1,25-Dihydroxyvitamin D₃ suppresses high glucose-induced angiotensinogen expression in kidney cells by blocking the NF-κB pathway

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Deb DK, Chen Y, Zhang Z, Zhang Y, Szeto FL, Wong KE, Kong J, Li YC. 1,25-Dihydroxyvitamin D₃ suppresses high glucose-induced angiotensinogen expression in kidney cells by blocking the NF-κB pathway. Am J Physiol Renal Physiol 296: F1212–F1218, 2009. First published February 4, 2009; doi:10.1152/ajprenal.00002.2009.—The renin-angiotensin system (RAS) is a major mediator of renal injury in diabetic nephropathy. Our previous studies demonstrated that 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃] plays a renoprotective role by suppressing the RAS, with renin and angiotensinogen (AGT) as the main targets. The mechanism whereby 1,25(OH)₂D₃ transcriptionally suppresses renin gene expression has been elucidated; however, how vitamin D regulates AGT remains unknown. Exposure of mesangial cells or podocytes to high glucose (HG; 30 mM) markedly stimulated AGT expression. In mesangial cells, the stimulation was inhibited by 1,25(OH)₂D₃ (20 nM) or NF-κB inhibitor BAY 11–7082, suggesting the involvement of NF-κB in HG-induced AGT expression and the interaction between 1,25(OH)₂D₃ and NF-κB in the regulation. Plasmid pNF-κB-Luc luciferase reporter assays showed that 1,25(OH)₂D₃ blocked HG-induced NF-κB activity. EMSA and ChIP assays demonstrated increased p65/p50 binding to a NF-κB binding site at −1734 in the AGT gene promoter upon high glucose stimulation, and the binding was disrupted by 1,25(OH)₂D₃ treatment. Overexpression of p65/p50 overcame 1,25(OH)₂D₃ suppression, and mutation of this NF-κB binding site blunted 1,25(OH)₂D₃ suppression of the promoter activity. In mice lacking the vitamin D receptor, AGT mRNA expression in the kidney was markedly increased compared with wild-type mice, and AGT induction in diabetic mice was suppressed by treatment with a vitamin D analog. These data indicate that 1,25(OH)₂D₃ suppresses hyperglycemia-induced AGT expression by blocking NF-κB-mediated pathway.

vitamin D receptor; renin-angiotensin system; diabetic nephropathy

THE INTRARENAL RENIN-ANGIOTENIN system (RAS) has been implicated as a major mediator of progressive renal injury in diabetic nephropathy, the most common renal complication of diabetes mellitus (3, 7). The kidney is able to synthesize all components of the RAS, including renin, renin receptor, angiotensinogen (AGT), and ANG II receptors independent of the systemic RAS (11), and local activation of the intrarenal RAS by high glucose is a key event that leads to diabetic nephropathy. High glucose is known to stimulate renin and ANG II synthesis in mesangial cells (MCs) and podocytes (5, 15, 25, 27), and intrarenal renin and AGT levels are increased in diabetic animals (1, 35). Previous studies established that accumulation of intrarenal ANG II contributes to progression of renal injury in multiple ways. For example, ANG II can increase glomerular capillary pressure and permeability, upregulates cytokine and extracellular matrix synthesis, and induces oxidative stress and podocyte injury (3, 7, 20). Clearly, an increase in AGT expression in the kidney contributes to renal accumulation of ANG II, the major effector of renal injury.

1,25-Dihydroxyvitamin D₃ [1,25(OH)₂D₃] is a multifunctional hormone that exerts its actions by binding to the vitamin D receptor (VDR), a member of the nuclear receptor superfamily (10). We demonstrated that 1,25(OH)₂D₃ possesses renoprotective property against hyperglycemia-induced renal injury by suppressing the renal RAS. 1,25(OH)₂D₃ is a negative endocrine regulator of renin biosynthesis and directly transrepresses renin gene transcription (13, 29). Diabetic mice lacking VDR developed more severe renal damage than wild-type mice because of more robust activation of the intrarenal RAS, including more induction of renin and AGT (31). Recently, we demonstrated that vitamin D analogs can be used to block the compensatory renin increase in a combination therapy with classic RAS inhibitors, and this combination generated synergistic therapeutic effects against diabetic nephropathy (33). On the other hand, we also showed that 1,25(OH)₂D₃ downregulates AGT induction in diabetes (31), but the mechanism has not been elucidated.

AGT is 453-amino acid polypeptide (18) and the only known substrate for renin, which cleaves AGT to ANG I. Thus, alteration in AGT expression has a direct impact on RAS activation. AGT is abundantly produced in the liver; however, lower levels of AGT are expressed in other tissues. In the kidney, AGT expression is expressed and markedly induced in MCs and podocytes in diabetic state (5, 15, 25, 27). In this study, we investigated the molecular mechanism whereby 1,25(OH)₂D₃ suppresses AGT induction in MCs in a high-glucose environment, and our data indicate that the NF-κB pathway is targeted by 1,25(OH)₂D₃ in this important regulation.

MATERIALS AND METHODS

Cell culture. Mouse MC line (ATCC, Manassas, VA) was routinely maintained in DMEM/F12 supplemented with 10% FBS in 5% CO₂ incubator at 37°C. Podocyte line (17) was cultured to 80% confluence in RPMI-1640 supplemented with 10% FBS and 50 U/ml γ-interferon. The cells were subcultured at 37°C without γ-interferon (nonpermissive condition) in low-glucose (LG) media for 3–4 days before being used for experiment. For high-glucose (HG) stimulation, cells were first synchronized in serum-free DMEM for 48 h at 37°C and then changed to LG DMEM media containing 5 mM glucose and 10% FBS or to HG DMEM media containing 30 mM glucose and 10% FBS and cultured for 24–48 h in the presence or absence of 1,25(OH)₂D₃ before being used for total RNA extraction, nuclear extraction, or cell lysate preparations as described in the following experiments. All
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in vitro experiments were repeated at least two to three times with similar results, and each data point was obtained from triplicate samples.

**RT-PCR.** First-strand cDNAs were synthesized from total RNAs using MML-V reverse transcriptase (Invitrogen) and hexanucleotide random primers. The cDNAs were used as the template for PCR amplification using mouse AGT-specific primers, 5'-TCTTGGC-GCACTCTGCTTTTCT-3' (forward), and 5'-TTCTACGATG-GCAAAGAAGTGGTCA-3' (reverse). The internal control for the PCR reaction was GAPDH.

**Immunostaining.** MCs were cultured on coverslips in LG or HG media in the presence or absence of 20 nM 1,25(OH)2D3 for 24 h, fixed with 10% formalin for 15 min, and stained with ANG I/II-specific antibody (Santa Cruz Biotechnology). The signal was visualized with FITC-conjugated secondary antibody.

**AGT promoter construct and luciferase reporter assays.** The 5' upstream region from −1768 to +22 in the mouse AGT gene was amplified by PCR using primers 5'-CGGGTACCAAGCAGAGGATACCC-3' (forward) and 5'-AGTACATATGCAAGGTCAGGATCC-3' (reverse) and cloned into the KpnI/NcoI sites of pGL3 basic luciferase vector (Promega) to generate reporter plasmid pAGT-Luc. Reporter plasmid pAGTmut-Luc that carried mutations at the −1734 NF-κB site (mutated from 5'-GGGAAATTCCT-3' to 5'-GGGAAATTCC-3') was generated using the RapidChange mutagenesis kit from Stratagene. Mutations were confirmed by DNA sequencing. Cells were transfected using Lipofectamine 2000 (Invitrogen) in serum-free LG media with pAGT-Luc, pAGTmut-Luc, or pNF-κB-Luc as indicated in the experiment. Six hours after transfection the cells were exposed to LG or HG media in the presence or absence of 20 nM 1,25(OH)2D3 for 24 h. The cells were lysed and luciferase activity was determined using Luciferase Assay Systems (Promega) as reported previously (29). In some experiments, the cells were cotransfected with p65 and p50 expression plasmids pcDNA-p65 and pcDNA-p50, originally constructed by J. F. Habener (MGH, Harvard Medical School, Boston, MA).

**EMSA.** Nuclear extract preparations and EMSA were performed as described previously (29). Briefly, double-strand NF-κB probe end-labeled with γ-32P-ATP was incubated with nuclear extracts at room temperature for 20 min in the presence of 100 μg/ml poly(dI.dC) and the mixture was electrophoresed on a 4% nondenaturing polyacrylamide gel. The NF-κB probe was 5'-GGCTAAGGGAAATTCCTGGTCAT-3' (underlined is core NF-κB binding site). The specificity of protein-DNA interaction was confirmed by competition with an excess amount of unlabeled probes of the same sequence, the canonical NF-κB probe, NF-κBc (5'-AGTTGAGGGCAATTCCAGGC-3'; Santa Cruz Biotechnology), or the mutated probes NF-kBmut 5'-GGCTAAGGAcATTCTGGTCAT-3'. The presence of p65 or p50 in the DNA-protein complex was confirmed with antibody supershift assays using anti-p65 or anti-p50 antibody (Santa Cruz Biotechnology).

**Chromatin immunoprecipitation assays.** Chromatin immunoprecipitation (ChIP) assays were carried out as described previously (29) using a commercial kit from Upstate Biotechnology (Lake Placid, NY). Briefly, MCs were pretreated with or without 20 nM 1,25(OH)2D3 in serum-free media for 24 h, and then exposed to the LG or HG media containing 10% FBS overnight. After treatment with 1% formaldehyde to cross-link histones to DNA, cells were lysed and sonicated to shear the chromatin. The sonicated chromatin was incubated with anti-p65 antibody or anti-p50 antibody. The chromatin-antibody complex was precipitated with protein-A-agarose beads. The DNA isolated from the complex was subject to PCR amplification using the following primers flanking the NF-κB site in AGT promoter: 5'-GGCTAAGGGGAAGCACAAG-3' (forward) and 5'-CTTCCCTGGAACACAAG-3' (reverse).

**Animals.** Generation of VDR-null mice has been reported previously (14). Streptozotocin (STZ)-induced diabetic mice and their treatment with paricalcitol have been described previously (33). The animal studies were approved by the Institutional Animal Care and Use Committee at The University of Chicago.

**Statistical analysis.** Data values were presented as means ± SD. Statistical comparisons were made using Student’s t-test, with P < 0.05 being considered significant.

**RESULTS**

As shown in Fig. 1, in both MCs and podocytes, 24-h exposure to HG (30 mM glucose) media stimulated AGT mRNA expression compared with cells cultured in LG (5 mM glucose) media, and the induction was completely blocked in the presence of 20 nM 1,25(OH)2D3 (Fig. 1, A and B). Therefore, 1,25(OH)2D3 suppression of HG-induced AGT expression appears to be a general phenomenon in kidney cells. Immunostaining of MCs with ANG I/II-specific antibody confirmed that HG markedly stimulated AGT and ANG I/II production in the cytoplasm, and 1,25(OH)2D3 attenuated this stimulation (Fig. 1C). To address whether the HG stimulatory effect on AGT expression was due to high osmolality, MCs were exposed to LG, HG, or LG + 25 mM mannitol for 24 h. As reported previously by others (25), mannitol showed some stimulatory effect on AGT expression; however, the effect was very small compared with that of HG (Fig. 1, D and E). Thus, the osmolar effect on AGT expression was minimal. In the following studies, we used MCs as a model to investigate the molecular mechanism underlying the regulation of AGT by HG and vitamin D.

NF-κB is a dimeric transcription factor that plays important roles in kidney disease (8). HG is known to stimulate NF-κB activity, and 1,25(OH)2D3 is known to suppress NF-κB activity in MCs and other cell types (22, 32). We therefore tested the possibility that HG induced AGT via activation of NF-κB, whereas 1,25(OH)2D3 suppresses HG-induced AGT by blocking NF-κB activity. As shown in Fig. 2, when MCs were transfected with pNF-κB-Luc reporter plasmid, the induction of luciferase activity by HG was blocked by 1,25(OH)2D3 as well as Bay 11–7082 (Fig. 2B). These data suggest a key role of NF-κB in HG-induced AGT expression and predict a cis-NF-κB element in the AGT gene promoter that mediates the HG effect. Indeed, in silico survey of the mouse AGT gene promoter identified a putative NF-κB binding site 5'-AGGGAATACTCC-3' at −1734, which shares a high degree of homology to the canonical AGT site 5'-GGGCGATTCCCC-3' (designated as NF-κBc).

To assess whether the putative NF-κB site in the AGT promoter is functional, we performed EMSAs using a 32P-labeled double-strand probe corresponding to this NF-κB and its flanking sequence. As shown in Fig. 3, this NF-κB probe formed a complex with nuclear proteins in MC nuclear extracts (Fig. 3A, lane 1), and this complex was competed off by an excess amount of unlabeled probe of the same sequence (Fig. 3A, lanes 2, 3, and 4) or unlabeled canonical NF-κBc (Fig. 3A, lanes 8, 9, and 10), but not by the mutant NF-κBmut probe bearing mutations at the core NF-κB site (Fig. 3A, lanes 5, 6, and 7). This complex was recognized by antibody against p65 or p50, leading to formation of supershifted complexes (Fig. 3B, lanes 6 and 9), indicating that this cis-DNA site was bound by p65/p50 NF-κB heterodimers. Importantly, the formation of the DNA-p65/p50 complex was markedly induced by HG, and...
the HG-induced complex was clearly reduced when the cells were treated with 20 nM 1,25(OH)2D3 (Fig. 3B, lanes 2-5). These data demonstrated that this NF-κB site in the AGT gene promoter interacted with p65 and p50, and the interaction was readily affected by HG and 1,25(OH)2D3 treatment. These data strongly suggest that 1,25(OH)2D3 blunted HG-induced AGT expression by blocking the NF-κB binding activity.

We then assessed the suppression of NF-κB interaction with the AGT gene promoter by ChIP assays. The PCR primers used in the ChIP assays were designed to flank the NF-κB site on the AGT promoter for detection of NF-κB binding (Fig. 4A). The ChIP assay data showed that HG markedly induced p65 or p50 binding to the NF-κB site in MCs; however, in the presence of 20 nM 1,25(OH)2D3, HG stimulation of p65 or p50 binding was greatly attenuated to the baseline levels (Fig. 4B). These results confirmed the repressive effect 1,25(OH)2D3 on NF-κB binding to the AGT promoter.

We further explored the mechanism involved in the regulation of AGT expression by measuring AGT gene promoter activity. A 1.8-kb 5′-flanking fragment of the mouse AGT gene spanning −1786 to +22 was cloned and placed in front of luciferase reporter in pGL3 plasmid. This promoter region contained the −1734 NF-κB site (Fig. 5A). When the pAGT-Luc plasmid was used to transfect MCs, the AGT promoter activity was induced by about 300% in the presence of HG, and 1,25(OH)2D3 treatment significantly reduced the AGT promoter activity by more than 50% under either LG or HG condition (Fig. 5B). Two mutant clones were studied with similar results (Fig. 5B). To address whether p65/p50 is able to overcome the 1,25(OH)2D3 suppression, MCs were cotransfected with pAGT-Luc and plasmids expressing p65 and p50. As shown in Fig. 5C, cotransfection of p65/p50 led to a dramatic increase in the promoter activity, and 1,25(OH)2D3 treatment had little effect on the induction (Fig. 5C). These results confirmed that 1,25(OH)2D3 inhibited AGT gene tran-
scription induced by HG via blocking the activity of NF-κB in kidney cells.

Finally, we investigated vitamin D regulation of AGT in vivo. We showed previously that in mice lacking VDR, hepatic AGT expression was unaltered (13); however, in the kidney the baseline levels of AGT were significantly higher in VDR-null mice compared with wild-type counterparts (Fig. 6A), consistent with the repressive action of vitamin D on renal AGT expression. We also measured AGT levels in the kidney samples from a previous study where wild-type mice were induced to diabetes with STZ with or without vitamin D analog paricalcitol treatment (33). AGT expression in the kidney was significantly induced compared with the nondiabetic control; when the diabetic mice were treated with paricalcitol at 0.4 μg/kg for 10 wk, the induction of renal AGT expression was normalized (Fig. 6B). These data confirm that 1,25(OH)2D3 downregulates hyperglycemia-induced AGT expression in vivo in a VDR-dependent manner.

DISCUSSION

Our previous works showed that vitamin D protects the kidney against diabetic nephropathy by suppressing the activation of the intrarenal RAS (31, 33). One important mechanism underlying this protection is that 1,25(OH)2D3 transrepresses renin gene transcription via targeting the cAMP-PKA pathway (29). In the present study, we demonstrated that 1,25(OH)2D3 also suppresses hyperglycemia-induced AGT expression in the kidney by blocking NF-κB activation of the AGT gene transcription. This work provides new insight into the mechanism whereby vitamin D regulates the RAS in renoprotection and thus has important implications in therapeutic treatment of diabetic nephropathy.

The expression of AGT in extrahepatic tissues contributes critically to the activation of the local RAS. In the kidney, local activation of the intrarenal RAS plays key roles in mediating renal damage in diabetes. MCs and podocytes are the major cell types that are critically involved in the development of diabetic nephropathy. In vitro studies documented that both MCs and podocytes express local RAS that is activated when these cells are exposed to HG (5, 21, 25, 27). When HG induces renin and AGT, local ANG II production is markedly increased in these cells, leading to detrimental effects. Although HG stimulation of AGT expression has been reported in a number of cell types including MCs, podocytes, and proximal tubular cells (5, 21, 25, 27), the molecular mechanism remains unclear. HG is known to also activate NF-κB in kidney cells and in patients with diabetic nephropathy (30). Our data presented in this study connect the gap between HG and AGT, because we demonstrated that NF-κB mediates the HG-induced expression of AGT. We identified a functional NF-κB binding site in the AGT gene promoter. This site was bound by p65/p50 heterodimer in the presence of HG stimulation, in association with the induction of the promoter activity.
renal diseases (8), plays a critical role in hyperglycemia-induced AGT production in the kidney. In fact, NF-κB also regulates other proteins involved in diabetic nephropathy, such as chemokine MCP-1 (9, 26), which promotes macrophage infiltration. An early study showed that protein kinase C signaling pathway was involved in HG induction of AGT in proximal tubular cells (30), and in fact PKC is known to activate NF-κB (24).

Adding to the understanding of vitamin D’s renoprotective activity, here we presented strong evidence that 1,25(OH)2D3 regulates AGT via blocking the activity of NF-κB. We showed that treatment with 1,25(OH)2D3 blocked the induction of AGT by HG at multiple levels including protein synthesis, mRNA expression, and transcriptional activity of the AGT gene promoter. Accompanying the suppression of AGT is the disruption of p65/p50 heterodimer binding to the NF-κB site in the AGT gene promoter, demonstrated by both EMSA and ChIP assays. Importantly, mutation of this NF-κB site not only blunted the response of AGT to HG, but also eliminated the downregulation by 1,25(OH)2D3. Our prior work indicates that 1,25(OH)2D3 inhibits HG-induced MCP-1 production and macrophage infiltration also by blocking the NF-κB pathway (32). Therefore, 1,25(OH)2D3 appears to use a common mechanism to regulate a panel of key factors involved in kidney disease.

In recent years, a great deal has been known as to how 1,25(OH)2D3 inhibits NF-κB activation; however, there remain controversies. Data from the literature suggest that 1,25(OH)2D3 may regulate NF-κB by a number of mechanisms. In fibroblasts lacking the VDR, the activity of NF-κB is higher compared with wild-type cells, indicating that the VDR has an intrinsic repressive effect on NF-κB (22). Early studies showed that 1,25(OH)2D3 can modulate NF-κB activity by suppressing the increase in p105/p50 and c-rel in activated lymphocytes (28), or by inhibiting RelB transcription in dendritic cells (4). On the other hand, liganded VDR was found to be able to physically bind to p65 in fibroblasts and osteoblasts (16, 22), suggesting that VDR-p65 interaction may prevent p65 DNA binding and/or nuclear translocation. Sequestration of p65 by liganded VDR, rather than blockade of p65 nuclear translocation, was reported as a mechanism for paricalcitol to inhibit renal inflammation in the unilateral ureteral obstruction model (23). We and others demonstrated that 1,25(OH)2D3 can stabilize IκBα protein, the inhibitor that blocks NF-κB nuclear translocation, to attenuate NF-κB activity in fibroblasts, keratinocytes, and pancreatic islet cells (6, 19, 22). Our previous study showed that 1,25(OH)2D3 appears to stabilize IκBα rather than directly induces VDR-p65 interaction, to arrest p65 nuclear translocation in the MCs, and this is the mechanism

![Fig. 5. 1,25(OH)2D3 suppresses HG-induced AGT promoter activity.](attachment:image1)

| A | WT | -1768 | -1734 | +22 | Luc |
| Mutant | AGGGAAATTCC | Luc |
| B | LG | LG+D | HG | HG+D |
| C | pcDNA | p65/p50 |

Fig. 5. 1,25(OH)2D3 suppresses HG-induced AGT promoter activity. A: pAGT-Luc and pAGTmut-Luc constructs illustrating the NF-κB site and its mutation. B: luciferase reporter assays. MCs were transfected with wild-type (WT) pAGT-Luc or pAGTmut-Luc (2 mutant clones). The transfected cells were cultured in LG or HG media in the presence or absence of 20 nM 1,25(OH)2D3 (+D). Luciferase activity was determined after 24 h. C: overcome of vitamin D suppression by p65/p50 overexpression. MCs were co-transfected with pAGT-Luc and plasmids expressing p65 and p50, pcDNA-p65 and pcDNA-p50, respectively. The cells were grown in LG or HG media in the presence or absence of 20 nM 1,25(OH)2D3 (+D) before luciferase activity was assayed. #P < 0.05 vs. LG. *P < 0.05 vs. corresponding untreated samples.

Fig. 6. Regulation of renal AGT expression in vivo. A: effect of vitamin D receptor (VDR) inactivation on AGT expression in the kidney. Renal AGT mRNA levels in 4-mo-old WT and VDR(−/−) mice at baseline were measured by RT-PCR. Total RNAs were extracted from whole kidneys. *P < 0.05 vs. WT; n = 4 in each genotype. B: renal AGT mRNA expression in diabetic WT mice with or without paricalcitol (Pari; 0.4 μg/kg) treatment for 10 wk starting from week 3. The mice were induced to diabetes with streptozotocin (STZ) for 13 wk before death. Total RNAs were extracted from whole kidneys. #P < 0.05 vs. C. *P = 0.05 vs. STZ; n = 4 in each genotype.
whereby 1,25(OH)2D3 inhibits HG-induced MCP-1 expression in these cells (32). Therefore, it is reasonable to speculate that 1,25(OH)2D3 blocks HG-induced AGT expression by a similar mechanism.

The in vivo data further support the repressive action of vitamin D on AGT expression. Although VDR inactivation had little effect on hepatic AGT expression (13), AGT expression in the kidney was upregulated in mice unable to synthesize vitamin D on AGT expression. Although VDR inactivation had little effect on hepatic AGT expression (13), AGT expression in the kidney was upregulated in mice unable to synthesize vitamin D(3). However, the difference in the effect of vitamin D signaling on AGT expression between the liver and kidney may be explained by the difference in VDR levels in these two organs. VDR is abundantly expressed in the kidney, whereas the expression in the liver is very low (2). Moreover, our previous study showed that in diabetic state the induction of AGT in the kidney was more robust in VDR(−/−) mice than in wild-type mice (31), and in the present study we demonstrated that vitamin D analog was able to attenuate the renal AGT induction in wild-type diabetic mice after 10-wk treatment. This is consistent with the in vitro data.

In summary, in the current study we demonstrated that NF-κB is critically involved in HG-induced AGT expression in the kidney, and vitamin D attenuates AGT induction by blocking the NF-κB signaling pathway. This finding strengthens the concept that vitamin D protects against hyperglycemia-induced kidney injury by targeting the RAS, which has important implications to the prevention and intervention of diabetic nephropathy.

GRANTS

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