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Effects of dopamine on angiotensin Ⅱ-induced stimulation of Na^+ uptake in primary cultured rabbit renal proximal tubule cells

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초대배양한 신장 근위세뇨관세포에서 ANG Ⅱ의 Na^+ uptake 촉진효과에 대한 dopamine의 효과

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초 록 : 신장 근위세뇨관세포들은 사구체에서 여과된 물질의 재흡수, 분비 및 대사에 관여하는 여러 호르몬들의 수용체들을 가지고 있다. 이들중에서 dopamine(DA)과 angiotensin Ⅱ(ANG Ⅱ)가 Na^+/H^+ 상호운반계 조절에 중요한 역할을 하고 있다. 본 연구는 초대배양한 토끼 신장 근위세뇨관세포의 Na^+ uptake에 있어서 DA과 ANG Ⅱ의 상호관계를 알아보고자 실시하였다.

DA은 농도의존적으로 Na^+ uptake를 유의성 있게 억제하였다(10^{-6}M ; 83.2±7.2%, 10^{-3}M ; 67.2±3.8% vs. control)($p < 0.05$). DA_1 작동제(SKF 38393, 10^{-6}M)는 대조군의 81.4±6.7% 까지 Na^+ uptake를 유의성 있게 억제하였으나($p < 0.05$) DA_2 작동제는 영향을 미치지 않았다. DA_1 길항제(SCH 23390, 10^{-6}M)에 의해 DA의 Na^+ uptake 억제효과는 차단되었으나 DA_2 길항제(spiperone, 10^{-6}M)에 의해서는 영향을 받지 않았다. DA과 대조적으로 10^{-11}M ANG Ⅱ는 AT_1 수용체를 통하여 대조군의 120.7±4.9% 까지 Na^+ uptake를 유의성 있게 촉진하였다($p < 0.05$). DA 및 10^{-11}M ANG Ⅱ를 병합처리하였을 때 DA은 농도의존적으로 ANG Ⅱ에 유도된 Na^+ uptake 촉진효과를 유의성 있게 차단하였다($p < 0.05$). 한편 ANG Ⅱ에 의해 유도된 Na^+ uptake 촉진작용은 DA_1 또는 DA_2 작동제에 의해 차단되었으나 DA에 의한 차단효과는 DA_1 및 DA_2 길항제를 병합처리하였을 때만 반전되었다.

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결론적으로 DA은 DA_1 수용체를 통하여 Na^+ uptake를 억제하였으나 ANG Ⅱ에 의한 Na^+ uptake 촉진작용의 억제에는 DA_1 및 DA_2 수용체 모두가 관여하였다.

Key words : kindey, dopamine, angiotensin Ⅱ, Na^+/H^+ antiport.

Introduction

The renal proximal tubule cells contain a variety of cellular membrane receptors which, upon binding of their selective agonists or endogenous hormones, lead to alteration in reabsorption, secretion, and metabolism. There are a number of hormones that have been shown to modulate proximal tubule Na^+ reabsorption through their effects on the luminal Na^+/H^+ antiporter activity[1,2]. Among these hormones, DA and ANG Ⅱ represent two powerful hormone systems in regulation of Na^+/H^+ antiporter activity and have been involved in hypertension in the kidney[3~5].

DA receptors which are classified into the DA_1 and DA_2, are located at various regions within the kidney including renal vasculature, juxtaglomerular cells, and the renal tubules[6,7]. DA has been reported to inhibit Na^+ transport[8]. But it is not yet documented which receptor is related to the regulation of Na^+ transport in the proximal tubule cells(PTCs).

ANG Ⅱ has been reported to have a biphasic effect on Na^+ uptake in the proximal tubules: low dosages of ANG Ⅱ stimulate Na^+ uptake while high dosages of ANG Ⅱ inhibit[9,10]. ANG Ⅱ receptors, which are classified into the ANG Ⅱ type Ⅰ and Ⅱ, are located in the renal tissues including proximal tubules, juxtaglomerular cells[11]. Especially, low dosages of ANG Ⅱ are closely involved in renal hypertension development and directly stimulate Na^+ reabsorption through ANG Ⅱ receptor in the PTCs. Since alterations in the balance of responsiveness of proximal tubule to DA and ANG Ⅱ have important implications for net sodium and water reabsorption, we aimed to study the interrelation between DA and ANG Ⅱ.

The PTCs utilized in this study, have been observed to retain a number of differentiated typical functions of the renal proximal tubules, including Na^+-dependent alpha methyl-D-glucoside uptake, Na^+-dependent phosphate uptake, and parathyroid hormone-sensitive cAMP production[12,13]. Therefore this primary culture system in hormonally defined, serum free culture conditions is a powerful tool for studying interaction between DA and ANG Ⅱ in the Na^+/H^+ antiport system. In the present study, we examined the interaction between DA and ANG Ⅱ on Na^+ uptake in primary cultured rabbit renal proximal tubule cells.

Materials and Methods

Materials : Male New Zealand White rabbits (1.5~2.0kg) were used for these experiments. Dulbecco's Modified Eagel's Medium, Nutrient Mixture F-12 (Ham), Class Ⅳ collagenase and soybean trypsin inhibitor were purchased from Life Technologies (Grand Island, NY). Angiotensin Ⅱ (ANG Ⅱ), dopamine (DA), spiperone (DA_2 antagonist), ouabain, insulin, hydrocortisone, transferrin, and BSA fraction V were obtained from Sigma Chemical (St. Louis, MO). PD123319 was purchased from Parke-Davis. Losartan (DuP 753) and $^{22}Na^+$ were purchased from DuPont/New England Nuclear. SKF 38393 (DA_1 agonist), SCH 23390 (DA_1 antagonist), and quinpirole (DA_2 agonist) were purchased from Research Biochemicals (Natick, MA). All other reagents were of the highest purity commercially available. Liquiscint was obtained from National Diagnostics (Parsippany, NY). Iron oxide was prepared by the method of Cook and Pickering[14]. Stock solutions of iron oxide in 0.9% NaCl were sterilized using an autoclave and diluted with phosphate buffered saline prior to use.

Isolation of rabbit renal proximal tubules and culture

conditions : Primary rabbit renal proximal tubule cell cultures were prepared by a modification of the method of Chung *et al*[12]. The basal medium, D-MEM/F-12, pH 7.4, was a 50 : 50 mixture of Dulbecco's Modified Eagle's Medium and Ham's F-12. The basal medium was further supplemented with 15mM HEPES buffer (pH 7.4) and 20mM sodium bicarbonate. Immediately prior to the used of the medium, three growth supplements (5μg/ml insulin, 5μg/ml transferrin, and 5×10^{-8}M hydrocortisone) were added. Water utilized in medium preparation was purified by means of a Milli Q deionization system. Kidneys of a male New Zealand White rabbit were perfused via the renal artery, first with PBS, and subsequently with D-MEM/F-12 containing 0.5% iron oxide (wt/vol) until the kidney turned grey-black in color. Renal cortical slices were prepared by cutting the renal cortex and then homogenized with 4 strokes of a sterile glass homogenizer. The homogenate was poured first through a 253μm and then a 83μm mesh filter. Tubules and glomeruli on top of the 83μm filter were transferred into sterile D-MEM/F-12 medium containing a magnetic stirring bar. Glomeruli (containing iron oxide) were removed with a magnetic stirring bar. The remaining proximal tubules were briefly incubated in D-MEM/F-12 containing 80μm/ml collagenase (Class Ⅳ) and 0.025% soybean trypsin inhibitor. The dissociated tubules were then washed by centrifugation, resuspended in D-MEM/F-12 containing the three supplements, and transferred into tissue culture dishes. PTCs were maintained at 37℃, in a 5% CO_2-humidified environment in D-MEM/F-12 medium containing the three supplements. Medium was changed one day after plating and every three days thereafter.

Na^+ uptake experiment : The confluent monolayers were incubated with DA or/and 10^{-11}M ANG Ⅱ with and without their receptor agonists and antagonists for 4 hrs before Na^+ uptake experiments. Uptake experiment was conducted as described by the method of Rindler *et al*[15]. For Na^+ uptake studies, the medium was removed by aspiration. Before the uptake period, the monolayers were washed twice with 100mM Tris-HCl buffer, pH 7.4. Na^+ uptake was measured at 37℃ for 30 mins in an uptake buffer (10mM Tris, 1mM $CaCl_2$, 1mM $MgCl_2$, 140mM Choline chloride) containing 0.25μCi/ml Na^+ and 5×10^{-5}M ouabain (pH 7.4). At the end of the incubation period, the monolayers were gently washed three times with ice cold 100mM Tris-HCl buffer, pH 7.4, and the cells were solubilized with 1 ml of 0.1% SDS. To determine the Na^+ incorporated intracellulary, 900μl of each sample was removed and counted in a liquid scintillation counter (Beckmann Co.). The remainder of each sample was used for protein determination[16]. The radioactivity counts in each sample were then normalized with respect to protein and were corrected for zero-time uptake per mg protein. All uptake measurements were made in triplicate.

Statistical analysis : Results were expressed as means± standard error (S.E.). The difference between two mean values was analyzed by Student's *t*-test. The difference was considered statistically significant when $p < 0.05$.

Results

Dose response effects of DA on Na^+ uptake : Fig 1 shows the dose response effects of DA on Na^+ uptake. DA at concentrations of 10^{-9}~10^{-3}M was applied to PTCs for 4 hrs. Addition of DA to PTCs inhibited Na^+ uptake in a dose-dependent manner. 10^{-6}M and 10^{-3}M DA inhibited Na^+ uptake (10^{-6}M DA : 83.2±7.2% control, 10^{-3}M DA : 67.2±3.8% control, respectively ; $p < 0.05$). 10^{-6}M DA close to physiological concentration was used to this study.

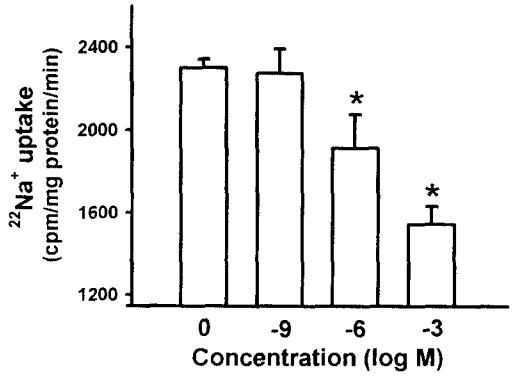

Fig 1. Dose response effects of dopamine (DA) on Na^+ uptake. PTCs were incubated with DA (10^{-9}~10^{-3}M) for 4 hrs. Values are the means±S.E. of 12 experiments performed on 4 different cultures. *$p < 0.05$ vs. control.

Effects of DA receptor agonists and antagonists : To determine the receptor subtype mediating the DA-induced inhibition of Na^+ uptake, PTCs were exposed to the DA_1 agonist (SKF 38393, 10^{-6}M), DA_2 agonist (quinpirole, 10^{-6} M), DA_1 antagonist (SCH 23390, 10^{-6}M), and DA_2 antagonist (spiperone, 10^{-6}M). As shown in Fig 2, the inhibitory effect of DA on Na^+ uptake was mediated via the DA_1 receptor because DA_1 agonist but not DA_2 agonist inhibited Na^+ uptake (DA_1 : 81.4±6.7% control ; $p < 0.05$, DA_2 : 103.0±7.6% control ; p = NS), and the inhibitory effect of DA was also abolished by DA_1 antagonist but not by DA_2 antagonist.

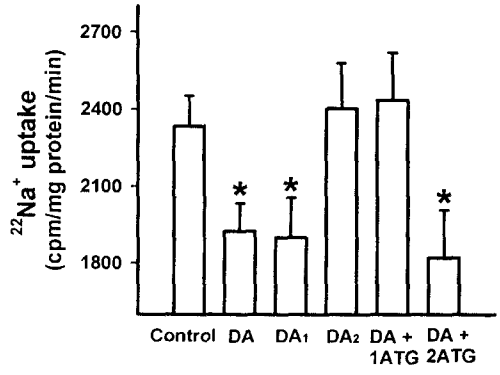

Fig 2. Effects of DA_1, DA agonists, and antagonistis on Na^+ uptake. DA (DA, 10^{-6}M), DA_1 agonist SKF 38393 (DA_1, 10^{-6}M), DA_2 agonist quinpirole (DA_2, 10^{-6}M), DA_1 antagonist SCH 23390 (1ATG, 10^{-6}M), and DA_2 antagonist spiperone (2ATG, 10^{-6}M) were treated to the PTCs for 4 hrs. Values are the means±S.E. of 9 experiments performed on 3 different cultures. *p < 0.05 vs. control.

Effects of ANG Ⅱ and ANG Ⅱ receptor antagonists on Na^+ uptake : 10^{-11}M ANG Ⅱ was treated to PTCs for 4 hrs before uptake experiment. 10^{-11}M ANG Ⅱ stimulated Na^+ uptake by 120.7±4.9% control. To determine the receptor subtype mediating the ANG Ⅱ-induced stimulation of Na^+ uptake, cells were exposed to the specific receptor antagonist losartan [ANG Ⅱ receptor subtype 1 (AT_1) antagonist, 10^{-8}M] or PD123319 [ANG Ⅱ receptor subtype 2 (AT_2) antagonist, 10^{-8}M] in the absence or presence of 10^{-11}M ANG Ⅱ. As shown in Fig 3, losartan prevented 10^{-11}M ANG Ⅱ-induced stimulation of Na^+ uptake but PD123319 did not (10^{-11}M ANG Ⅱ : 120.7±4.9% control vs. ANG Ⅱ plus losartan : 101.1±6.4% control ; $p < 0.05$).

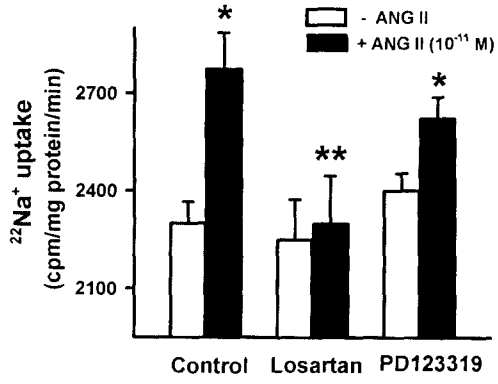

Fig 3. Effects of angiotensin Ⅱ (ANG Ⅱ) receptor antagonists on Na^+ uptake. PTCs were treated with ANG Ⅱ (10^{-11}M) alone or together with losartan (AT_1 receptor antagonist, 10^{-8}M), or PD123319 (AT_2 receptor antagonist, 10^{-8}M). Values are the means±S.E. of 18 experiments performed on 6 different cultures. *p < 0.05 vs. control. **p < 0.05 vs. ANG Ⅱ alone.

Interaction between the DA and ANG Ⅱ on Na^+ uptake : When DA (10^{-9}~10^{-3}M) was added simultaneously, the stimulatory effects of ANG Ⅱ were abolished in a DA dose-dependent manner (Fig 4). To determine which receptor subtype mediate the antagonistic effect of ANG Ⅱ-induced stimulation of Na^+ uptake, PTCs were incubated with ANG Ⅱ (10^{-11}M) alone or together with DA, DA_1 agonist,

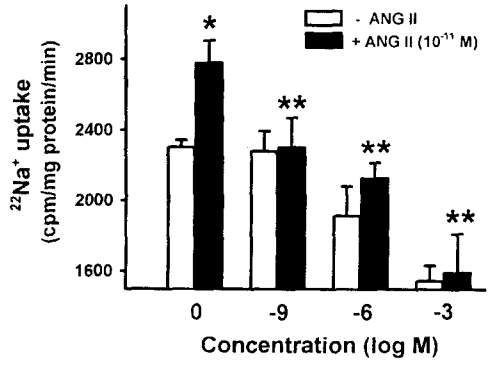

Fig 4. Effects of DA on ANG Ⅱ-induced stimulation of Na^+ uptake. PTCs were incubated with ANG Ⅱ (10^{-11}M) alone or together with DA (DA, 10^{-9}~10^{-3}M) for 4 hrs. Values are the means±S.E. of 12 experiments performed on 4 different cultures. *p < 0.05 vs. ANG Ⅱ alone.

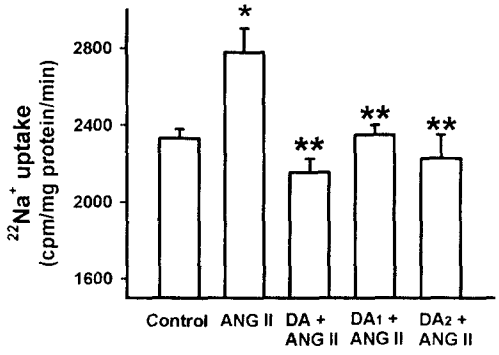

Fig 5. Effects of DA and DA agonists on ANG Ⅱ-induced stimulation of Na^+ uptake. PTCs were incubated with ANG Ⅱ (10^{-11}M) alone or together with DA (10^{-6}M), DA_1 agonist SKF 38393 (10^{-6}M), or DA_2 quinpirole (10^{-6}M) for 4 hrs. Values are the means±S.E. of 9 experiments performed on 3 different cultures. *p < 0.05 vs. control, **p < 0.05 vs. ANG Ⅱ.

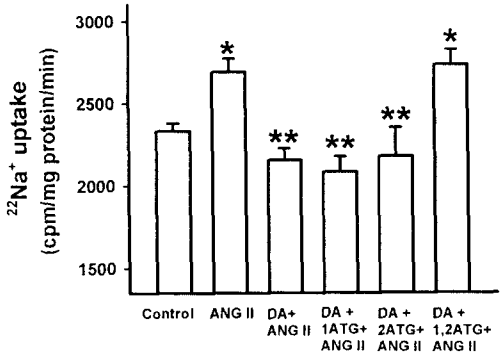

Fig 6. Effects of DA antagonists on ANG Ⅱ-induced stimulation of Na^+ uptake. PTCs were incubated with ANG Ⅱ (10^{-11}M) alone or together with DA (10^{-6}M) and/or with DA_1 antagonist SCH 23390 (1ATG, 10^{-6}M), DA_2 antagonist spiperone (2ATG, 10^{-6}M), or both antagonists for 4 hrs. Values are the means±S.E. of 9 experiments performed on 3 different cultures. *p < 0.05 vs. control, **p < 0.05 vs. ANG Ⅱ.

and DA_2 agonist. Both DA_1 and DA_2 agonists exhibited the effect of DA (Fig 5). The antagonistic effect of DA was not reversed by DA_1 or DA_2 antagonists; however, a complete reversion required the combination of both DA_1 and DA_2 antagonists (Fig 6). These results indicate that both DA_1 and DA_2 receptors mediated the inhibitory effect of DA on ANG Ⅱ-induced stimulation of Na^+ uptake.

Discussion

The kidney plays an important role in the regulation of blood pressure and body fluid homeostasis[17]. The proximal tubules are a major site of salt and water reabsorption in the mammalian nephron. The Na^+ reabsorption of proximal tubule are under the control of various hormones including ANG Ⅱ, DA[18,19]. DA was active at a concentration of 10^{-6}M; plasma and peritubular concentrations of DA are lower than 10^{-6}M, but DA is produced locally in the kidney, and the intracellular concentration of DA may be in the micromolar range[20,21]. Few data are available on the effects of DA in the PTCs in hormonally defined, serum free culture conditions, but in the present study, we showed that DA inhibited Na^+ uptake in a dose-dependent manner in the PTCs (Fig 1). The results of this study corroborate inhibition of the Na^+/H^+ antiporter demonstrated in rat proximal nephron segments and in renal brush-border membrane[22,23].

Kidney has two types of DA receptors : DA_1 and DA_2. In the present study, the results summarized in Fig 2 demonstrate that the inhibition of Na^+ uptake by DA in the PTCs was reproduced by the DA_1 agonist SKF 38393, whereas the DA_2 agonist quinpirole had no effec on Na^+ uptake. It was completely abolished by DA_1 antagonist SCH 23390 but not by DA_2 antagonist spiperone. That this action of DA is mediated via its DA_1 receptor is further supported by several other results[7,22] that the DA_1 but not DA_2 receptor is mainly associated with inhibition of renal Na^+ transport. In rat renal cortical brush-border membrance vesicles DA and the DA_1 agonist, SKF 82526, but not DA_2 agonist, LY 171555, decreased Na^+ uptake apparently by inhibiting Na^+/H^+ antiport activity. This effect was blocked by the DA_1 antagonist, SCH 23390[24]. Indeed, DA_1 receptors are predominantly located in proximal tubules, but DA_2 receptors in glomeruli and mesangial cells[6,25,26]. But Bello Reuss *et al*[27] reported that DA and DA agonists had no effect on fluid transport in the isolated perfused proximal straight tubule of the rabbit. In contrast, it was reported that DA increased luminal uptake of Na^+ by activation of the Na^+/H^+ antiport in isolated rabbit proximal tubule cells[28]. Whether these ap-

parently confliction reports are related to differences in experimental model system or receptor subtypes remains to be determined.

Although the effects of DA have previously been assessed singularly, this agent has not been investigated in terms of the interactions that this may have with other hormones on Na^+ uptake in the PTCs. In contrast to DA, ANG Ⅱ stimulated Na^+ uptake via a AT_1 receptor (Fig 3). The ANG Ⅱ-induced stimulation of Na^+ uptake was markedly attenuated by DA (Fig 4). This effect of DA was mediated via both DA_1 and DA_2 receptors, because DA_1 and DA_2 agonists exerted similar effects (Fig 5), and the effect of DA was prevented only by the combination of DA_1 and DA_2 antagonists (Fig 6). This result is also supported by the report that DA_2 receptors are involved in the antagonistic effect of DA on ANG Ⅱ stimulation of Na^+ uptake, and thus provides an additional role of DA_2 receptors in the inhibitory effect of DA on proximal tubule Na^+ reabsorption[20]. Bertorello *et al*[29] also reported the role of DA_1 and DA_2 receptors in the results that sodium pump activation may require simultaneous activation of both DA_1 and DA_2 receptors in the proximal tubule. Cheng *et al*[30] reported that DA, acting through DA_1, acting DA_1 receptors, decrease AT_1 receptor expression in proximal tubule, suggesting the interaction between AT_1 receptor and DA_1 receptor. However, in the present study, in addition to DA_1, DA_2 had effect on the inhibition of ANG Ⅱ-induced stimulation of Na^+ uptake. Further studies about the these signal pathways are needed.

In summary, DA inhibits ANG Ⅱ-induced stimulation on Na^+ uptake by DA_1 but not DA_2 receptors mediate the effects of DA to inhibit Na^+ uptake while both DA_1 and DA_2 receptors mediated the antagonistic effect of DA on ANG Ⅱ stimulation of Na^+ uptake.

Conclusion

The present study examined the interaction between DA and ANG Ⅱ on Na^+ uptake in PTCs. DA caused a dose-dependent inhibition of Na^+ uptake. DA_1 agonist but not DA_2 agonist inhibited Na^+ uptake, and the inhibitory effect of DA was abolished by DA_1 antagonist but not by DA_2 antagonist. In contrast to DA, ANG Ⅱ stimulated Na^+ uptake via AT_1 receptor. When DA and ANG Ⅱ were added together, DA blocked ANG Ⅱ-induced stimulation of Na^+ uptake in a dose-dependent manner. Both DA_1 and DA_2 agonists inhibited stimulatory effect of ANG Ⅱ on Na^+ uptake. This inhibitory effect of DA was reversed only by the combination of both DA_1 and DA_2 antagonists. In conclusion, DA inhibits Na^+ uptake through DA_1 receptors, while both DA_1 and DA_2 receptors mediate the inhibitory effect of DA on ANG Ⅱ-induced stimulation of Na^+ uptake.

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