Aquaporin-1 (AQP1) is a water channel that is induced by hypertonicity. The present study was undertaken to clarify the osmoregulation mechanism of AQP1 in renal medullary cells. In cultured mouse medullary (mIMCD-3) cells, AQP1 expression was significantly induced by hypertonic treatment with impermeable solutes, whereas urea had no effect on AQP1 expression. This result indicates the requirement of a hypertonic gradient. Hypertonicity activated ERK, p38 kinase, and JNK in mIMCD-3 cells. Furthermore, all three MAPKs were phosphorylated by the upstream activation of MEK1/2, MKK3/6, and M KK4, respectively. The treatments with MEK inhibitor U0126, p38 kinase inhibitor SB203580, and JNK inhibitor SP600125 significantly attenuated hypertonicity-induced AQP1 expression in mIMCD-3 cells. In addition, hypertonicity-induced AQP1 expression was significantly reduced by both the dominant-negative mutants of JNK1- and JNK2-expressing mIMCD-3 cells. NaCl-inducible activity of AQP1 promoter, which contains a hypertonicity response element, was attenuated in the presence of U0126, SB203580, and SP600125 in a dose-dependent manner and was also significantly reduced by the dominant-negative mutants of JNK1 and JNK2. These data demonstrate that the activation of ERK, p38 kinase, and JNK pathways and the hypertonicity response element in the AQP1 promoter are involved in hypertonicity-induced AQP1 expression in mIMCD-3 cells.
Functional analysis of the AQP1 promoter containing the HRE sequence also demonstrated that the AQP1 promoter activity was stimulated by hypertonicity and regulated by MAPK pathways.

EXPERIMENTAL PROCEDURES

Cell Line and Culture Condition—mIMCD-3 cells used in this study were obtained from the American Type Culture Collection. Cells were cultured at 37 °C and 5% CO₂ in Dulbecco’s modified Eagle’s/12 medium supplemented with 10% fetal bovine serum.

Reverse Transcription-PCR—Total RNA was isolated from mIMCD-3 cells using a TRIzol reagent (Invitrogen). Two micrograms of total RNA was reverse-transcribed and then directly amplified by PCR using two sets of primers: AQP1 sense primer, 5'-CGGGCCTGTCACTGATCATCATACGTGCACTCCA-3' (nucleotides 276–301); AQP1 antisense primer, 5'-CCC-AATGGAACGCCACCCACAGGAAA-3' (nucleotides 632–666); glyceraldehyde-3-phosphate dehydrogenase sense primer, 5'-ATGGGAAAGTTTGTCATACACGGGAA-3' (nucleotides 184–208); glyceraldehyde-3-phosphate dehydrogenase antisense primer, 5'-TGGCAAGTTTCTCCAGGGCGGACGT-3' (nucleotides 729–753). The PCR amplification was performed for 30 cycles as follows: 94 °C for 30 s, 60 °C for 60 s, and 72 °C for 60 s. The PCR products were analyzed on a 2% agarose gel and visualized by ethidium bromide staining.

Immunoblot Analysis—mIMCD-3 cells grown on 6-cm dishes were washed with ice-cold phosphate-buffered saline and suspended with 10 mM Tris-HCl, pH 7.5, containing 200 mM sucrose and homogenized by a Tenbroeck homogenizer. The homogenate was centrifuged at 15000 × g for 10 min at 4 °C. The supernatant was collected, and protein concentration was measured using the Bradford protein assay method (Bio-Rad protein assay kit). Protein (10 μg) from the cell extract was resolved on a 12% SDS-polyacrylamide gel and transferred to a polyvinylidene fluoride membrane. The membrane was incubated with a rabbit polyclonal anti-human AQP1 antibody for 1 h. As a protein loading control, the membrane was also incubated with anti-β-actin antibody (Sigma). For the analysis of MAPK signaling pathways, cells were lysed with ice-cold lysis buffer (50 mM β-glycerophosphate, pH 7.2, 0.5% Triton X-100, 0.1 mM sodium vanadate, 2 mM MGCl₂, 1 mM EGTA, 1 mM dithiotreitol). The lysates were resolved on a 12% SDS-polyacrylamide gel and transferred to a polyvinylidene fluoride membrane. The membrane was incubated with antibodies to phospho-ERK, ERK, phospho-p38, p38, phospho-JNK, JNK, phospho-mitogen-activated ERK kinase (MEK) 1/2, MEK1/2, phospho-MAPK kinase (MKK) 3/6, MKK3, phospho-MKK4 (Cell Signaling Technology Inc., Beverly, MA), or MKK4 (StressGen, Victoria, British Columbia, Canada). After washing, the membrane was incubated with anti-rabbit IgG horseradish peroxidase secondary antibody (Amersham Biosciences). The immuno-reactive bands were visualized by enhanced chemiluminescence method (PerkinElmer Life Sciences).

Plasmid Construction for Reporter Assay—The plasmid pCAT-basic (Promega, Madison, WI) was used to examine the promoter activity of the 5'-flanking region in the human AQP1 gene (17, 20, 21). The AQP1 promoter construct (–54/–22) (CP-54), which contains the HRE sequence, was generated by PCR and ligated into Hind III and XhoI sites of pCAT-basic vector. The sense primer corresponded to nucleotides –54 to –33 and contained an engineered Hind III restriction site. The antisense primer for amplification corresponded to nucleotides +23 to +4 and contained an engineered XhoI restriction site. The CAT construct was confirmed by sequence analysis.

Transient Transfections and CAT Assay—The transient transfection experiment was performed by the modification of previous reports (17, 20–22). mIMCD-3 cells were resuspended at 2 × 10⁵ cells/ml in Dulbecco’s modified Eagle’s/12 medium without serum and transfected by electroporation under 300 V at 500 microfarads in a 0.4-mm cuvette. Each transfection was performed with 10 μg of the AQP1 promoter-CAT construct (CP-54) and 5 μg of the plasmid pSV-β-galactosidase (Promega) on a total volume of 500 μl. After overnight incubation, cells were incubated with or without 100 mM NaCl. After a 48-h incubation, the cells were harvested, and cell extracts were isolated using the reporter lysis buffer (Promega). β-Galactosidase activity was measured in every experiment for normalization. CAT activity was measured using 3-thiordichloroacetlyl-1,1-4′-chlorophenyl (Amersham Biosciences) and the phase extraction method.

RESULTS

Hypertonicity-induced AQP1 Expression in mIMCD-3 Cells—A previous study demonstrated that AQP1 expression was induced by hypertonic medium supplemented with NaCl in mouse renal medullary (mIMCD-3) cells (16). To examine the hypertonic induction of AQP1 in mIMCD-3 cells, cells were incubated in medium supplemented with hyperosmotic agents (NaCl and urea) and impermeable osmotolytes (raffinose, glucose, sucrose, and sorbitol). After the treatment with hyperosmolar medium, cell lysates were immunoblotted by using anti-AQP1 antibody. AQP1 protein expression was increased by NaCl, raffinose, glucose, sucrose, and sorbitol but not urea (Fig. 1A). These data indicate that AQP1 induction by hypertonicity requires a hypertonic gradient. Next, to investigate the time course for hypertonic induction of AQP1 protein, mIMCD-3 cells were incubated in hypertonic medium by the addition of 100 mM NaCl. Samples were harvested at specific times for immunoblot analysis. As shown in Fig. 1B, AQP1 protein significantly increased by 12 h after exposure to hypertonic medium and peaked at 16–20 h.

To test the AQP1 induction in medium osmolality, cells were incubated in medium by the addition of NaCl, raffinose, or glucose with different hyperosmolality. A minimum addition of 50 mM NaCl, 100 mM raffinose, or 100 mM glucose to the medium was needed to increase AQP1 protein expression in mIMCD-3 cells, and stronger induction of AQP1 was obtained by the exposure to higher medium osmolality (Fig. 2). However, the addition of 200 mM raffinose to the medium showed much less AQP1 expression than that of 100 and 150 mM raffinose, because the cell viability significantly decreased at that condition. Taken together, these data indicate that AQP1 expression in mIMCD-3 cells is significantly increased in hypertonic condition in a time- and dose-dependent fashion.

Transcriptional and Post-transcriptional Regulations of Hypertonicity-induced AQP1 Expression in mIMCD-3 Cells—Hypertonicity-induced AQP1 expression may be caused by mRNA induction or stability or protein stability. To distinguish the mechanism, cells were pretreated with the RNA synthesis inhibitor actinomycin D or protein synthesis inhibitor cycloheximide and then incubated under isotonic or hypertonic condition. The expression levels of AQP1 mRNA and protein were examined by reverse transcription-PCR and immunoblot analysis, respectively. As shown in Fig. 3, pretreatment with actinomycin D or cycloheximide completely inhibited NaCl-induced AQP1 mRNA and protein expressions. These results suggest that both transcriptional and post-transcriptional regulations are required for AQP1 induction by hypertonicity.
Aquaporin-1 Induction by Hypertonicity

To determine whether MAPK-mediating signaling was involved in hypertonic induction of AQP1 in mIMCD-3 cells, antibodies specific for either the phosphorylated or total form of each of three MAPKs were used. Cells were treated with hypertonic condition containing 100 mM NaCl or 200 mM urea for 10 min, and then the phosphorylation of all three MAPKs were investigated by immunoblot analysis. NaCl significantly activated the ERK, p38 kinase, and JNK pathways in mIMCD-3 cells, whereas urea activated only the ERK pathway (Fig. 4). These data confirmed the results reported previously (18, 19).

Next, activation of MAPKs is mediated by MEK or MKKs. ERK is activated by MEK1 and MEK2, whereas p38 kinase is activated by MKK3 and MKK6, and JNK is activated by MKK4 (24–28). To further investigate the differential activation of MAPKs in mIMCD-3 cells in response to hypertonicity, the phosphorylation for the upstream activation of MAPKs was assessed using antibodies specific for the phosphorylated or total form of MEK1/2, MKK3/6, or MKK4. As shown in Fig. 4, NaCl activated the MEK1/2, MKK3/6, and MKK4 pathways, whereas urea activated only the MEK1/2 pathway. Thus, NaCl significantly stimulated the phosphorylation of all three sub-families of MAPKs in mIMCD-3 cells, but urea only the ERK phosphorylation.

Inhibition by MAPK Inhibitors on Hypertonicity-induced AQP1 Expression—To determine whether the activation of ERK, p38 kinase, and JNK was involved in the regulation of hypertonicity-induced AQP1 expression, a MEK inhibitor, U0126, a p38 kinase inhibitor, SB203580, and a novel specific JNK inhibitor, SP600125 (29, 30), were used. To investigate the specificity of each MAPK inhibitor, mIMCD-3 cells were pretreated with the different concentrations of U0126, SB203580, or SP600125, and then NaCl-induced ERK, p38 kinase, and JNK phosphorylations were analyzed by immunoblot. As shown in Fig. 5, all three MAPK inhibitors revealed the specific selectivity for other MAPKs within the range of a given concentration.

On the basis of the result in Fig. 5, we proceeded to assess the effect of MAPK inhibitors on NaCl-induced AQP1 protein expression. Cells were pretreated with each MAPK inhibitor and stimulated with NaCl. Cell lysates were analyzed by immunoblot. Results were normalized to expression of β-actin by densitometry of immunoblot (Fig. 6). NaCl-induced AQP1 expression was significantly blocked by U0126 (0.5–2.5 μM), SB203580 (0.5–2.5 μM), and SP600125 (2–10 μM). The treatment of a higher concentration with each MAPK inhibitor almost completely abolished NaCl-induced AQP1 expression (data not shown). Therefore, this result provides that AQP1 induction by hypertonicity requires the activation of ERK, p38 kinase, JNK pathway.

Inhibition by Dominant-negative Mutants of JNK Isoforms on Hypertonicity-induced AQP1 Expression—As an alternative approach to the involvement of JNK pathway on hypertonicity-
Aquaporin-1 Induction by Hypertonicity

Effect of MAPK inhibitors on NaCl-induced AQP1 expression in mIMCD-3 cells. After pretreated with U0126 (0.5, 1, or 2.5 μM), SB203580 (0.5, 1, or 2.5 μM), or SP600125 (2, 5, or 10 μM) for 30 min, cells were incubated in hypertonic medium containing 100 mM NaCl for 16 h. Cells were harvested, and total protein was analyzed by immunoblot. The membranes were also incubated with anti-β-actin antibody as a protein loading control in immunoblot. Each protein blot was analyzed by densitometry. AQP1 expression in 100 mM NaCl was assigned as 100%. Values represent the mean ± S.E. of five independent sets of experiments.

Effect of Potent ERK Stimulators on AQP1 Expression—Our results demonstrated that both NaCl and urea activated the ERK pathway. To determine whether the ERK activation is sufficient to induce AQP1 expression, arginine vasopressin, phorbol-12-myristate 13-acetate (PMA), or ionomycin (10 or 100 nM) for 10 min. Cells were harvested, and total protein was analyzed by immunoblot. Transfection efficiency to each experiment was determined by β-galactosidase activity. Each protein blot was analyzed by densitometry. AQP1 expression in 100 mM NaCl was assigned as 100%. Values represent the mean ± S.E. of three independent sets of experiments.

Effect of dominant-negative mutants of JNK isoforms on NaCl-induced AQP1 expression in mIMCD-3 cells. Cells were cotransfected with the dominant-negative mutants of JNK1 (JNK1-DN) or JNK2 (JNK2-DN) and pSV-β-galactosidase plasmids followed by treatment without or with 100 mM NaCl for 16 h. Cells were harvested, and total protein was analyzed by immunoblot. The membranes were also incubated with anti-β-actin antibody as a protein loading control in immunoblot. Transfection efficiency to each experiment was determined by β-galactosidase activity. Each protein blot was analyzed by densitometry. AQP1 expression in 100 mM NaCl was assigned as 100%. Values represent the mean ± S.E. of three independent sets of experiments.

Effect of Potent ERK Stimulators on AQP1 Expression—Our results demonstrated that both NaCl and urea activated the ERK pathway. To determine whether the ERK activation is sufficient to induce AQP1 expression, arginine vasopressin, phorbol-12-myristate 13-acetate (PMA), or ionomycin (10 or 100 nM) for 10 min. Cells were harvested, and total protein was analyzed by immunoblot. Transfection efficiency to each experiment was determined by β-galactosidase activity. Each protein blot was analyzed by densitometry. AQP1 expression in 100 mM NaCl was assigned as 100%. Values represent the mean ± S.E. of three independent sets of experiments. Similar results were obtained in the other two experiments.

DISCUSSION

In the book *From Fish to Philosopher*, Smith suggests that the capacity to conserve solute-free water excretion by activating a urinary concentrating mechanism was an important factor in the evolution from fresh water fishes to land-dwelling
Aquaporin-1 Induction by Hypertonicity

Aquaporin-1 (AQP1) is a water channel protein that plays a critical role in the urinary concentrating mechanism. Its induction by hypertonicity is mediated by the sequential activation of MAPK (mitogen-activated protein kinase) pathways. The induction of AQP1 gene by hypertonicity results from a critical factor in the urinary-concentrating mechanism (36), where hypertonicity activates all three MAPK signaling pathways (ERK, p38 kinase, and JNK) in mIMCD-3 cells. These signaling pathways are shown to mediate hypertonicity-induced AQP1 expression. Specifically, it was demonstrated that the blockade of any one of ERK, p38 kinase, or JNK signaling pathway by a specific inhibitor significantly reduced hypertonicity-induced AQP1 expression.

Hypertonicity activated all three MAPK signaling pathways (ERK, p38 kinase, and JNK) in mIMCD-3 cells. These signaling pathways were shown to mediate hypertonicity-induced AQP1 expression. Specifically, it was demonstrated that the blockade of any one of ERK, p38 kinase, or JNK signaling pathway by a specific inhibitor significantly reduced hypertonicity-induced AQP1 expression. U0126, SB203580, or SP600125 selectively inhibited the ERK, p38 kinase, or JNK pathway in a dose-dependent fashion, respectively. Interestingly, the partial ERK inhibition by SB203580 was observed at 5 μM but not 2.5 μM (data not shown). The maximal dose used in the present study was 2.5 μM. The similar observation was previously reported by Yang et al. (23) and suggested a potential interrelationship between ERK and p38 kinase activation. Although SP600125, which was recently identified as a specific JNK inhibitor, blocked the JNK activation in a dose-dependent fashion, it has been demonstrated that this inhibitor also had a partial p38 inhibition at a concentration higher than the maximal dose used in the present study (29). It should be noted that mIMCD-3 cells are highly sensitive to pharmacological inhibition of MAPK signaling pathway. Furthermore, we showed that the blockade of JNK pathway by dominant-negative mutants of JNK1 and JNK2 as an alternative approach significantly reduced hypertonicity-induced AQP1 expression. Taken together, our findings suggest that the activation of all three MAPK is indispensable for AQP1 induction by hypertonicity.

In mIMCD-3 cells, although NaCl activated the ERK, p38 kinase, and JNK, urea activated only the ERK. Although both NaCl and urea activated the ERK, only NaCl induced AQP1 expression. Furthermore, other ERK stimulators such as arginine vasopressin, phorbol-12-myristate 13-acetate, and ionomycin did not induce AQP1 expression under isotonic or hypertonic condition. These results indicate that the ERK activation is necessary but not sufficient to induce AQP1 expression by hypertonicity. A similar study also demonstrates that hypertonicity-induced AQP5 expression in mouse lung epithelial cells was mediated by the ERK-dependent pathway, although the ERK activation was not sufficient for AQP5 induction by hypertoncity (40). The detailed regulatory mechanism via MAPK pathways in hypertonicity-induced AQP1 expression is still unclear. Our data suggest that the three MAPKs may be necessary to phosphorylate transcriptional factors that bind to hypertonicity-responsive elements in the AQP1 gene.

The induction of AQP1 gene by hypertonicity results from a sequential MAPK-signaling pathway that directly affects the promoter region of AQP1 gene. Previous studies demonstrate that the genes of the sodium/myo-inositol cotransporter (41), sodium/chloride/betaine cotransporter (42), and aldose reductase (43) are up-regulated in response to hypertonicity. The tonicity responsive enhancer (TonE) consensus sequence present in these genes mediates the transcriptional stimulation. It seems that AQP1 induction by hypertoncity is mediated by an osmotic response element such as TonE. However, no TonE consensus sequence is present in a 1.8-kilobase AQP1 promoter region (20). We recently characterized a novel HRE in the AQP1 gene that is different from TonE consensus sequence (17). Using the AQP1 promoter-chloramphenicol acetyltrans-
ferase construct that contains the HRE sequence, we showed that any of three MAPK specific inhibitors and dominant-negative mutants of JNK1 or JNK2 significantly reduced NaCl-induced AQP1 promoter activity in a dose-response manner. In contrast, urea did not induce the promoter activity. In addition, the promoter activity was not affected by U0126, SB203580, or SP600125 under isotonic conditions. Thus, the novel HRE, which only responds to hypertonicity, is essential for the transcriptional regulation of hypertonicity-induced AQP1 expression. Identification of a transactivating HRE-binding protein that binds to the HRE should further elucidate the transcriptional regulation of hypertonicity-induced AQP1 expression.

In summary, the present results demonstrate that hypertonicity-induced AQP1 expression is regulated by ERK, p38 kinase, and JNK activation and the HRE in the AQP1 promoter. Inhibition of each MAPK pathway results in significant reduction of hypertonicity-induced AQP1 expression, indicating that all three MAPK signaling pathways are indispensable for AQP1 induction.

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REFERENCES
1. Agre, P., Preston, G. M., Smith, B. L., Jung, J. S., Raina, S., Moon, C., Guggino, W. B., and Nielsen, S. (1993) Am. J. Physiol. 265, F463–F476
2. Preston, G. M., and Agre, P. (1991) Proc. Natl. Acad. Sci. U. S. A. 88, 11110–11114
3. Preston, G. M., Carroll, T. P., Guggino, W. B., and Agre, P. (1992) Science 256, 385–387
4. Nielsen, S., Smith, B. L., Christensen, E. I., Knepper, M. A., and Agre, P. (1993) J. Cell Biol. 120, 371–383
5. Nielsen, S., Knepper, M. A., Kwon, T., and Frokiaer, J. (2001) Diseases of the Kidney and Urinary Tract. pp. 109–134, Lippincott Williams and Wilkins, Philadelphia, PA
6. Hoffmann, E. K., and Simonos, L. O. (1989) Physiol. Rev. 69, 315–382
7. Yancey, P. H., Clari, M. E., Hand, S. C., Bowlus, R. D., and Somero, G. N. (1982) Science 217, 1214–1222
8. Cohen, D., Wasserman, J., and Gallans, S. (1991) Am. J. Physiol. 261, C594–C601
9. Dasgupta, S., Hohnan, T. C., and Carper, D. (1992) Exp. Eye Res. 54, 461–470
10. Burg, M. B., Kwon, E. D., and Kultz, D. (1997) Annu. Rev. Physiol. 59, 437–455
11. Burg, M. B., Kwon, E. D., and Kultz, D. (1996) FASEB J. 10, 1588–1606
12. Fushimi, K., Uchida, S., Hara, Y., Hirata, Y., Marumo, F., and Sasaki, S. (1993) Nature 361, 549–552
13. Nielsen, S., DeGiovanni, S. R., Christensen, E. I., Knepper, M. A., and Harris, H. W. (1993) Proc. Natl. Acad. Sci. U. S. A. 90, 11663–11667
14. Unemishis, F., Verba, J. M., and Verkman, A. S. (2000) Biophys. J. 78, 1024–1035
15. Jeng, W., Cooper, D. R., Bittle, P., and Ramirez, G. (1999) Biochem. Biophys. Res. Commun. 266, 240–248
16. Jeng, W., Mathieson, I. M., Ibara, W., and Ramirez, G. (1998) Biochem. Biophys. Res. Commun. 245, 804–809
17. Unemishis, F., and Schrier, R. W. (2002) Biochem. Biophys. Res. Commun. 292, 771–775
18. Zhang, Z. and Cohen, D. M. (1996) Am. J. Physiol. 271, F1234-F1238
19. Berl, T., Srinwaradana, G., Ao, L., Butterfield, L. M., and Heasley, L. E. (1997) Am. J. Physiol. 272, F305-F311
20. Unemishis, F., and Verkman, A. S. (1998) Genomics 47, 341–349
21. Unemishis, F., and Schrier, R. W. (2002) Biochem. Biophys. Res. Commun. 303, 913–917
22. Unemishis, F., and Verkman, A. S. (1998) Genomics 50, 373–377
23. Yang, X.-Y., Zhang, Z., and Cohen, D. M. (1999) Am. J. Physiol. 277, F176–F185
24. Derijard, B., Raingeaud, J., Barrett, T., Wu, I. H., Han, J., Ulevitch, R. J., and Davis, R. J. (1995) Science 267, 682–685
25. Sanchez, I., Hughes, R. T., Mavros, B. J., Yee, K., Woodgett, J. R., Avruch, J., Kyrxiaki, J. M., and Zou, L. I. (1994) Nature 372, 794–798
26. Han, J., Wang, X., Jiang, Y., Ulevitch, R. J., and Lin, S. (1997) FEBS Lett. 403, 19–22
27. Han, J., Lee, J. D., Jiang, Y., Li, Z., Feng, L., and Ulevitch, R. J. (1996) J. Biol. Chem. 271, 2886–2891
28. Foltz, I. N., Gerl, R. E., Wieler, J. S., Luckach, M., Salmon, R. A., and Schrader, J. W. (1998) J. Biol. Chem. 273, 9344–9351
29. Bennett, B. L., Sasaki, D. T., Murray, B. W., O’Leary, E. C., Sakata, S. T., Xu, W., Leisten, J. C., Motivall, A., Pierce, S., Satoh, Y., Bhagwat, S. S., Manning, A. M., and Anderson, D. W. (2001) Proc. Natl. Acad. Sci. U. S. A. 98, 13681–13686
30. Han, Z., Boyle, D. L., Chang, L., Bennett, B., Karin, M., Yang, L., Manning, A. M., and Firestein, G. S. (2001) J. Clin. Invest. 108, 73–81
31. Smith, H. W. (1991) From Fish to Philosopher: The Story of Our Internal Environment, Little, Brown, and Co., Boston, MA
32. Schrier, R. W., Berl, T., and Anderson, R. J. (1979) Am. J. Physiol. 236, F321–F322
33. Berl, T., and Schrier, R. W. (1997) Renal and Electrolyte Disorders, 6th Ed., pp. 1–64, Lippincott-Raven, Philadelphia, PA
34. Elbashir, M., Selbo, A., Gilbert, S., Ishida, M., Barberis, C., Antaramian, A., Brahet, P., and Rosenthal, W. (1992) Nature 357, 333–335
35. Knepper, M. A., Wade, J. B., Terris, J., Kelbarger, C. A., Marples, D., Mandon, B., Chou, C.-L., Kissher, B. K., and Nielsen, S. (1996) Kidney Int. 49, 1712–1717
36. Nielsen, S., Chou, C.-L., Marples, D., Christensen, E. I., Kissher, B. K., and Knepper, M. A. (1995) Proc. Natl. Acad. Sci. U. S. A. 92, 1033–1037
37. Ma, T., Yang, B., Gillespie, A., Carlson, E. J., Epstein, C. J., and Verkman, A. S. (1998) J. Biol. Chem. 273, 18321–18326
38. King, L. S., Choi, M., Fernandez, P. C., Cartron, J. P., and Agre, P. (2001) N. Engl. J. Med. 345, 175–179
39. Leitch, V., Agre, P., and King, L. S. (2001) Proc. Natl. Acad. Sci. U. S. A. 98, 2894–2898
40. Hoffert, J. D., Leitch V., Agre, P., and King, L. S. (2000) J. Biol. Chem. 275, 9070–9077
41. Rim, J. S., Atta, M. G., Dahl, S. C., Berry, G. T., Handler, J. S., and Kwon, H. M. (1998) J. Biol. Chem. 273, 20615–20621
42. Miyakawa, H., Wou, S. K., Chen, P. C., Dahl, S. C., Handler, J. S., and Kwon, H. M. (1998) Am. J. Physiol. 274, F753–F761
43. Ferraris, J. D., Burg, M., Jung, K.-Y., Bedford, J. J., Burg, M. B., and Garcia-Perez, A. (1996) J. Biol. Chem. 271, 18318–18321

F. Unemishis and R. W. Schrier, unpublished observation.
Hypertonicity-induced Aquaporin-1 (AQP1) Expression Is Mediated by the Activation of MAPK Pathways and Hypertonicity-responsive Element in the AQP1 Gene

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