myo-Inositol oxygenase (MIOX) catalyzes the oxidative cleavage of myo-inositol (MI) to give d-glucuronic acid, a committed step in MI catabolism. d-Glucuronic acid is further metabolized to xylitol via the glucuronate-xylulose pathway. Although accumulation of polyols such as xylitol and sorbitol is associated with MI depletion in diabetic complications, no causal relationship has been established. Therefore we are examining the role of MIOX in diabetic nephropathy. Here we present evidence that the basis for the depletion of MI in diabetes is likely to be mediated by the increased expression of MIOX, which is induced by sorbitol, mannitol, and xylitol in a porcine renal proximal tubular epithelial cell line, LLC-PK1. To understand the molecular mechanism of regulation of MIOX expression by polyols, we have cloned the human MIOX gene locus of 10 kb containing 5.6 kb of the 5′ upstream sequence. Analysis of the 5′ upstream sequence led to the identification of an osmotic response element (ORE) in the promoter region, which is present −2 kb upstream of the translation start site. Based on luciferase reporter and electrophoretic mobility shift assays, polyols increased the ORE-dependent expression of MIOX. In addition, we demonstrate that the activity of the promoter is dependent on the binding of the transcription factor, tonicity element-binding protein, or osmotic response element-binding protein, to the ORE site. These results suggest that the expression of MIOX is up-regulated by a positive feedback mechanism where xylitol, one of the products of MI catabolism via the glucuronate-xylulose pathway, induces an overexpression of MIOX.

myo-Inositol (MI), the dominant form of the physiological inositol isomers, is utilized in many tissues and cell types as a precursor for the synthesis of second messengers and also as an organic osmylyte (1). The first committed step in MI metabolism is catalyzed by the monooxygenase, myo-inositol oxygenase (MIOX, EC 1.13.99.1), which occurs predominantly in the proximal tubular epithelial cells of the kidney cortex (2). The enzymatic reaction involves the oxidative cleavage of the ring in MI between C-6 and C-1 to give d-glucuronic acid. The d-glucuronate formed in animals by this mechanism is successively converted in subsequent steps to L-gluconate, 3-keto-L-gulonate, L-xylulose, xylitol, D-xylulose, and D-xylulose 5-phosphate, which then enters the pentose phosphate cycle (Fig. 1). Studies in human pentosuric patients confirmed this is the only pathway of MI catabolism (3). We have recently reported the cloning and expression of MIOX, where we demonstrated that d-chiro-inositol, a MI isomer that exhibits insulin-like signaling properties (4), is also a substrate for MIOX (2).

myo-Inositol has been suggested to play an important role in the etiology of diabetes mellitus, particularly with respect to the progression of diabetic nephropathy, neuropathy, retinopathy, and diabetic cataract. In diabetic complications, increased glucose levels are associated with high sorbitol accumulation in the kidney, retina, nerve, and lens, which is then followed by depletion of MI (5–9). Aldose reductase (ALR2) has been proposed to participate in the polyol pathway by catalyzing the reduction of glucose to sorbitol in a NADPH-dependent manner (10). Most of the effort to treat diabetic complications has been centered on the correction of increased polyol sugars with the use of ALR2 inhibitors, like Sorbinil®, as potential drugs for the treatment of diabetics. Whereas the correction of MI depletion also presents a promising approach to amelioration of diabetic complications, the mechanisms of depletion remain unidentified. Little is known about the regulation of MIOX levels in tissues during diabetic conditions, which might be in part because of the paucity of any genomic information as well as the lack of availability of cDNA and antibody probes for MIOX. myo-Inositol treatment has been shown to have a beneficial effect in restoring the impaired motor nerve conduction velocity and disruption of structural elements in the nerve as a result of increased nerve cluster density (6, 11). Supplementation of MI is also known to restore the reduction in the turnover of phosphate groups in phosphoinositides like phosphatidylmyoinositol bisphosphate (12). To our knowledge, there is no report in the literature that links MIOX with diabetes-associated metabolic derangements.

Depletion of tissue MI and accumulation of sorbitol and xylitol seems to be a common feature observed in most of the pathologies associated with diabetes; however, the mechanism of depletion of MI in diabetes remains largely unknown. Our studies reported here are based on the hypothesis that in the kidney cortex, osmotic gradients of metabolites, including polyols, lead to the activation of MIOX expression. It is well established that the expression of several renal-specific genes is under the influence of osmotic stress, via a plethora of cellular signaling events, including the protein kinase pathways and...
transcription factors (13, 14). The signaling cascade activated by hyperosmolar stress leads to the activation of osmotic response element-binding protein (OREBP), which shares significant homology with the toxicity-responsive element-binding protein (TonEBP), a transcription factor that belongs to the Rel family, which also includes nuclear factor-κB and nuclear factor of activated T cells (NFATs) (15).

The present study is aimed at investigating the transcriptional activation of MIOX by polyols in the renal proximal tubular epithelial cell line, LLC-PK1. We present evidence that the human MIOX promoter constructs are activated in tubular epithelial cells and that the region of activation maps to an ORE-like sequence in the distal promoter. This is the binding site for OREBP/TonEBP, a key regulator of gene expression on 4-chamber glass slides for 24 h with 50 mM sorbitol or phosphate-buffered saline (PBS). Cells were fixed using ice-cold methanol and washed in PBS with 0.3% Tween 20 (PBST). Blocking was performed with 10% normal goat serum (Santa Cruz Biotechnology) for 2 h on a shaker, followed by incubation with the primary antibody for 2 h (anti-MIOX; 4°C). The slides were washed with PBST three times and incubated with antirabbit fluorescein isothiocyanate secondary antibody (1:1000). The slides were covered with VectaShield® (Vector Labs) containing 4′,6-diamidino-2-phenylindole (DAPI) for imaging analysis.

Preparation of Cytoplasmic and Nuclear Extracts for Western Blot Analysis—The cytosolic and nuclear extracts were prepared from LLC-PK1 cells subjected to different treatments using lysis buffer that contained 10 mM Hepes, 60 mM KCl, 1 mM EDTA, 0.075% (v/v) Nonidet P-40, 1 mM dithiothreitol, 1 mM phenylmethylsulfonyl fluoride, 2 μg/ml leupeptin, 2 μg/ml aprotinin, and 0.5 mg/ml benzamidine. The cells were treated with lysis buffer for 15 min and centrifuged at 1500 × g for 4 min to separate the cytoplasmic and nuclear fractions. The pellet was washed with the lysis buffer without Nonidet P-40, salt concentration of the nuclear extraction buffer was adjusted to 400 mM, and nuclear proteins were extracted. The cytoplasmic and nuclear proteins were centrifuged at 20,000 × g for 15 min at 4 °C. The supernatants were used for Western blot analysis. The supernatants were used for Western blot analysis. The supernatants were used for Western blot analysis. The supernatants were used for Western blot analysis.
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Electrophoretic Mobility Shift Assay—Nuclear fractions were isolated from LLC-PK1 cells cultured in the absence or presence of additives as described (21). Five micrograms of total nuclear protein were incubated with the hMIOX-ORE double stranded probe (5’-CCTTCTCCAGGAAAAGCTTTACCTCC-3’ and 5’-GGAGGTTAAAGGCTTTC-CCTGAGGGAGC-3’) that was 3’ OH end-labeled with Biotin-N4-CTP by the terminal deoxynucleotidyl transferase reaction using LightShift® chemiluminescent electrophoretic mobility shift assay kit as per the manufacturer’s instructions (Pierce). Unlabeled double stranded oligonucleotide was used as a competitor in the sorbitol-treated cell extracts. The binding buffer contained 12 mM HEPES-KOH, pH 7.9, 60 mM KCl, 5 mM MgCl2, 0.12 mM EDTA, 0.3 mM phenylmethylsulfonyl fluoride, and 0.3 mM dithiothreitol. For supershift assays, anti-NFAT5 (2 μg) and anti-glyceraldehyde-3-phosphate dehydrogenase (GAPDH) antibodies were normalised for uniform loading. Densitometry data of the MIOX and glyceraldehyde-3-phosphate dehydrogenase bands is shown in the lower panel. The ratio of MIOX to glyceraldehyde-3-phosphate dehydrogenase was used to calculate -fold increase with respect to the PBS-treated control. n = 3

Statistical Analysis—Results are given as mean ± S.D. Statistical significance of differences between treatment groups in these studies was determined by Student’s t test. The minimal level of significance chosen was p < 0.05.

RESULTS

Induction of MIOX Expression by Hyperosmolarity—Hyperosmolarity has been shown to activate the transcription of a large number of genes, including ALR2 and SMIT in different renal cell lines (16, 19). We have employed the porcine renal proximal tubular epithelial cell line (LLC-PK1) that expresses MIOX to test the inducibility of MIOX by hyperosmolar stress. Fig. 2 shows the changes in MIOX protein expression in LLC-PK1 cells upon exposure to medium supplemented with polyols, in this case, mannitol, sorbitol, and xylitol. The induction of MIOX expression was compared with the control cells that only received PBS. The LLC-PK1 cells treated with mannitol, sorbitol, or xylitol exhibited a 5–6-fold increase in MIOX expression compared with the iso-osmotic control (Fig. 2; compare lane 1 and lanes 5–7). Addition of glucose (27 mM) and xylose (5 mM) also resulted in a 5-fold increase in the expression of MIOX (Fig. 2, lanes 3 and 4). There was an increase in the expression of MIOX in cells maintained in hyperosmotic medium containing NaCl by ~3-fold. These results suggest that, in the LLC-PK1 cells, the expression of the MIOX gene is regulated by hyperosmotic stress in the form of salt, polyols, and/or sugars in the medium. Furthermore, these results also validate the use of LLC-PK1 cell line as an in vitro culture system to identify the cis-acting element in the MIOX gene that is involved in osmotic regulation of transcription by polyols.

Cloning and Characterization of Human MIOX 5’-Flanking Region—A human PAC clone (RPCI 574N16) digested with NotI, was used to isolate a 30-kb DNA fragment by pulse-field gel electrophoresis. Southern blot analysis clearly indicated that the 30-kb fragment contained the human MIOX gene (Fig. 3A). Further digestion of the 30-kb fragment by SmaI and HpaI produced an expected 10-kb fragment that was rescued into pGL3 Basic vector, blunted end with SmaI (Fig. 3B). Instead of using pBeloBacII, which is commonly employed for cloning larger (>8 kb) fragments, we have chosen the pGL3 Basic vector as a cloning vector because of its high copy number and relative ease of blunt-ended cloning. The human gene for MIOX spans ~10 kb and, based on human chromosome 22q13.33 sequence available online, MIOX consists of 10 exons and 9 introns. The 10-kb MIOX genomic DNA clone contained a sequence up to 5.6 kb upstream of the translation start (+1) site. The 5’ upstream sequence also contained a possible TATA box (TATAAT) 71 bases upstream as indicated by the examination of the sequence. Preliminary analysis of the sequence of the 5.6-kb region indicated that a putative consensus ORE was present at 2.1 kb upstream of the start site. Three clones were isolated by primary PCR screening, out of which, only one clone was confirmed to contain the MIOX gene when we used hMIOX cDNA as a probe in Southern blot analysis (Fig. 3C). The clone, 10hMIOX1, which was found to span ~5.6 to ~4 kb relative to the translation start site, was used to derive another clone that contained ~2.6 to ~52 bp fused in-frame to the luciferase reporter coding region in the pGL3 Basic vector (2.6hMIOXLuc). This clone was used for the functional analysis of the MIOX promoter, particularly with respect to the hyperosmotic regulation by polyols.

To locate the ORE of the human MIOX gene, the 2.6hMIOXLuc was transfected into porcine renal proximal tubular epithelial cells. Twelve hours after transfection, cells were switched to either iso-osmotic or hyperosmotic medium. After 24 h of incubation in this media, cells were harvested for luciferase, β-galactosidase, and protein assays as described under “Materials and Methods.” As shown in the top panel of Fig. 4, transfected cells incubated in hyperosmotic medium exhibited a marked increase in luciferase activities than those incubated in iso-osmotic medium, suggesting that the 2.6-kb fragment contained an ORE. Some of the most common polyols tested to activate the transcription included mannitol, sorbitol, and xylitol. All three polyols led to an increase in luciferase activity by ~3–4-fold over the iso-osmotic controls (Fig. 4, top panel). In addition, a 3–4-fold increase in luciferase activities was seen with glucose and xylose treatments (Fig. 4, top panel). Consistent with the sequence analysis for the presence of ORE in the 5’ upstream sequence, inclusion of the 5.6-kb upstream fragment did not affect the osmotically induced transcription activity (data not shown). Therefore, we only used the 2.6-kb 5’ upstream sequence for further analysis.

To confirm the role of the ORE in the 2.6-kb 5’ upstream region of hMIOX gene, we prepared a deletion mutant (1.9hMIOXLuc) that lacked the ORE. Transient transfection analysis in LLC-PK1 cells, identical to the conditions with the 2.6hMIOXLuc, totally obliterated the osmotic response in the presence...
of mannitol, sorbitol, and xylitol (Fig. 4, lower panel). These results indicate that the ORE is located between −1900 and −2600 that is required for a robust osmotic response. Compared with the human gene, where only one ORE was present, the mouse gene for Miox showed that the promoter had at least 4 putative OREs with close homology to the consensus ORE at −2032, −1749, −1429, and −854 (Fig. 5).

Interaction of Osmotic Response Region with the Transcription Factors—To confirm that the putative osmotic response element situated between −2600 to −1900 indeed interacts with the NFAT5 family of transcription factors, TonEBP/OREBP, we performed gel mobility shift analysis using the ORE core-sequence present in the 5′ upstream sequence (−2019) of the hMIOX gene as a probe. As shown in Fig. 6A, two prominent bands were observed when the probe was incubated with nuclear extracts from LLC-PK1 cells exposed to hyperosmotic media irrespective of the type of osmolyte used. However, in competition assays that used molar excess of unlabeled probe, only the affinity toward the lower band was affected; whereas, the upper band remained unaffected. Nuclear extracts from LLC-PK1 cells maintained in isosmotic medium resulted in a similar banding pattern, but a much weaker signal (Fig. 6A, lane 1). The binding of ORE in sorbitol-treated cells could be competed out by the addition of excess oligonucleotide probe (Fig. 6A, lane 7), indicating the specificity of interaction of the DNA with the transcription factor. In addition, treatment of cells with glucose and xylose also led to an increase in ORE binding activity suggesting that glucose and xylose may exert their effect, in part, via the formation of respective polyols, sorbitol, and xylitol. Further-
more, incubation of the nuclear extracts from sorbitol-treated cells with anti-NFAT5 polyclonal antibodies produced a supershift of the hMIOX ORE probe, further confirming the specificity of interaction (Fig. 6A, lane 8). The presence of NFAT5 in the nuclei of sorbitol-treated cells was tested by simple Western immunoblot analysis that clearly indicated a 190-kDa band corresponding to the OREBP. Immunofluorescence analysis of LLC-PK1 cells exposed to sorbitol exhibited increased translocation of TonEBP/OREBP into the nucleus than in the cells cultured in isosmotic media (Fig. 7). These studies revalidate the results obtained with the gel mobility shift analysis and confirm the increased translocation of TonEBP/OREBP followed by binding ORE in sorbitol-treated cells as a possible mechanism of increased expression of MIOX.

**DISCUSSION**

Previous studies from many laboratories, including ours (2, 22–25), have reported that MIOX occurs predominantly in the cortical region of the kidney. In the cortex, proximal tubule epithelial cells are responsible for the uptake of the majority of water and nearly all metabolites from the filtrate. Imbalances in osmolytes, like in diabetes, can therefore have a negative impact on the function of these cells and the kidney. During hyperglycemia, however, there is even greater imbalance of osmolytes because of the presence of excessive glucose as well as polyols that are generated from glucose via the sorbitol and xylitol pathways (26). These polyols have been reported to induce the expression of several genes mainly via the activation of OREBP and/or TonEBP, which belong to the NFAT5 family of transcription factors (13). The hyperosmotic response has been demonstrated not only in proximal tubular epithelial cells but also in other cells of the kidney as well as extrarenal tissues such as the retina and lens epithelial cells (27–29). Important to this discussion is our observation that MIOX is also expressed in epithelial cells of human lens and retina, in addition to proximal tubular epithelial cells (data not shown).

In the present study, we have demonstrated the up-regulation of MIOX expression by hyperosmolarity, particularly by common cellular polyols like mannitol, sorbitol, and xylitol. The biogenesis of these polyols is linked to hyperglycemia via the ALR2 and glucuronate-xylulose pathways (30). Interestingly, glucuronate is the product of the MIOX-catalyzed oxidation of MI that may contribute, in part, to the formation of xylitol and other pentose phosphates, particularly xylulose 5-phosphate. As mentioned earlier, MIOX is the only enzyme that catabolizes MI. Therefore, modulation of MIOX levels may hold the key to depletion of MI during diabetes. Intracellular levels of MI have been reported to decrease in tissues affected by hyperglycemia (7, 31); however, the underlying mechanism for this depletion is not known. To explain the molecular basis for MI depletion and its relationship with the transcriptional regulation of MIOX expression by hyperosmolar stress, we have examined the promoter of human MIOX for the presence of putative OREs. Similar ORE sequences have been conclusively shown to mediate the hyperosmotic response in ALR2, SMIT, and taurine transporters (32). We have found that the human MIOX gene has only one ORE at −2100 in the entire 5.6-kb 5′ upstream sequence. The sequence homology searches with the mouse Miox gene indicate the presence of 4-consensus putative sequences with a conserved core sequence of 5′-CGAAA-3′ in the 5′ upstream region (Fig. 5), suggesting that the osmotic regulation of MIOX expression may occur via a similar mechanism in different mammals. It is likely that all four OREs, which are situated between −2100 to −850 of the mouse Miox gene, are active independent of each other or may function in concert as in the human ALR2 gene (17). In this context, the mouse Miox gene promoter is also being analyzed in our laboratory (data not shown).

Consistent with the sequence identities with respect to the ORE in the human MIOX 5′ upstream region, results of the transient transfection analysis with 2.6hMIOXLuc and 1.9hMIOXLuc revealed that the region between −2600 to −1900 was essential for the severalfold induction of luciferase activity in LLC-PK1 cells exposed to mannitol, sorbitol, and xylitol. To confirm that the observed effect was indeed because of the occupancy of the transcription factor, we performed gel mobility shift analysis with the hMIOX ORE probe along with supershift assays with anti-NFAT5 polyclonal antibodies. The gel shift assays conclusively proved that the observed increases in the luciferase activities were because of the increased binding of TonEBP/OREBP and also the binding was appeared to be very specific. However, with the 27-bp hMIOX ORE fragment as a probe in the gel mobility shift assay, two bands were observed (Fig. 6). Whereas, the lower band (faster migrating band) showed differences in its binding activity and was easily competed by unlabeled oligonucleotide probe in the presence of sorbitol, the upper band (slower migrating band) did not show any difference (Fig. 6). This is consistent with that reported in
the literature (17), which appears to be because of two different types of DNA/protein interactions. Alternatively, it is possible that the slower migrating band may contain aggregates of protein-DNA complexes generated through protein/protein interaction.

Sequence homology searches with the pig expression sequence tag data base indicated that the OREBP encoded by the pig genome exhibits over 90% homology to the human protein. Furthermore, the presence of NFAT5 was confirmed by Western blot analysis in the nuclear extracts of LLC-PK1 cells suggesting that the expression of MIOX is likely driven byTonEBP/OREBP in response to polyols (Fig. 6B). Results of the immunofluorescence analysis of LLC-PK1 cells indicates that these cells possess NFAT5 and that its translocation from the cytoplasm into the nucleus is driven by hyperosmolar stress (Fig. 7). Nevertheless, it is difficult to distinguish whether the effect is because of one particular transcription factor or both. It appears that both the ORE and TonE share a putative consensus core-binding sequence NGGAAAWDHMC(N) and are responsible for mediating hyperosmotic induction of many genes, including MIOX. The sequence in the human MIOX gene that mediates the hyperosmotic response is AG-GAAAGCCT. Sequence analysis of the ORE site in the human MIOX gene suggests that the site is likely an ORE site rather than a TonE site. Comparison of the DNA binding domains of OREBP and TonEBP revealed that the amino acid residues in this region are very highly conserved. However, it has been reported that within the core sequence, which NFAT and OREBP recognize, NFAT5 (TonEBP) recognizes GGAAAA; whereas, OREBP recognizes TGAAAA (16, 33). It is possible that TonEBP, which is a closely related transcription factor that differs from OREBP at the N terminus (13), may still drive the transcription of MIOX in response to hyperosmolar stress by polyols. Furthermore, the functional dichotomy may stem from different signaling pathways that are activated by polyols in cells. In fact, it is not clear at present as to how signaling networks are activated by polyols and the particular kinase processed involved in the process. Recently, the role of an ataxia telangie-
taxia kinase (ATM kinase) was described to be the major activator of polyol-dependent kinase pathways that signals through the p38 mitogen-activated protein kinase leading to the activation of TonEBP (15). However, the increased expression of MIOX by sugars suggests interplay of additional signaling mechanisms.

The increases in luciferase activity with glucose and xylose could be the result of activation of transcription factors other than the OREBP/TonEBP. Studies regarding the regulation of MIOX via ORE and TonE have suggested that the expression of MIOX is likely driven by the MI-glucuronate-xylulose pathway (36). Previous research from our laboratory suggests that glucuronate produced by MIOX is rapidly shuttled into aldehyde reductase (ALR1) such that its cyclization to a hemiacetal is prevented (36). Recent data from our laboratory indicates that the two proteins interact when co-expressed in LLC-PK1 cells, which may facilitate the channeling of glucuronate through the pathway (data not shown). In addition, the entry of intermediary metabolites of other metabolic pathways at various points of the glucuronate-xylulose pathway could also act as an additional source of xylitol and xylulose 5-phosphate. Of special mention is the additional contribution of xylitol by increased ALR2 expression during hyperglycemia, which could establish a positive feedback loop on MIOX expression.

In conclusion, we have reported here, for the first time, the cloning and characterization of the human MIOX gene along with its promoter. Furthermore, we have characterized the underlying mechanism of up-regulation of expression of MIOX by polyols and sugar metabolites to be dependent on the activation of transcription factor, OREBP. Studies are underway to correlate the transcriptional regulation of MIOX via ORE and other cis-elements to reduced MI levels in diabetes using animal models.

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Up-regulation of Human myo-Inositol Oxygenase by Hyperosmotic Stress in Renal Proximal Tubular Epithelial Cells
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