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Alpha and Beta Adrenergic Agonists Stimulate Water Absorption in the Rat Proximal Tubule

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Summary. Simultaneous capillary and luminal microperfusion studies were performed in the rat proximal tubule to determine the effects of the beta agonist isoproterenol and the alpha agonist phenylephrine on water absorption. Capillary and luminal perfusion solutions were composed such that organic solutes were not present, no bicarbonate was present in the lumen, and no chloride gradient was imposed. Under such conditions, water absorption (Jv) averaged 0.36 ± 0.11 nl·min^{-1}·mm^{-1}. The addition of isoproterenol to the capillary solution in concentrations of 10^{-6} and 10^{-4} M resulted in significantly higher Jv's of 0.68 ± 0.10 and 0.71 ± 0.11 nl·min^{-1}·mm^{-1}, respectively. The enhancing effect of isoproterenol was inhibited by the beta blocker propranolol (10^{-4} M), but not by the alpha blocker phentolamine (10^{-7} M). The addition of phenylephrine (10^{-6} M) to the capillary perfusion solution also resulted in a significantly higher Jv of 0.84 ± 0.14 nl·min^{-1}·mm^{-1}, an effect inhibited by phentolamine (10^{-7} M), but not by propranolol (10^{-4} M). Neither phentolamine nor propranolol alone in the concentrations indicated had an effect on water absorption. These experiments indicate that both alpha and beta agonists stimulate water absorption in the superficial proximal tubule of the rat. This effect appears to be relatively specfic for each class of agonist, as demonstrated by the effects of the specific antagonists.

Key words: catecholamines·sodium transport·microperfusion

A direct role for catecholamines on renal sodium metabolism has been suggested from the results of a number of experimental investigations. DiBona and Kim et al. have recently published excellent reviews of the subject [11, 19]. The systemic infusion or stimulation of endogenous release into the circulation of alpha or beta agonists, however, could have diverse physiologic effects on cardiac function, vascular tone, blood flow distribution, and on the release of other hormones and/or humors. Given the biologic activity of such agents, it is often difficult to discern whether the observed change in sodium excretion derives as a direct consequence of the catecholamines on renal tubular sodium transport or as an indirect consequence of some other action of the agent. As will be reviewed in the discussion section, several recent studies, of both a functional and histologic nature, have more directly implicated a direct effect of catecholamines on sodium transport [2–6, 14, 28, 29]. The present studies were designed to obtain more direct information on the action of alpha and beta agonists on water absorption in the superficial proximal convoluted tubule of the rat. The techniques employed were simultaneous microperfusion of the peritubular capillaries and their adjacent proximal convoluted tubules. The agonist and/or inhibitors were added to the capillary solutions only.

Materials and Methods

Male Sprague-Dawley rats were anesthetized with pentobarbital (50 mg/kg) injected intraperitoneally and prepared for micropuncture as previously described [26]. During preparation for study, a volume of isotonic saline equal to 1% of body weight was infused intravenously to replace surgical losses of fluid. Isotonic saline was infused intravenously at a rate of 1.2 ml/hr for the duration of the experiment. Peritubular capillaries were impaled with glass micropipettes and continuously perfused at a rate of approximately 3 μl/min. The peritubular capillary perfusion solution contained 125 mM NaCl, 25 mM $NaHCO_3$, and 4 mM KCl (pH 7.4).[1] In the area of the capillary blanch, segments of the proximal convoluted tubule were continuously microperfused between oil blocks at a rate of 17 nl/min, as previously described [26]. The luminal perfusion solution contained 125 mM NaCl, 25 mM Na cyclamate, 4 mM KCl, and [methoxy-^{3}H] inulin (New England Nuclear, Boston). The

[1] No calcium was added to the microperfusion solution. Analysis of the solution by X-ray fluorescence spectrometry, however, indicated that it contained 0.25 mM calcium. Although the minimal calcium concentration required to maintain the integrity of the cell is not known with certainty, a value of 20 μM calcium appears to be sufficient for the colon [12].

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solution was gased with 95% O_2/5% CO_2 and the pH adjusted to 7.4 with 0.15 N NaOH or 0.15 N HCl. The concentration of calcium was 0.25 mM. The catecholamine and catecholamine blockers were added to the capillary perfusion solutions only in the concentrations indicated in the Results section. Only one set of solutions was examined in any individual animal. At the end of each microperfusion, a latex cast was made and the length of perfused segment determined by microdissection.

The radioactivity of perfusion solutions and collected samples was determined in Biofluor (New England Nuclear, Boston) in a Tri-carb liquid scintillation counter (Packard Instruments Co., Downers Grove, IL). The perfusion rate was calculated from the equation.

Perfusion rate $(nl \cdot min^{-1}) = (CF/PF)_{In} \times$ collected volume $\times$ min^{-1} where CF and PF are the counts per min of [^{3}H] inulin in the collected fluid (CF) and initial perfusion solution (PF), respectively. Water absorption (Jv) was calculated from the expression

Jv $(nl \cdot min^{-1} \cdot mm^{-1}) = (1-[PF/CF]_{In}) \times$ perfusion rate $\times$ L^{-1} where L is the length of perfused tubule. The results are expressed as the mean $\pm$ SEM. Statistical comparisons were made using the t test for unpaired data.

Results

Using the control perfusion solutions containing no agonist or antagonist, Jv averaged 0.36 ± 0.11 $nl \cdot min^{-1} \cdot mm^{-1}$, a value nearly identical to that previously reported using the identical perfusion solutions [25]. The addition of isoproterenol in concentrations of 10^{-8}, 10^{-6}, and 10^{-4} M to the capillary perfusion solution resulted in Jv's of 0.49 ± 0.15, 0.68 ± 0.10, and 0.71 ± 0.11 $nl \cdot min^{-1} \cdot mm^{-1}$, respectively. The values obtained with 10^{-6} and 10^{-4} M isoproterenol were significantly higher than control values. The addition of propranolol (10^{-4} M) to a solution containing isoproterenol in a concentration of 10^{-4} M resulted in a Jv of 0.37 ± 0.08 $nl \cdot min^{-1} \cdot mm^{-1}$, a value not significantly different from control. Propranolol alone in the capillary perfusion solution had no significant effect on Jv. The addition of phentolamine (10^{-7} M) to a solution containing isoproterenol (10^{-6} M) resulted in a Jv of 0.68 ± 0.09 $nl \cdot min^{-1} \cdot mm^{-1}$, a value not significantly different from that obtained with the solution containing isoproterenol (10^{-4} M) alone.

Phenylephrine added to the capillary perfusion solution in concentrations of 10^{-8} and 10^{-6} M resulted in Jv's of 0.40 ± 0.14 and 0.84 ± 0.14 $nl \cdot min^{-1} \cdot mm^{-1}$, respectively. The value obtained with 10^{-6} M was significantly higher than control. 10^{-4} M phenylephrine resulted in Jv's of nearly zero and were associated with changes in tubule morphology observed grossly through the microscope. The details of the effects of 10^{-4} M phenylephrine were not explored further and were taken to indicate a toxic effect. The stimulating effect of 10^{-6} M phenylephrine was inhibited by phentol-

Table 1. Effect of catecholamines on water absorption in the proximal tubule

Perfusion solution	N	Length (mm)	Perfusion rate ($nl \cdot min^{-1}$)	Water absorption ($nl \cdot min^{-1} \cdot mm^{-1}$)	P
1. Control	19	1.5 ± 0.1	17.2 ± 0.2	0.36 ± 0.11	
2. Isoproterenol					
10^{-8} M	13	1.6 ± 0.2	17.0 ± 0.5	0.49 ± 0.15	NS *vs.* control
10^{-6} M	14	1.6 ± 0.1	17.0 ± 0.6	0.68 ± 0.10	<0.05 *vs.* control
10^{-4} M	18	1.5 ± 0.1	16.5 ± 0.3	0.71 ± 0.11	<0.05 *vs.* control
3. Isoproterenol (10^{-4} M) + Propranolol (10^{-4} M)	18	1.5 ± 0.1	17.3 ± 0.4	0.37 ± 0.08	NS *vs.* control; <0.01 *vs.* isoproterenol (10^{-4} M)
4. Isoproterenol (10^{-4} M) + Phentolamine (10^{-7} M)	12	1.5 ± 0.1	16.9 ± 0.4	0.68 ± 0.09	<0.05 *vs.* control
5. Propranolol (10^{-4} M)	8	1.6 ± 0.1	17.6 ± 0.5	0.41 ± 0.15	NS *vs.* control
6. Phenylephrine					
10^{-8} M	13	1.3 ± 0.1	17.8 ± 0.6	0.40 ± 0.14	NS *vs.* control
10^{-6} M	16	1.5 ± 0.1	17.3 ± 0.5	0.84 ± 0.14	<0.05 *vs.* control
7. Phenylephrine (10^{-6} M) + Phentolamine (10^{-7} M)	14	1.7 ± 0.1	16.5 ± 0.6	0.45 ± 0.14	NS *vs.* control; <0.05 *vs.* phenylephrine (10^{-6} M)
8. Phenylephrine (10^{-6} M) + Propranolol (10^{-4} M)	13	1.7 ± 0.1	16.9 ± 0.4	0.78 ± 0.11	<0.05 *vs.* control
9. Phentolamine (10^{-7} M)	11	1.8 ± 0.1	17.2 ± 0.1	0.24 ± 0.08	NS *vs.* control

Results are expressed as the mean $\pm$ SEM. N is the number of tubules. NS = not significant.

amine (10^{-7} M) but not by propranolol (10^{-4} M). Phentolamine (10^{-7} M) alone in the capillary perfusion solution resulted in a *Jv* of 0.24 ± 0.08 nl·min^{-1}·mm^{-1} (P = NS versus control). Higher concentrations of phentolamine resulted in a *Jv* of nearly zero and visual changes similar to those observed with phenylephrine (10^{-4} M) noted above.

Discussion

Before directly considering the results of the present studies, it is worth considering some aspects of the experimental design. The technique of simultaneous perfusion of both the capillary and the lumen is a powerful *in vivo* tool for studying the function of the proximal convoluted tubule. As compared to other studies which have employed these techniques, in the present studies the capillary perfusion rate was higher and the perfusion solution contained no protein and a relatively low concentration of calcium [16]. In prior studies utilizing the same capillary perfusion solutions, it has been observed that, in the luminal perfusion solutions, the replacement of cyclamate with either chloride or bicarbonate results in a higher rate of water absorption [25]. This is a rate similar to that observed by other investigators using a lower capillary perfusion rate and a more physiologic capillary perfusion solution [16]. Thus, it is unlikely that the perfusion rate *per se* or its possible effects on hydrostatic pressure, the presence or absence of protein, or the calcium concentration in the capillary perfusion solution are important determinants of the rates of water absorption under the conditions of study. In addition, the results obtained utilizing the cyclamate luminal microperfusion solution are comparable to those previously reported [1, 18, 21]. In the present studies, an isotopic marker was not added to the capillary solution to detect the presence of fluid leaks from capillary to lumen. In our prior experience utilizing these techniques, leaks of this type are usually associated with calculated *in vivo* perfusion rates of at least 20% higher than the setting of the microperfusion pump. The excellent agreement between the *in vivo* and *in vitro* rates observed in each of the sub-groups of experiments indicates that capillary-to-lumen leak of fluid was not a significant variable.

The choice of experimental design and perfusion solutions was predicated on the desire to examine the influence of catecholamines when present initially only on the capillary side of the cell and under circumstances which might permit some insights into the mechanism of action of catecholamines on water transport. Under the conditions of the present study, water absorption is most likely related to primary active sodium absorption, since other determinants of water absorption such as sodium-organic solute co-transport, bicarbonate reabsorption, and a lumen-to-capillary concentration gradient of chloride would not be applicable. While it is not certain that the rate of water absorption under these conditions is due only to sodium absorption, prior studies have indicated that the addition of cyanide to an identical capillary solution, and to an identical cyclamate-containing luminal perfusion solution, reduced the rate of water absorption to zero [25].

In the present experiments, agonists were selected which were relatively specific for their ability to stimulate a single class of receptors. The specificity of the agonists is also supported by some of the results of the present study, as will be noted. The addition of the beta agonist isoproterenol to the capillary perfusion solution resulted in a higher *Jv* than the control solution. The stimulating effect of isoproterenol was abolished when the beta antagonist propranolol was also added to the capillary solution. The addition of the alpha receptor blocker, phentolamine, did not block the effects of isoproterenol on water absorption. Propranolol alone had no effect on *Jv*. In an analogous manner, the alpha agonist phenylephrine also stimulated water absorption, an effect inhibited by phentolamine, but not by the beta antagonist propranolol. Phentolamine alone did not influence *Jv*. The results of these investigations would seem to support the conclusions that, in the superficial proximal convoluted tubule of the rat and under the conditions of study, the alpha and beta agonists enhance water absorption.

The concentrations of drugs used in some of these studies exceed concentrations in plasma [10]. However, since nerve endings are known to abut on the peritubular capillaries themselves, the local tissue concentrations under normal circumstances may exceed plasma concentration [24]. Moreover, the capillary environment in the present studies was artificial and, conceivably, the relative affinities of the agonists for their receptors may not accurately reflect that occurring when blood is flowing in the peritubular capillary circulation. For these latter reasons, the findings that neither the alpha nor beta antagonists alone affected *Jv*, should not be interpreted to indicate that, under conditions where capillary blood flow is intact, catecholamines have no basal influence on the measured rates of water absorption.

A large number of prior studies have directly or indirectly examined the role of catecholamines in the renal handling of sodium by the kidney. Given the diverse physiologic actions of these compounds, it is often difficult or impossible to determine whether the alterations in the urinary excretion of sodium are a direct action of these agents on renal sodium transport. The reader is referred to excellent reviews on this subject [11, 19]. We wish to highlight, however, a few studies which we believe bear directly on the results of the present investigations. Renal nerves have been demonstrated to exist and end along the peritubular capillary network and, possibly, in the renal tubular cells themselves [2, 3]. Recent studies using isolated anti-basement vesicles have indicated the presence of beta-receptors [13]. These results, then, suggest that the catecholamines may arrive at the antiluminal border of the cell by capillary blood flow or may be generated locally by renal nerves. Receptors for catecholamines exist at this border of the cell, raising the possibility of a functional correlate. Besarab et al. utilized the isolated perfused kidney technique and suggested that both alpha and beta agonists reduce the urinary excretion of sodium and enhance its rate of reabsorption [6]. These studies, however, do not permit the localization of the nephron site of action, nor is the possibility excluded that the agonist may have stimulated or inhibited some other controlling mechanism for sodium reabsorption. In studies in both the rat and the dog, denervation results in a decrease in tissue catecholamine concentration and a decrease in sodium reabsorption in the proximal tubule [5, 27, 29]. Stimulation of the renal nerves results in enhanced reabsorption [28]. In both circumstances, the effect appears to be direct and cannot be explained by alterations in filtration rate or renal blood flow. In a recent set of studies related to the question of effects of catecholamines on proximal tubular water absorption, Bello-Reuss has employed the techniques of isolated *in vitro* microperfusion of rabbit tubules [4]. In the presence of an alpha blocker, the addition of isoproterenol to the bathing solution enhanced *Jv*. The enhancing effect of isoproterenol was abolished by propranolol. The findings of the present studies in the rat are consistent with these results. Although not definitive, alpha adrenergic stimulation resulted in a small decrease in *Jv* in the rabbit tubule, a finding at variance with the present results. The present results in the rat, however, agree with the findings of Chan in the rat [9]. Using an analogous experimental design, this investigator reported that the addition of norepinephrine to the capillary perfusion solution enhanced water absorption, and that this response was inhibited by phenoxybenzamine. It is possible, therefore, that the differences in the responses to alpha agonists between the rat and the rabbit represent species differences.

Despite the demonstration of an effect of catecholamines on proximal tubular water absorption, it is important to recognize that the effect of these agents on sodium excretion in the intact animal may differ from those observed under highly artificial experimental circumstances. Changes in cardiac function, vascular tone, concentration of catecholamine-stimulated hormones, renal blood flow and blood flow distribution, and changes in glomerular filtration rate (GFR) may have overriding influences on the rates of sodium reabsorption in the proximal tubule. Moreover, it remains possible, and recent evidence would suggest, that catecholamines may have actions on other nephron sites along the tubule [17].

The mechanism by which isoproterenol and phenylephrine enhance *Jv* is not known with certainty. In some tissues, catecholamines are known to stimulate adenlyate cyclase and result in the generation of cyclic adenosine monophosphate [20, 22]. Chabardes et al., however, have recently reported that isoproterenol does not stimulate cyclic adenosine monophosphate production in dissected segments of the rabbit proximal tubule [8]. In addition, prior evidence would indicate that cyclic adenosine monophosphate inhibits water absorption in the proximal tubule [1]. In some tissues, catecholamines increase the activity of Na^+-K^+ ATPase, either directly or by reducing the availability of naturally occurring inhibitors of the enzyme [7, 13, 23, 27]. We are unaware of any direct information of this type in renal tissue. In the present studies, the luminal perfusion solution did not contain bicarbonate or organic solutes, and no chloride gradient was imposed across the cell. It seems reasonable to suggest, therefore, that *Jv* was determined by the active transport of sodium. Thus, if the catecholamines increased the activity of the Na^+-K^+ ATPase pump at the basolateral membrane, *Jv* would be increased. Other explanations, however, are possible. Clearly, additional studies will be required to determine the mechanisms by which catecholamines stimulate water absorption.

In summary, the present studies indicate that the alpha agonist phenylephrine and the beta agonist isoproterenol enhance water absorption in the rat proximal convoluted tubule. These effects are relatively specific, as demonstrated by the antagonist studies. Under the conditions of study, these

catecholamines appear to have a direct effect on primary active sodium transport distinct from the systemic effects of these agents.

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