Protein-tyrosine Phosphatase Reduces the Number of Apical Small Conductance K⁺ Channels in the Rat Cortical Collecting Duct*

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Previous studies have demonstrated that an increase in the activity of protein-tyrosine kinase (PTK) is involved in the down-regulation of the activity of apical small conductance K⁺ (SK) channels in the cortical collecting duct (CCD) from rats on a K⁺-deficient diet (1). We used the patch clamp technique to investigate the role of protein-tyrosine phosphatase (PTP) in the regulation of the activity of SK channels in the CCD from rats on a high K⁺ diet. Western blot analysis indicated that PTP-1D is expressed in the renal cortex. Application of 1 μM phenylarsine oxide (PAO) or 1 mM benzylphosphonic acid, agents that inhibit PTP, reversibly reduced channel activity by 95%. Pretreatment of CCDs with PAO for 30 min decreased the mean NP, reversibly from control value 3.20 to 0.40. Addition of 1 μM herbimycin A, an inhibitor of PTK, had no significant effect on channel activity in the CCDs from rats on a high K⁺ diet. However, herbimycin A abolished the inhibitory effect of PAO, indicating that the effect of PAK is the result of interaction between PTK and PTP. Addition of brefeldin A, an agent that blocks protein trafficking from Golgi complex to the membrane, had no effect on channel activity. Moreover, application of colchicine, a microtubule inhibitor, or paclitaxel, a microtubule stabilizer, had no effect on channel activity. In contrast, PAO still reduced channel activity in the presence of brefeldin A, colchicine, or paclitaxel. Furthermore, the effect of PAO on channel activity was absent when the tubules were bathed in 16% sucrose-containing bath solution or treated with concanavalin A. We conclude that PTP is involved in the regulation of the activity of SK channels and that inhibition of PTP may facilitate the internalization of the SK channels.

The CCD plays a key role in the regulation of K⁺ secretion. K⁺ secretion occurs by a two-step process; K⁺ enters the cell across the basolateral membrane by Na-k⁺-ATPase and exits the cell across the apical membrane through apical secretory K⁺ channels (2). It is generally believed that the SK channels provide the major pathway for K⁺ across the apical membrane (2–6). Aldosterone and vasopressin play an important role in the regulation of K⁺ secretion (2). The effect of aldosterone on K⁺ secretion may be indirect and most likely results from an increase in an electrochemical driving force for K⁺ across the apical membrane as well as from stimulation of Na-K-ATPase (3, 7, 8). In addition to aldosterone, dietary intake of K⁺ regulates K⁺ secretion; high K⁺ intake increases whereas low K⁺ intake decreases urinary K⁺ secretion (9). The effect of the dietary K⁺ intake on K⁺ secretion is achieved partially by changing the number of the apical SK channels (7, 8). The effect of high K⁺ intake on the number of secretory K⁺ channels is not mediated by aldosterone because the number of SK channels is not increased in rats infused with aldosterone or on a low sodium diet, a maneuver that increases aldosterone secretion (8). Thus, it is possible that an aldosterone-independent pathway mediates the effect of dietary intake of K⁺.

We have previously demonstrated that the number of SK channels decreased in rats on a K⁺-deficient diet (1). Additionally, we have found that the expression and enzyme activity of c-Src increased in the kidney of animals on a K⁺-deficient diet. Moreover, inhibition of PTK increased the number of the SK channels in the CCD from rats on a K⁺-deficient diet. This suggests that an increase in PTK activity may be partially responsible for the down-regulation of the SK channels in the CCD from animals on a K⁺-deficient diet. Since tyrosine phosphorylation is determined by PTK and by PTP (10), it is conceivable that PTP should also be involved in the regulation of the number of the apical SK channels.

In this study, we present novel results demonstrating that inhibiting PTP reduces the number of the apical SK channels in the CCD obtained from rats on a high K⁺ diet. The effect of inhibiting PTP on channel activity is the result of increasing the internalization of the SK channels from the apical membrane of the CCD.

EXPERIMENTAL PROCEDURES

Preparation of CCDs—Pathogen-free Sprague-Dawley rats of either sex (5 weeks) were used in the experiments and were purchased from Taconic Farms, Inc. (Germantown, NY). The animals were put on a high K⁺ diet (w/w, 10%) (Harlan Teklad, Madison, WI) for 10–14 days before use. The weight of the animals used for experiments was between 100 and 120 g. Rats were killed by cervical dislocation, and kidneys were removed immediately. Several thin slices of the kidney (1–1.5 mm) were cut and placed on an ice-cold Ringer solution until dissection. The dissection was carried out at room temperature, and two watch-make forceps were used to isolate the single CCD. To immobilize the tubules, we placed them on a 5 × 5-mm coverglass coated with Cell-Tak (Becton Dickinson Inc., Bedford, MA) and then transferred them to a chamber (1000 μl) mounted on an inverted Nikon microscope. The CCDs were superfused with Heps-buffered NaCl solution, and the temperature of the chamber was maintained at 37 ± 1 °C by circulating warm water surrounding the chamber. The CCD was cut open with a sharpened micropipette to expose the apical membrane.

Patch Clamp Technique—An Axon200A patch clamp amplifier was used to record channel current. The current was low pass-filtered at 1 kHz by an eight-pole Bessel filter (902LPF, Frequency Devices, Haverhill, MA) and digitized at a sampling rate of 44 kHz by a VR-10B digital data recorder and stored on videotape (Hitachi FX600). For analysis, data stored on the tape were collected to an IBM-compatible

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§ The abbreviations used are: CCD, cortical collecting duct; PAO, phenylarsine oxide; PTK, protein-tyrosine kinase; PTP, protein-tyrosine phosphatase; SK, small conductance K⁺.
Pentium computer (Gateway 2000) at a rate of 4 KHz and analyzed using the pClamp software system 6.04 (Axon Instruments, Burlington, MA). Channel activity was defined as

\[ N_{Po} = \sum (t_1 + t_2 + \ldots + t_n) \quad (\text{Eq. 1}) \]

t is the fractional open time spent at each of the observed current levels. The slope conductance of the channel was calculated by measurement of K\(^+\) current at several membrane potentials.

**Western Blot**—Protein samples extracted from the kidney cortex were separated by electrophoresis on 8% SDS-polyacrylamide gels and transferred to nitrocellulose membranes. The membranes were blocked with 10% nonfat dry milk in Tris-buffered saline, rinsed, and washed with 1% milk in Tween-Tris-buffered saline. The PTP-1D, PTP-1B, and PTP-1C antibodies were obtained from Transduction Laboratories (Lexington, KY) and were diluted at 1:1000. The c-Src antibody was obtained from Santa Cruz Biotechnology (Santa Cruz, CA) and was diluted at 1:1000. The protein concentration used for immunoblot was 50 \( \mu \)g. The PTPs and c-Src were detected and quantitatively analyzed by fluorescence phosphorimaging.

**Experimental Solution and Statistics**—The pipette solution contained (in mM) 140 KCl, 1.8 MgCl\(_2\), and 10 HEPES (pH = 7.4). The bath solution for cell-attached patches was composed of (in mM) 140 NaCl, 5 KCl, 1.8 CaCl\(_2\), 1.8 MgCl\(_2\), 5 glucose, and 10 HEPES (pH = 7.4). For inside-out patches, the bath solution had the same composition as that in cell-attached except that free Ca\(^{2+}\) was reduced to 100 nm. Herbimycin A and benzylphosphonic acid-(AM)\(_2\) were purchased from Biomol (Plymouth Meeting, PA). Phenylarsine oxide (PAO), brefeldin A, paclitaxel (Taxol), and colchicine were obtained from Sigma. PAO and herbimycin A were dissolved in the Me\(_2\)SO solution, whereas colchicine and Taxol were dissolved in ethanol and methanol, respectively. The final concentrations of Me\(_2\)SO, ethanol, or methanol were less than 0.1% and had no effect on channel activity.

Data are shown as mean \( \pm \) S.E., and paired or unpaired Student’s t test was used to determine the significance between the two groups. Statistical significance was taken as \( p < 0.05 \).

**RESULTS**

We used Western blot analysis to detect the expression of c-Src, PTP-1B, PTP-1C, and PTP-1D in the renal cortex obtained from rats on a normal chow and on a high K\(^+\) diet (7 days). Fig. 1 is a representative Western blot showing the presence of c-Src (\( a \)) and PTP-1D (\( b \)) in the renal cortex. It is apparent that the expression of c-Src was significantly lower (51 ± 5% of the control, \( n = 5 \)) in the renal cortex from rats on a high K\(^+\) diet than that on a normal diet. However, the expression level of PTP-1D in the renal cortex was not significantly different between the two groups. We failed to identify the expression of PTP-1B and PTP-1C in the renal cortex (data not shown).

To explore the role of PTP in the regulation of apical SK channels in the CCD, we studied the effect of PAO, an inhibitor of PTP (11–13), on the activity of SK channels in the tubules from rats on a high K\(^+\) diet. Fig. 2 is a representative channel recording showing the effect of PAO on channel activity in a cell-attached patch. Addition of 1 mM PAO reduced channel activity by 95 ± 8% (\( n = 30 \)) within 10–15 min. The effect of PAO was reversible because removal of PAO restored the channel activity to the control level within 30 min. To exclude the possibility that PAO was a channel blocker, we examined the effect of PAO on channel activity in inside-out patches and found that PAO had no effect on SK channels in inside-out patches (data not shown). Moreover, the effect of PAO was mimicked by 1 mM benzylphosphonic acid-(AM)\(_2\), another inhibitor of PTP. Addition of benzylphosphonic acid reduced the channel activity by 94 ± 8% (\( n = 5 \)). This indicated that the effect of PTP was the result of inhibition of PTP. Fig. 3 summarizes the results obtained from experiments in which the effect of 1 mM PAO, 1 mM benzylphosphonic acid-(AM)\(_2\) on the apical SK channels was investigated in the CCD from rats on a high K\(^+\) diet. Inhibition of PTP reduced channel activity by 63 ± 6% and 95 ± 5% within 10 and 15 min, respectively (\( n = 35 \)). In addition, we examined the \( N_{Po} \) of SK channels per patch under control conditions and in the presence of PAO. The mean \( N_{Po} \) of the SK channels was 3.2 ± 0.2 (\( n = 87 \)) under control conditions in the CCD from rats on a high K\(^+\) diet. Pretreatment of the CCDs with 1 mM PAO for 30 min reduced the mean \( N_{Po} \) to 0.4 ± 0.1 (\( n = 42 \)) (Fig. 4). The mean \( N_{Po} \) returned to 2.6 ± 0.2 (\( n = 32 \)) 30 min after removal of PAO (Fig. 4). This further suggested that the effect of PAO is reversible. The PAO-induced decrease in \( N_{Po} \) is most likely the result of reducing the number of the functional SK channels rather than decreasing the channel open probability because the \( P_o \) of the SK channels was the same (control, 0.92, PAO, 0.92) (data not shown).

After establishing that inhibition of PTP reduced the number of the SK channels, we tested the possibility that the effect of inhibition of PTP was the result of decreasing the insertion of the SK channel into the cell membrane. Thus, we investigated the effect of brefeldin A, an agent that blocks the protein trafficking from Golgi complex to the cell membrane (14). Brefeldin A has been shown to decrease the insertion of epithelial sodium channels expressed in oocytes (15). However,
addition of 5 μM brefeldin A failed to decrease channel activity in any 10 patches within 30 min (Fig. 5A). In contrast, addition of 1 mM PAO reduced the activity of the SK channels by 96 ± 7% (n = 7) in the same tubules in which brefeldin A had no effect on channel activity (Fig. 5, A and B). Therefore, it is unlikely that the effect of PAO resulted from inhibiting a brefeldin A-sensitive trafficking pathway. Since the insertion of SK channels may take place by an endoplasmic reticulum-independent and brefeldin A-insensitive recycling pathway, we extended our study to examine the effects of colchicine and Taxol, agents which inhibit and freeze microtubule, respectively. Fig. 6 summarizes results from five experiments investigating the effect of 5 μM colchicine or 10 μM Taxol on the channel activity. It is apparent that neither colchicine nor Taxol had a significant effect on channel activity within 15–20 min. In contrast, PAO still reduced the channel activity by 94 ± 9% in the presence of colchicine and 95 ± 9% in the presence of Taxol. We next examined the possibility that inhibition of PTP might facilitate the internalization of the SK channels from cell membranes. We investigated the effect of PAO in the presence of 8% or 16% sucrose, which blocks the endocytosis of the cell membrane (16, 17). Fig. 7 summarizes the results of experiments in which the effect of 1 μM PAO on the activity of the SK channels was examined in the presence of 8% and 16% sucrose, respectively. From inspection of Fig. 7, it is clear that the effect of PAO was significantly attenuated (70 ± 6% of the control, n = 7) in the presence of 8% sucrose-containing bath solution and completely abolished in the 16% sucrose-containing bath solution (95 ± 5% of the control value, n = 7). The notion that the PAO-induced decrease in NPo may be induced by increasing the internalization of the SK channels, is further supported by
experiments in which the effect of PAO on channel activity was examined after the tubules were treated with concanavalin A, an agent that has been shown to block the endocytosis of receptors (16–18). Addition of concanavalin A had no significant effect on channel activity (data not shown). However, the effect of PAO was abolished in the presence of concanavalin A (Fig. 8) and the \( N_{\text{Po}} \) in the presence of PAO and concanavalin A was 96 ± 6% of the control value (\( n = 7 \)).

After establishing that inhibition of PTP may facilitate the internalization of the SK channels from the cell membranes, we investigated the possibility that the effect of PAO was the result of enhancing the PTK-induced phosphorylation process. Accordingly, the activity of the SK channels was diminished by a PTK-dependent pathway. We studied the effect of PAO after the CCDs were treated with 1 \( \mu \)M herbimycin A. We confirmed the previous finding that addition of herbimycin A had no significant effect on channel activity in the CCD from rats on a high K\(^+\) diet (1). However, pretreatment of CCDs with herbimycin A significantly attenuated the effect of PAO. Fig. 9 summarizes the results from eight experiments in which the effect of PAO was examined in the presence of herbimycin A. It is clear that blockade of PTK abolished the PAO-induced decrease in channel activity since PAO reduced the channel activity only by a modest 25 ± 3% (\( n = 10 \)), a value that was significantly smaller than that in the absence of herbimycin A.

**DISCUSSION**

Two types of K\(^+\) channels, Ca\(^{2+}\)-activated maxi-K\(^+\) and SK channels, are present in the CCD. The SK channels are mainly responsible for K\(^+\) secretion in the CCD (2–4, 7, 19). This conclusion is based on the observation that SK channels have high channel open probability and channel density. In addition, the maxi-K\(^+\) channels have been found to be expressed mainly in intercalated cells, which are not involved in K\(^+\) secretion (20). It is generally believed that ROMK channels are the key components of the native SK channels since the biophysical properties of the SK channels are the same as those of ROMK channels (2, 3, 21–23).

Our previous study and others have demonstrated that the number of the apical SK channels increases by 1–2-fold in the CCDs obtained from rats on a high K\(^+\) diet (7, 8). It has been suggested that the effect of high K\(^+\) intake on the SK channels...
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was not directly mediated by aldosterone since infusion of aldosterone failed to increase channel activity. This notion is also suggested by previous renal clearance studies in which K⁺ secretion was partially restored in adrenalectomized animals receiving basal aldosterone levels and a high K⁺ intake (24). In contrast, K⁺ secretion was still blunted in animals receiving only high levels of aldosterone (24). Therefore, it is possible that aldosterone is not directly responsible for mediating the effect of dietary K⁺ intake on the number of SK channels. In addition, high K⁺ intake-induced increase in the channel number was not the result of an increase in the transcription level. Frindt et al. (25) have used in situ hybridization to demonstrate that the level of mRNA encoding ROMK channel is the same between the CCDs from rats on normal diet and those on a high K⁺ diet. This suggests that the effect of dietary K⁺ intake on the channel activity is achieved at the post-translational level.

We have shown previously that the protein expression of c-Src increased significantly in the kidney from animals on a K⁺-deficient diet in comparison with those on a high K⁺ diet (1). Moreover, inhibition of PTK increased the number of the apical SK channels in the CCDs from rats on a K⁺-deficient diet. In contrast, inhibition of PTK had no significant effect on channel activity in tubules from animals on a high K⁺ diet (1). We have postulated that an increase in PTK activity is involved in suppressing the channel activity in the CCDs from rats on a K⁺-deficient diet. An increase in PTK activity is expected to enhance the PTK-induced tyrosine phosphorylation. Since tyrosine phosphorylation is controlled by both PTK and PTP, it is conceivable that the PTP should also play an important role in the regulation of the number of the apical SK channels. PTP1D is an Src homology 2 domain containing PTPs and is ubiquitously distributed in a variety of tissues (26). Our Western blot analysis demonstrated that the PTP-1D is expressed in the renal cortex while no detectable level of PTP-1C and PTP-1B is present in the kidney. The expression level of PTP-1D in the renal cortex from rats on a high K⁺ diet is not significantly different from those on a control diet. Since the activity of PTP-1D in the tubules from rats on different K⁺ diets was not assessed, it is not known whether the enzyme activity of PTP-1D is higher in the kidney from rats on a high K⁺ diet than those on a normal diet. However, we confirmed the previous finding that c-Src expression was significantly lower in the kidney from rats on a high K⁺ diet than those on a control diet or on a K⁺-deficient diet. In addition, we have previously reported that the enzyme activity of c-Src decreased significantly in the kidney obtained from rats on a high K⁺ diet (1). Thus, it is conceivable that a decrease in PTK activity should increase the tyrosine dephosphorylation process in the tubules from rats on a high K⁺ diet.

Two lines of evidence strongly suggest that tyrosine phosphorylation and dephosphorylation are involved in the regulation of the number of the apical SK channels. First, inhibition of PTP reversibly reduced the number of the functional SK channels in the CCD from rats on a high K⁺ diet. In contrast, inhibition of PTK increased the channel activity in the tubules from rats on a K⁺-deficient diet. Second, the effect of PAO on channel activity was completely abolished by inhibition of tyrosine kinases, although application of herbimycin A alone had no effect on channel activity in the tubules from rats on a high K⁺ diet. The absence of response to herbimycin A of the CCD from rats on a high K⁺ diet may be due to the fact that PTK-induced inhibition is suppressed by PTP because of low activity of c-Src. This notion was also suggested by the present observation that the inhibitory effect of PTK on channel activity could be demonstrated when PTP activity was blocked by PAO. Thus, the number of the functional SK channels is determined by the interaction between PTP and PTK.

The mechanism by which inhibition of PTP reduced the number of the apical SK channels is not known. There are at least three possibilities by which PTP could regulate the channel activity. First, the SK channel could be phosphorylated by PTK. Thus, the phosphorylation of tyrosine residue inhibits, whereas the dephosphorylation increases, the channel activity. Indeed, the tyrosine phosphorylation/dephosphorylation regulates the Ca²⁺-activated K⁺ channels (27), delayed rectifier K⁺ channels (28), and voltage-gated K⁺ channels (K₁,1.3) (29). However, the previous finding that application of exogenously active c-Src failed to inhibit the SK channel did not support the possibility that direct tyrosine phosphorylation/dephosphorylation regulates the activity of the SK channels in the CCD (1). The second possibility is that inhibition of PTP may block the insertion of the SK channels through a recycling or a secretory pathway and, accordingly, reduce the number of SK channels in the apical membrane. However, this possibility was not supported by observations that addition of brefeldin A, colchicine, and Taxol had no effect on channel activity. In contrast, PAO reduced the number of the SK channels in the same CCD in which other agents failed to affect channel activity. Thus, although we could not completely exclude the second possibility, it is unlikely that a decrease in channel insertion is mainly responsible for mediating the effect of inhibiting PTP in the present study. The third possibility is that inhibition of PTP increased the internalization of the SK channels. This notion was supported by the observations that the effect of PAO was abolished by a hypertonc bath solution as well as by concanavalin A treatment. Hypertonic solution has been shown to inhibit the membrane endocytosis (16, 17) and concanavalin A has been shown to block the internalization of G protein-coupled receptors by binding to glycoproteins in the cell membrane. Therefore, our experimental results strongly suggest that the effect of inhibition of PTP on the internalization of the SK channels is an important mechanism by which inhibiting PTP reduces the number of the SK channels in the CCD.

A large body of evidence indicates that PTK and PTP are involved in the regulation of endocytic internalization of a variety of receptors and transporters. Overexpression of c-Src has been shown to enhance the internalization of epidermal growth factor receptor (30). It was reported that β₂-adrenergic receptor-mediated ERK activation requires the receptor endocytosis, which is initiated by binding c-Src to β-arrestin (16, 31). PTKs are involved in the regulation of the endocytic rate of glucose transporter (GLUT4) through tyrosine phosphorylation of dynamin (12, 32).

The mechanism by which PTK and PTP regulate channel trafficking is not known. It has been shown that Src interacts with dynamin and synapsin in neuronal cells (33) and cytoskeleton-binding proteins (34). This suggests that PTK and PTP may regulate the membrane protein trafficking by tyrosine phosphorylation/dephosphorylation of cytoskeleton-binding proteins as well as by vesicle transport proteins (34).

Our experimental results have demonstrated that enhancing tyrosine phosphorylation by inhibiting PTP decreases, whereas augmentation of tyrosine dephosphorylation by inhibiting PTK increases, the number of the SK channels in the CCD. We have further demonstrated that the level of PTK, such as c-Src, is up-regulated in the kidneys from rats on a K⁺-deficient diet. In contrast, the level of PTK is diminished in the kidney from a high K⁺ diet (1). However, it is not clear how dietary intake of K⁺ affects the PTK activity. The intracellular acidosis has been shown to stimulate the activity of c-Src (35) and hypokalemia is known to induce the intracellular acidosis. Thus, it is possible that intracellular pH may mediate the effect of dietary intake
of K+ on PTK activity. Thus, we need further experiments to explore this possibility.

We conclude that the interaction of PTK with PTP plays a key role in the regulation of the number of the secretory K+ channels. Stimulation of PTK or inhibition of PTP decreases the number of the functional SK channels in the CCD, and the effect may be the result of enhancing the internalization of the SK channels.

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