The rat renal urea transporter UT-A includes four isoforms. UT-A1, UT-A3, and UT-A4 are transcribed from a single initiation site at the 5'-end of the gene; a distinct internal initiation site is used for UT-A2 transcription. We cloned 1.3 kilobases (kb) of the 5'-flanking region upstream of the transcription start site of UT-A1, UT-A3, and UT-A4. This region contains three CCAAT sequences but lacks a TATA motif. A toxicity-responsive enhancer (TonE) was identified at -377bp. The 1.3-kb full fragment subcloned into pGL3 vector induced luciferase activity in Madin-Darby canine kidney cells and in mouse inner medullary collecting duct cells in isotonic medium. Luciferase activity was increased significantly in hypertonic medium, whereas deletion or mutation of the TonE sequence abolished this response. Electrophoretic mobility shift assay using the 5' UT-A TonE sequence as DNA probe showed formation of a specific DNA-protein complex with nuclear extracts from cells exposed to hypertonic medium and was weakly detectable in isotonic controls. A supershift in the mobility of the DNA-protein complex was observed with antiserum targeted to the TonE-binding protein (TonEBP). Co-transfection with dominant-negative TonEBP abolished the luciferase activity induced by the UT-A 1.3-kb construct under hypertonic and isotonic conditions. These data suggest that the TonE/TonEBP pathway mediates toxicity-responsive transcriptional regulation of UT-A1, UT-A3, and UT-A4 expression.

Excretion of highly concentrated urine allows mammals to eliminate waste products while preserving body water to survive on dry land. Urea, the major end product of protein metabolism, and sodium chloride contribute the most to maintaining high osmolality in the renal inner medulla. In this region of the kidney, high levels of urea are present in both intra- and extracellular compartments. Whereas urea can be viewed as an osmolyte, in high concentrations this solute is known to desta-

bilibize essential enzymatic activities (1, 2). In this respect, urea differs substantially from non-perturbing osmolytes such as polyols, methanolamines, and amino acids, which protect renal medullary cells during hypertonic stress (3–6). Information about the adaptation of renal medullary cells to urea has begun to emerge (7, 8). Epithelial cells of the inner medullary collecting duct (IMCD)1 and descending thin limbs of Henle’s loop are capable of rapidly transporting urea by a facilitated transport process that is mediated by the renal urea transporter UT-A. The mechanisms involved in regulating urea transport in these nephron segments are for the most part still unclear.

Four rat UT-A isoforms encoded by a single gene have been identified (9–11). UT-A1, UT-A3, and UT-A4 are transcribed from a transcription site at the 5'-end of the gene, whereas UT-A2 is transcribed from a distinct internal transcription start site (12). UT-A1, UT-A3, and UT-A4 are expressed in the highly hypertonic renal inner medulla whereas UT-A2 is normally expressed in the outer medulla. Additional variants of UT-A1, UT-A2, and UT-A3, referred to as UT-A1b, UT-A2b, and UT-A3b, have been identified that include alternative 3'-untranslated sequences but show a distribution similar to the parent transcript (12).

A consensus sequence for the TonE has been described (13), and the trans-activating factor for the TonE cis-element, TonEBP, was recently cloned (14). This pathway mediates increased transcription of genes involved in the accumulation of compatible osmolytes by renal cells in response to hypertonicity, (15–18). The role of this toxicity-regulated pathway in other aspects of inner medullary cell physiology is still unclear.

The purpose of this study is to characterize part of the 5'-flanking region of the rat UT-A gene, to search for promoter activity and to identify factors that may be important in the transcriptional regulation of UT-A1, UT-A3, and UT-A4 expression in the renal medulla.

**EXPERIMENTAL PROCEDURES**

Identification of the 5'-Flanking Region of the Urea Transporter Gene

UT-A—1.3 kb of the 5'-flanking region of the UT-A gene was obtained by PCR amplification of SpeI and SacI digests of rat genomic DNA using the Genome walker kit (CLONTECH Laboratories, Inc., Palo Alto, CA). Gene-specific antisense primers (GSP-1: nt 86–110, 5'-ACCTCAGATGACTTGGACTTGCTTG-3' and GSP-2: nt 61–85, 5'-TGAGCATTTCAAGGGCAGAAAAAGAG-3') were designed based on the published cdna sequence of rat UT-A1. The first PCR was performed with GSP-1 and adapter primer-1 as follows: 94 °C, 5 s; 92 °C, 15 s; 72 °C, 4 min (57 times); 94 °C, 5 s; 92 °C, 15 s; 67 °C 4 min (52 times). The second

The abbreviations used are: IMCD, inner medullary collecting duct; kb, kilobase; TonE, toxicity-responsive enhancer; TonEBP, TonE-binding protein; MDCK, Madin-Darby canine kidney cells; nt, nucleotides; PCR, polymerase chain reaction; EMSA, electrophoretic mobility shift assay; bp, base pairs; UT-A, rat renal urea transporter; F/R, firefly/Renilla luciferase activity ratio; TonEDN, dominant-negative form of TonEBP; tk, thymidine kinase.

---

* This work was supported in part by National Institutes of Health Grants P01-DK5268, R01-DK41707, R01-DK53917, and Grant-in-aid 96006090 from the American Heart Association. Part of this work was presented at the Experimental Biology Meeting, April 15–18, 2000 in San Diego, CA (Nakayama, Y., Peng, T., Sands, J. M., and Bagnasco, S. M. (2000) *FASEB J.*, 14, A348 (abstr.).) The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

† To whom correspondence should be addressed: Dept. of Pathology, Emory University School of Medicine, WMB Rm. 7105 A, 1639 Pierce Dr., NE, Atlanta, GA 30322. Tel.: 404-727-4026; Fax: 404-727-8540; E-mail: sbagnas@emory.edu.

‡ From the Renal Division, Department of Medicine and the Department of Pathology, Emory University School of Medicine, Atlanta, Georgia 30322.
Bgl isoforms. Restriction sites are indicated as the 5’ exon 2 (131 bp), respectively. These two exons encode the first 300 bp of genomic clones were made by PCR, with sense primers corresponding to (the TonE sense-
9

GAAAACTCC-3
9

in the pGL3 constructs was mutated by PCR using the

activity (see the legend to Fig. 3).

For site-directed mutagenesis, the wild-type TonE sequence 5’-cagggtgAGGGACTCCattg-3’
lined) and the mutated antisense primer 5’-TGAGGGACTCC-3’

were maintained in isotonic medium (300 mosmol/kg H2O) after the transfection. Cells in the hypertonic group were switched to a 600 mosmol/kg H2O hypertonic medium 24 h after transfection. For 18 h the pGL3 constructs were transfected into the cells using Fugene 6 Transfection Reagent (Roche Molecular Biochemicals) according to the protocol suggested by the manufacturer. Transfection efficiency was determined by co-transfecting cells with an enhanced green fluorescent protein vector eGFP and by counting the cells expressing fluorescent protein under fluorescent light 24 h after transfection. Transfection efficiency was estimated to be about 20% with this method. For determination of promoter activity, 0.5 pmol (0.6–1.2 μg) pGL3 reporter construct and 10 ng of plasmid SV40, to control for transfection efficiency, were co-transfected into 50% confluent cells. After 72 h, the cell lysate was extracted with passive lysis buffer (Promega). Firefly luciferase activity from pGL3 reporter vector and Renilla luciferase activity from pRL-SV40 were measured by the Dual Luciferase assay system (Promega) on a TD-20/20 Luminometer (TURNER DESIGN, Sunnyvale, CA). Promoter activity was reported as the ratio between Firefly and Renilla luciferase activities in each sample. Differences between experimental and control cell groups were analyzed by 2-tailed, non-paired t test, with p < 0.05 indicative of statistical significance.

Preparation of Nuclear Extracts, Electrophoretic Mobility Shift Assay (EMSA), and Supershift Assay—MDCK or mIMCD3 cells were seeded in 10-cm dishes and when 50% confluent were switched to hypertonic medium (600 mosmol/kg H2O). Cells were maintained in hypertonic medium for 48 h before harvesting; control cells were maintained in isotonic medium unless otherwise indicated. After washing with chilled phosphate-buffered saline, cells were scraped in 1 mL of cold phosphate-buffered saline on ice and transferred into a pre-chilled 1.5-ml Eppendorf tube. Cells were pelleted by 3,500 rpm centrifugation at 4 °C, and the supernatant was discarded. Cell pellets were washed one time in 500 μL of buffer (10 mM HEPES buffer, pH 7.9, 1.5 mM MgCl2, 10 mM phenylmethylsulfonyl fluoride; and 1 mM dithiothreitol), centrifuged at 3500 rpm, and resuspended in 80 μL of the same buffer with 0.1% (v/v) Triton X-100 (Sigma) after the removal of the supernatant. After cell membrane disruption by 5 strokes with a Dounce glass homogenizer, nuclei were pelleted by centrifugation, washed, and resuspended in a buffer containing 20 mM HEPES, pH 7.9, 25% glycerol (v/v), 420 mM NaCl, 1.5 mM MgCl2, 0.2 mM EDTA, 1 mM dithiothreitol, 0.5 mM phenylmethylsulfonyl fluoride, 1.8 μg/mL aprotinin, and 5 μg/mL leupeptin. After a 30-min incubation on ice, samples were centrifuged at 14,000 rpm for 10 min at 4 °C, and the supernatant was saved as nuclear extract at −80 °C until usage. For EMSA, each 5 μg of nuclear extract was incubated for 30 min at room temperature with 22P- radiolabeled oligonucleotide probes: wild-type TonE probe, 5’-gaattcaagGATGGTTTCCACctg-3’ (TonE is in capital letters) and mutated TonE probe, 5’-gaattcaagGATGGTGCTCCACctg-3’ (mutated nucleotides are underlined). In the reaction buffer containing 12 mM HEPES, pH 7.9, 4 mM Tris-Cl, pH 7.5, 1 mM EDTA, pH 8.0, 1 mM dithiothreitol, 60 mM KCl, 1 mM glycerol (v/v), and 1 mM phenylmethylsulfonyl fluoride. The same reaction was also performed in the presence of 10- to 900-fold excess of wild-type or mutated radiolabeled probe to test specific binding. Electrophoresis was performed with a 5% polyacrylamide gel followed by autoradiography.

Supershift assay using specific anti-TonE-binding protein antisera was performed to confirm the specific binding between the TonE DNA sequence and the TonE-binding protein, TonEBP, as described previously (14). Antiserum for TonEBP and a dominant-negative form of TonEBP, subcloned into the pCDNA vector, were kindly provided by Dr. H. M. Kwon (Johns Hopkins University). The pGRE-tk promoter construct (19) was kindly provided by Dr. Jie Du (Emory University) and was used as a TonE-independent control promoter.

**Fig. 1.** Genomic clones spanning the 5’-flanking region of the UT-A gene. A vertical arrow indicates the start (−1258) of the genomic DNA segment upstream of the transcription start site (+1) of UT-A1, UT-A3, and UT-A4. This 1258-bp segment was tested for promoter activity as shown in Fig. 3. E1 and E2 refer to exon 1 (169 bp) and exon 2 (131 bp), respectively. These two exons encode the first 300 bp of the 5’-untranslated region in the cDNA sequence of the three UT-A isoforms. Restriction sites are indicated as E, EcoRI; S, SspI; D, DraI; B, BglII.
RESULTS

Analysis and Characterization of the 1.3-kb Segment from the 5′-Flanking Region of the UT-A Gene—Previously, we identified a transcription start site for UT-A1, UT-A3, and UT-A4, localized 21-bp upstream of the beginning of the 5′-untranslated region of UT-A1, distinct from the one for UT-A2 (12). We characterized about 1.3 kb from the 5′-flanking region of the rat UT-A gene. This sequence (GenBank™/EBI accession number AF214483) was identified in 3 independent genomic clones (BAC no. 409 L-16, BAC no. 578 J-7, and GW-1 Genome Walker Kit clone) upstream of the exon encoding the first 169 bp of UT-A1, UT-A3, and UT-A4. BAC no. 409 L-16 and BAC no. 578 J-7 include the two exons encoding the first 300 bp of these three isoforms (Fig. 1). This 1.3-kb segment of genomic DNA was fully sequenced from both strands and found to be 100% identical among the different genomic clones (Fig. 2). Sequence analysis of this region reveals three CCAAT sequences, two consensus sequences for AP-1, one for AP-2, three for the glucoconotidic response element GRE, and other putative cis-elements but no TATA motif. Interestingly, we identified a consensus sequence for Tn5 at ~377-bp upstream from the transcription start site.

Identification of Toxicity-sensitive Promoter Activity—To test the promoter activity of this region we used MDCK and mIMCD3 cells. Although mIMCD3 cells can express UT-A2 after prolonged exposure to hypertonic medium (20), neither mIMCD3 nor MDCK cells express UT-A1, UT-A3, or UT-A4 transporters. Both cell lines provide an established in vitro model to study the epithelium of the distal nephron, and MDCK cells are known to express tonicity-responsive genes, like the betaine/γ-aminobutyric acid (GABA) cotransporter (BGT1) (21). The entire 1.3-kb 5′-flanking region, as well as several deletions, subcloned into pGL3-Basic vector, were transfected into MDCK cells and/or mIMCD3 cells to measure the luciferase activity as a function of promoter activity. The 1.3-kb construct transfected into MDCK cells induced basal promoter activity in isotonic medium (0.93 ± 0.03 F/R luciferase activity ± S.D., n = 3), which increased to 2.78 ± 0.18 after exposure to hypertonic medium for 48 h, resulting in a 2.8-fold increase (Fig. 3A). Similar results were observed in mIMCD3 cells, where in isotonic medium the 1.3-kb construct induced detectable promoter activity (0.32 ± 0.01), which increased to 0.91 ± 0.02 after exposure to hypertonic medium for 48 h resulting in a 2.9-fold increase. The effect of progressive deletions was tested in MDCK cells (Fig. 3A). The largest deletion, a 300-bp insert devoid of TonE sequence, induced negligible luciferase activity in hypertonic medium and in isotonic control medium. However, after 48 h in hypertonic medium, each construct carrying the TonE sequence showed significantly higher luciferase activity compared with isotonic control. Mutation of the TonE sequence in the 1.3-kb pGL3 construct completely abolished the luciferase activity increase observed in hypertonic medium, but did not affect luciferase activity in isotonic medium (Fig. 3B). These observations indicate that the TonE motif found at ~377 in the 5′-flanking region of the UT-A gene is active and may be involved in regulating UT-A promoter activity in response to hypertonicity.

Detection of TonE/TonEBP Binding—By gel shift assay, a DNA-protein complex was demonstrated in mIMCD3 cells and in MDCK cells grown in hypertonic medium but was barely detectable in isotonic medium (Fig. 4). No binding was observed with a mutated TonE probe. Competition with excess unlabeled probe effectively prevented binding. Higher concentrations of excess unlabeled oligonucleotides in which the TonE sequence was mutated did not prevent binding. These results demonstrate specific binding between TonE and a nuclear protein that is enhanced in hypertonic conditions. To test whether TonEBP could be identified in the DNA-protein complex described above, we performed a supershift assay, using specific antisera toward TonEBP (Fig. 5). With this assay, we detected a significant upward shift in the mobility of the DNA-protein complex when antiserum was added into the reaction mixture containing nuclear extract from hypertonic cells. (Adding the anti-serum before adding the probe to the reaction mixture produced the same results.) These observations support specific binding between this TonE element in the 5′-
flanking region of the UT-A gene and TonEBP. Effect of Dominant-Negative TonEBP—To further examine the role of TonEBP in 5′-UT-A promoter activity and its response to hypertonicity, we tested the effect of co-transfecting MDCK cells with a dominant-negative form of TonEBP (14) subcloned into pCDNA3 in the presence of the 1.3-kb pGL3 construct (pUT-A) or with the tonicity-independent control promoter construct pGRE-tk (Fig. 6). These experiments were performed in MDCK cells maintained in hypertonic medium for 48 h. B, effect of TonE mutation on promoter activity in response to hypertonicity. Values are mean ± S.D., n = 3. Significant differences are indicated by asterisks. Experiments were repeated three times using different plasmid preparations. MDCK cells were maintained in hypertonic medium and in MDCK cells exposed to hypertonicity. Co-transfection with the dominant-negative TonEBP effectively decreased the 5′-UT-A promoter activity in hypertonic as well as in isotonic conditions, supporting a role of TonE and TonEBP in regulating the 5′-UT-A promoter activity. Minimal residual UT-A promoter activity was still detected in the presence of TonEDN, probably reflecting incomplete inhibition at the concentration used, as previously observed by Myiakawa et al. (14) with TonE-driven luciferase constructs. TonEDN did not significantly inhibit the activity of the pGRE-tk control promoter.

DISCUSSION

In this study, we demonstrate that the TonE/TonEBP pathway participates in regulating expression of the rat UT-A transporter UT-A by stimulating transcription from the 5′-region of the UT-A gene in hypertonic conditions. Our findings provide novel evidence that tonicity-responsive regulation mediated by the TonE/TonEBP pathway may affect the expression of genes that are not directly involved in osmoprotection in the renal inner medulla.

We characterized part of the 5′-flanking region upstream from the transcription start site for the rat UT-A1, UT-A3, and UT-A4. Our observations are consistent with a TATA-less promoter controlling the transcription from the 5′-flanking region of the UT-A gene. Analysis of luciferase expression reveals a modest level of promoter activity induced by transfecting this segment of genomic DNA into MDCK cells and mIMCD3 cells in isotonic (48 h) or isotonic medium.

that are not directly involved in osmoprotection in the renal inner medulla.

We characterized part of the 5′-flanking region upstream from the transcription start site for the rat UT-A1, UT-A3, and UT-A4. Our observations are consistent with a TATA-less promoter controlling the transcription from the 5′-flanking region of the UT-A gene. Analysis of luciferase expression reveals a modest level of promoter activity induced by transfecting this segment of genomic DNA into MDCK cells and mIMCD3 cells in isotonic conditions. However, the promoter activity is significantly increased in response to hypertonicity in both cell types. Of particular interest in this respect is the identification of a consensus sequence for TonE within approximately 400 bp from the 5′-transcription start site. With progressive deletion and mutation analysis, we show that this TonE motif is active in inducing the tonicity-sensitive increase in promoter activity. Our results suggest that this sequence by itself may influence UT-A transcriptional activity. However, analysis of a larger.
segment of genomic DNA further upstream from this region may reveal other TonE sequences that may additionally stimulate promoter activity as has been observed for other genes (15).

TonE-mediated stimulation of promoter activity involves binding to the trans-activating factor TonEBP, which has been characterized previously (14, 22). We identified a protein-DNA complex consistent with TonE/TonEBP binding in nuclear extracts from hypertonic cells, indicating that the 5′-flanking region of the UT-A gene (pUT-A), or the control construct pGRE-tk (pGRE), which does not include TonE motifs. Control cells were co-transfected with 3 μg pcDNA3 without insert, and either pUT-A or pGRE-tk. TonEDN inhibited pUT-A promoter activity in both isotonic and hypertonic condition (p < 0.01). No significant inhibition was detected in the promoter activity of the control construct pGRE-tk.

Fig. 6. Effect of dominant-negative TonEBP on promoter activity. The effect of TonEDN on promoter activity (F/R luciferase activity, mean ± S.D., n = 3) was assessed in separate studies in cells maintained in isotonic medium (A) or in cells exposed to hypertonicity for 48 h after transfection (B). MDCK cells were co-transfected with the dominant-negative form of TonEBP (TonEDN, 3 μg), and either the 1.3-kb pGL construct from the 5′-UT-A-flanking region of the UT-A gene (pUT-A), or the control construct pGRE-tk (pGRE), which does not include TonE motifs. Control cells were co-transfected with 3 μg pcDNA3 without insert, and either pUT-A or pGRE-tk. TonEDN inhibited pUT-A promoter activity in both isotonic and hypertonic condition (p < 0.01). No significant inhibition was detected in the promoter activity of the control construct pGRE-tk.

high expression of UT-A1, UT-A3, and of the UT-A3 variant UT-A3b mRNA transcript is detected physiologically in the inner medulla (12). The findings described in this study, together with the above in vivo observations, support the hypothesis that normally a basal level of transcriptional activity is needed to maintain a steadily high expression of UT-A1, UT-A3, UT-A3b, and to a lesser extent of UT-A1b, and UT-A4. A certain degree of constant activity for the TonE/TonEBP pathway could ensure adequate abundance of the UT-A urea transporters and possibly other genes in the hypertonic inner medulla. Interestingly, TonEBP abundance in the nucleus of inner medullary cells increases in water-deprived rats, presumably resulting in activation of toxicity-responsive transcription above basal levels (23).

We recently demonstrated significantly increased expression of UT-A3 and UT-A3b mRNA and negligible increases in UT-A1 and UT-A1b expression in the inner medulla of water-deprived rats compared with control animals (12). The reason behind the scarce effect of water deprivation on UT-A1 and UT-A1b mRNA abundance is not immediately apparent because both are transcribed from the same region as UT-A3 and UT-A3b, and their transcription should be similarly regulated. One would expect that during water deprivation, a higher toxicity in the inner medulla could activate the TonE/TonEBP pathway and stimulate transcription of UT-A1, UT-A1b, UT-A3, UT-A3b, and UT-A4 to an equivalent extent. Thus, the differential effect of water deprivation on the expression of UT-A1 and UT-A3 observed in rat inner medulla cannot be explained at the transcriptional level. This discrepancy may possibly be caused by factors affecting mRNA stability or splicing events that are currently unknown.

Further studies on the mechanisms regulating UT-A expression will be needed and may also explain why expression of UT-A1, UT-A3, and UT-A4 does not occur under normal culture conditions in any renal epithelial cell line, similar to Aquaporin 2 (24). Lack of expression of an unidentified trans-activating factor, activation of negative cis-elements, or other unknown mechanisms may prevent generation of these UT-A mRNA transcripts in cultured cells. The role of post-transcriptional events, which may influence expression of individual UT-A transporters in vitro and in vivo, remains to be elucidated.

Acknowledgments—The authors thank Dr. Moo Kwon (Johns Hopkins University) for the generous gift of TonEBP antiserum and the dominant-negative form of TonEBP and Dr. Jie Du (Emory University) for donating the pGRE-tk construct.

REFERENCES
1. Hand, S. C., and Somero, G. N. (1983) J. Biol. Chem. 258, 734–741
2. Burg, M. B., and Peters, E. M. (1998) Am. J. Physiol. 274, F762–F765
3. Bagnasco, S., Balaban, R., Fales, H. M., Yi-Ming Yang, and Burg, M. B. (1998) J. Biol. Chem. 263, 5872–5877
4. Bagnasco, S., Uchida, S., Balaban, R., Kador, P., and Burg, M. B. (1986) Proc. Natl. Acad. Sci. U. S. A. 84, 1718–1720
5. Yamashita, A., Uchida, S., Preston, A., Kwon, H. M., and Handler, J. S. (1993) J. Am. Physiol. 264, F20–F23
6. Uchida, S., Yamashita, A., Preston, A., Kwon, H. M., and Handler, J. S. (1993) J. Clin. Invest. 91, 1604–1607
7. Zhang, Z., Yang, X.-Y., and Cohen, D. M. (1999) Am. J. Physiol. 276, F753–F759
8. Tian, Q., Boss, G. R., and Cohen, D. M. (2000) Am. J. Physiol. 278, C372–C380
9. Shayanukl, C., Steel, A., and Hediger, M. A. (1996) J. Clin. Investig. 98, 2580–2587
10. Smith, C. P., Lee, W. S., Martí, S., Knepper, M. A., You, G., Sands, J. M., and Hediger, M. A. (1995) J. Clin. Investig. 96, 1556–1561
11. Karakaschian, A., Timmer, R. T., Klein, D. J., Gurn, R. B., Sands, J. M., and Bagnasco, S. M. (1999) J. Am. Soc. Nephrol. 10, 230–237
12. Bagnasco, S. M., Peng, T., Nakayama, Y., and Sands, J. M. (2000) Am. J. Physiol. 279, F762–F765
13. Miyakawa, H. S., Liu, S. K., Chen, C. P., Dahl, J. S., Handler, J. S., and Kwon, H. M. (1998) Am. J. Physiol. 274, F753–F761
14. Miyakawa, H. S., Liu, S. K., Dahl, C. S., Handler, J. S., and Kwon, H. M. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 2538–2542
15. Rim, J. S., Atta, M. G., Dahl, C. S., Berry, G. T., Handler, J. S., and Kwon, H. M. (1998) J. Biol. Chem. 273, 20615–20621
Transcriptional Regulation of the Rat UT-A Transporter

16. Takenaka, M., Preston, A. S., Kwon, E. D., and Handler, J. S. (1994) *J. Biol. Chem.* **269**, 29379–29381
17. Smaardo, F. L., Burg, M. B., and Garcia-Perez, A. (1992) *Am. J. Physiol.* **262**, C776–C782
18. Ferraris, J. D., Williams, C. K., Jung, K. Y., Bedford, J. J., Burg, M. B., and Garcia-Perez, A. (1996) *J. Biol. Chem.* **271**, 18318–18321
19. Schule, R., Muller, M., Kaltschmidt, C., and Renkawitz, R. (1988) *Science* **1418**, 1418–1420
20. Leroy, C., Basset, G., Gruel, G., Ripoche, P., Trinh-Trang-Tan, M. M., and Rousselet, G. (2000) *Biochem. Biophys. Res. Comm.* **271**, 368–373
21. Yamauchi, A., Uchida, S., Kwon, H. M., Preston, A., Robey, B., Garcia-Perez, A., Burg, M. B., and Handler, J. S. (1992) *J. Biol. Chem.* **267**, 649–652
22. Woo, S. K., Manuyo, D., Handler, J. S., and Kwon, H. M. (2000) *Am. J. Physiol.* **278**, C323–C330
23. Cha, J. H., Woo, S. K., Han, Y. H., Kim, K. H., Kim, J., and Kwon, H. M. (1999) *J. Am. Soc. Nephrol.* **10**, 51A
24. Furuno, M., Uchida, S., Marumo, F., and Sasaki, S. (1996) *Am. J. Physiol.* **271**, F854–F860
The TonE/TonEBP Pathway Mediates Tonicity-responsive Regulation of UT-A Urea Transporter Expression

Yushi Nakayama, Tao Peng, Jeff M. Sands and Serena M. Bagnasco

J. Biol. Chem. 2000, 275:38275-38280.
doi: 10.1074/jbc.M004678200 originally published online September 19, 2000

Access the most updated version of this article at doi: 10.1074/jbc.M004678200

Alerts:
  • When this article is cited
  • When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 24 references, 10 of which can be accessed free at
http://www.jbc.org/content/275/49/38275.full.html#ref-list-1