methysergide the icv 5-HT effects were completely abolished.

Incorporating all these findings, the role of central tryptaminergic system in regulating renal function may be formulated as shown in Fig. 4. Both 5-HT_1 and 5-HT_2 subtypes participate in regulating the excretory renal function, and the former mediate diuresis and natriuresis, whereas the latter lead to antidiuresis and antinatriuresis. Release of certain natriuretic factor (NF) and changes of renal hemodynamics may be the mechanisms responsible for the renal effects. 5-HT_2 receptors mediate antidiuresis by inhibiting the release of the NF or reducing the renal perfusion, and the blockade of 5-HT_1 by methysergide results in antidiuresis, with the preponderance of the 5-HT_2 influence. 5-HT_1 receptors transmit natriuresis mainly via release of the NF. And removing the antidiuretic influence of 5-HT_2 with KET results in natriuresis and diuresis, and also in augmented response to icv 5-HT, as shown in this study.

To substantiate the hypothesis, further evidence should be presented as to the nature, origin and releasing mechanism of the NF as well as on the mechanism of renal hemodynamic changes. Presently under investigation are the changes of renal nerve activity and the search for the nature of NF in special reference to the known endogenous factors such as atrial natriuretic factor (DeBold *et al.*, 1981; Currie *et al.*, 1984) and brain natriuretic factor (Sudoh, 1988). Furthermore, the influences of various agonists and antagonists with greater specificity should be also tested.

The fact that under the influence of ketanserin the icv 5-HT is capable of inhibiting the fractional sodium excretion by nearly 10%, an enormous magnitude unparalleled by any of the other endogenous biogenic amines, may speak for the importance of the roles played by the central tryptaminergic system in the physiological regulation of renal function.

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＝국문초록＝

가토신장기능에 미치는 뇌실내 Ketanserin의 영향

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5-Hydroxytryptamine(5-HT)를 가토뇌실내로 투여(icv)하면 이뇨와 Na배설증가가 초래되며, 이러한 작용은 5-HT_1 수용체길항제인 methysergide에 의하여 차단되므로 중추성 신장기능조절에 있어 중추 tryptamine계의 관련이 시사된 바 있다. 본 연구에서는 5-HT_2 길항제로 알려진 ketanserin (KET)를 이용하여 5-HT_2 수용체의 역할을 구명하고자 하였다. KET 120 μg(=0.3 μmoles)/kg icv는 신혈류역학에는 아무런 변동을 일으키지않으나 유의한 Na배설증가를 초래하여, 세뇨관에서의 Na 재흡수 감소가 시사되었다. 전신혈압은 약간 감소하였다. 정맥내 투여시에는 유의한 기능변동을 볼 수 없었다. 5-HT 200μg/kg icv는 경미하나 유의한 Na배설증가 및 이뇨작용을 나타냈다. 그러나 신장기능에 그다지 큰 영향을 미치지 않는 양인 40μg/kg의 KET icv후에는 5-HT의 작용이 크게 강화되어, Na배설분획이 9.3%에 달하였다. Norepinephrine, dopamine, histamine과 같은 다른 생체아민의 신장작용은 KET전처치에 의하여 영향받지 아니하였다. 본 연구는 중추 5-HT_1 수용체와는 반대로 중추 5-HT_2 수용체는 항이뇨 및 Na배설감소를 매개하고 있으며, 중추 tryptamine계는 신장기능을 이중적으로 조절하고 있음을 시사하였다.