We showed previously that decreased extracellular salt or chloride up-regulates the cortical thick ascending limb of Henle (cTALH) COX-2 expression via a p38-dependent pathway. The present studies determined that low salt medium increased COX-2 mRNA expression 3.9-fold control by 6 h in cultured cTALH, which was blocked by actinomycin D pretreatment, suggesting transcriptional regulation. Luciferase activity (normalized to β-galactosidase activity) of the full-length (−3400) COX-2 promoter in cTALH increased from 1.8 ± 0.3 in control media to 5.8 ± 0.7 in low salt (n = 9; p < 0.01). Low chloride medium had similar effects as low salt has on COX-2 promoter activity. Deletion constructs −815, −512, and −410 were similarly stimulated, but −385 could not be stimulated significantly by low salt (1.8 ± 0.3 versus 2.4 ± 0.5, n = 10). This suggested involvement of an NF-κB cis-element located in this region, which was confirmed by utilizing a construct with a point mutation of this NF-κB-binding site that was not stimulated by low salt medium. Co-incubation of the specific p38 inhibitor, SB203580 or PD169316, inhibited a low salt-induced increase in luciferase activity of the intact COX-2 promoter (5.8 ± 0.7 versus 1.1 ± 0.2, n = 8 and 1.4 ± 0.4, n = 4 respectively, p < 0.01). Mobility shift assays indicated that the low salt medium stimulated NF-κB binding activity, and this stimulation was inhibited by p38 inhibitors. To test whether p38 also increased COX-2 expression by increasing mRNA stability, cTALH were incubated in low salt for 2 h, and actinomycin was then added with or without SB203580. p38 inhibition led to a decreased half-life of COX-2 mRNA (from 68 to 18 min, n = 4–7, p < 0.05). Therefore, these studies indicate that p38 stimulates COX-2 expression in cTALH and macula densa by transcriptional regulation predominantly via an NF-κB-dependent pathway and by post-transcriptional increases in mRNA stability.
anti-Tamm Horsfall antibody, as previously described (8, 17, 18).

Briefly, the renal cortex was dissected, minced, and digested with 0.1% collagenase. After blocking with 10% bovine serum albumin, the sieved homogenates were incubated with goat anti-human Tamm Horsfall antisem (50 mg/ml) for 30 min on ice, followed by washing and addition to plastic Petri dishes coated with anti-goat IgG (8 mg/ml). Attached cells resistant to washing were dislodged and grown to confluence in Dulbecco’s modified Eagle medium/Ham’s F-12 medium with 10% fetal calf serum, 100 units/ml penicillin, and 100 μg/ml streptomycin at 37 °C in 95% air, 5% CO₂.

**Plasmid Constructs and Mutagenesis**—The proximal 3.2 kb of the mouse COX-2 promoter was cloned by reverse transcription-PCR from mouse kidney RNA with the 5’ primer (CAT GAA TTC TGT TCT GCC CTC ATG TATG ATG) and the 3’ primer (TAA GGT ACC GGT GGA GCT GCC AGG ATG CAG TGG A) and then subcloned into a luciferase reporter vector (Promega). The −815 and −512 deletion luciferase reporter constructs were a generous gift from Dr. Yamamoto (19). The mouse COX-2 promoter was cut with EcoRI and PvuII, blunted, and self-ligated to make the −385 deletion construct. The XhoI cutting site was introduced by point mutation to produce the −410 deletion construct. NF-κB and CREB point mutants were also constructed (Stratagene, La Jolla, CA). Briefly, the luciferase reporter plasmid containing the mutation for NF-κB or CREB was developed. After PCR amplification, the product was treated with endonuclease DpnI and then transformed to XL1-Blue supercompetent cells. All of the mutants and other plasmid constructs were verified by sequencing.

**Transfection and Luciferase Reporter Assay**—Primary cultured cTALH cells at 50–60% confluence were transiently transfected with LipofectAMINE reagent (Invitrogen). When the cells grew to confluence (48 h later), they were made quiescent with serum-free medium for 16 h and then changed to the indicated condition (e.g. low salt or low chloride medium) for 6 h. The content of low salt or low chloride medium was as previously described (16). The cells were extracted with lysis buffer (luciferase assay system; Promega), and their luciferase activities were measured with a LumiCount Microplate Luminometer (model luciferase assay system; Promega), and their luciferase activities were measured with a LumiCount Microplate Luminometer (model AL10000; Packard Bioscience Co., Meridian, CT). The results were normalized to β-galactosidase activity as previously described (20).

**RNA Extraction and Northern Blotting**—Primary cultured cTALH cells were homogenized in buffer containing 10 mM HEPES, pH 7.9, 10 mM KCl, 0.1 mM EDTA, 0.1 mM EGTA, 1 mM dithiothreitol, 0.5 mM phenylmethylsulfonyl fluoride, and 0.1 mM leupeptin. 10% Nonidet P-40 was added to make a final concentration of 0.5%, incubated on ice for 30 min, and centrifuged. After washing, the pellet was resuspended in 20 mM HEPES, pH 7.9, 400 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM dithiothreitol, 1 mM phenylmethylsulfonyl fluoride, 10% glycerol, and 0.1% leupeptin with 1/10 volume of 4 M KCl. EMSA was performed as described (24). Double-stranded NF-κB and CREB oligonucleotides were end-labeled with [32P]ATP by T4 polynucleotide kinase. 5 μg of nuclear protein was added to the reaction mixture, incubated for 30 min at 25 °C, and resolved on 6% nondenatured polyacrylamide gels. Antibody supershift EMSA was performed by incubating nuclear extracts with anti-p65, -p50, -p52, or -c-Rel antibody as described under “Experimental Procedures.” After quiescence, the cells were exposed to normal growth medium without serum or low salt medium for 6 h. Luciferase activity was normalized to β-galactosidase activity and expressed as fold control. ***, p < 0.01.

**RESULTS**

In previous studies we demonstrated that immunoreactive COX-2 protein increased in primary cultured cTALH in response to exposure to low salt or low chloride medium. Substitution of other cations for sodium did not affect COX-2 expression, whereas substitution of other anions for chloride led to increased COX-2 expression (16). In the present studies, we determined that COX-2 mRNA expression increased in low salt medium, with an apparent peaking within 6 h (3.9 ± 0.4-fold control) and increased expression observed for up to 16 h (3.4 ± 0.5-fold control) (Fig. 1A). When cells were preincubated with 5 μg/ml actinomycin D (25) for 20 min prior to exposure to low salt medium, increases in COX-2 mRNA expression were blocked (Fig. 1B). The time course of COX-2 mRNA increase and inhibition by actinomycin D were similar in low chloride medium (not shown).

Informatively, deletions of the murine COX-2 promoter were constructed (Fig. 2A) and transfected into cTALH cells. After quiescence, the cells were exposed to normal or low salt medium for 6 h, and luciferase activity was measured, normalized by β-galactosidase activity, and expressed as fold control (Fig. 2B). Luciferase activity of the vector transfected cells was identical if grown in normal medium or low salt medium (1.2 ±
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0.1-fold control, n = 14–18, NS). There were no significant differences of luciferase activity among the six groups when grown in normal medium. Low salt medium elevated the luciferase activity of full-length COX-2 promoter-transfected cells (5.2 ± 0.4-fold control, n = 10, p < 0.01). Low salt medium induced similar increases in promoter activity with the −815 construct (5.4 ± 0.6-fold control, n = 17–18, p < 0.01) and the −512 deletion construct (5.6 ± 0.5-fold control in low salt medium, n = 17–18, p < 0.01). However, there was no significant increase in luciferase activity by low salt medium in the −385 deletion construct (1.8 ± 0.2 in normal medium versus 2.4 ± 0.5-fold control in low salt medium, n = 10, NS). Of note, the murine COX-2 promoter contains putative CREB and NF-κB sites between −512 and −385. An additional deletion at −410 removed the putative CREB site but did not interrupt the NF-κB site. Fig. 2A indicated that the −410 deletion still responded to low salt stimulation (1.6 ± 0.2 in normal medium versus 5.5 ± 0.8-fold control in low salt medium, n = 8, p < 0.01). The NF-κB inhibitor, BAY 11–7082 (10 μM) (26) also inhibited the low salt medium-induced increase in luciferase activity in the −815 construct (2.7 ± 0.6-fold control, n = 8, p < 0.01) (Fig. 3).

To confirm a role for the putative NF-κB site in low salt medium-induced increases in luciferase activity, inactive mutations of the indicated NF-κB and CREB sites were constructed (19) (Fig. 4A). The CREB mutant construct had a significant increase in luciferase activity in response to the low salt medium, although the stimulation was somewhat less than what was observed with the wild type construct. In contrast, the NF-κB mutation completely blocked low salt medium-induced activation (Fig. 4B). Similar responses were seen in the low chloride medium (−815 deletion, from 1.7 ± 0.2 to 4.6 ± 1.0-fold control, n = 4, p < 0.01; NF-κB mutation, from 1.2 ± 0.1 to 1.3 ± 0.3-fold control, n = 4, NS). (Fig. 4C).

In EMSA of cTALH nuclear extracts incubated with a consensus NF-κB oligonucleotide, two specific bands were detected (Fig. 5A). Low salt medium incubation stimulated the NF-κB binding activity (Fig. 5B). CREB binding by nuclear extracts from cTALH cells exposed to low salt medium was also slightly decreased compared with control (Fig. 5C). Supershift assay indicated that the two bands seen in the NF-κB EMSAs were p65 and p50 (Fig. 5D).

Because activation of cytoplasmic NF-κB and translocation to the nucleus is regulated by phosphorylation of IκB, we determined IκB and pIκB expression in cTALH cells. Low salt medium decreased IκB expression (0.4 ± 0.1-fold control, n = 7, p < 0.01) (Fig. 6A) and increased immunoreactive pIκB expression (2.2 ± 0.2-fold control, n = 8, p < 0.05) (Fig. 6B).

When a p38-specific inhibitor, PD169316 (1 μM) (16) or SB 203580 (10 μM) (27), was added to low salt or low chloride medium, stimulation of luciferase activity in the −815 construct was decreased (PD169316, from 5.4 ± 0.3 to 1.4 ± 0.4-fold control, n = 6, p < 0.01; SB203580, 1.1 ± 0.2-fold control, n = 8, p < 0.05) (Fig. 3). EMSA further confirmed that SB203580 reduced the increases in NF-κB binding ability (Fig. 5B). SB203580 also inhibited increases in IκB phosphorylation stimulated by low salt (1.4 ± 0.1 of control medium, n = 8, NS).
FIG. 5. EMSA in cTALH cells exposed to low salt medium. A, NF-κB EMSA. Gel shift assays with NF-κB probes were performed as described under “Experimental Procedures.” Lane 1, negative control without nuclear extract; lanes 2–4, EMSA with nuclear extract from cTALH cells grown in normal growth medium; lane 5, specific competition with unlabeled NF-κB oligonucleotide; lane 6, nonspecific competition with unlabeled noncompetitor AP1 consensus oligonucleotide. B, low salt increases NF-κB binding, which is inhibited by the p38 inhibitor, SB203580. Lane 1, free probe only; lane 2, nuclear extracts of cTALH cells in normal growth medium; lane 3, low salt medium; lane 4, low salt medium combined + SB203580 (10 μM). C, low salt has less effect on CREB binding. Lane 1, free probe; lane 2, cTALH cells in normal growth medium; lane 3, low salt; lane 4, low salt + SB203580; lane 5, competition with unlabeled CREB oligonucleotide; lane 6, nonspecific competition with unlabeled noncompetitor AP1 consensus oligonucleotide. D, supershift assay of NF-κB binding. Lane 1, negative control without nuclear extract; lane 2, rabbit IgG; lane 3, NF-κB p65-specific antibody; lane 4, NF-κB p50-specific antibody; lane 5, simultaneous addition of p65 and p50 antibodies; lane 6, c-Rel antibody.

and prevented decreases in IκB levels (0.9 ± 0.1, n = 7, NS) (Fig. 6).

In other cell systems, alterations in COX-2 mRNA expression have been attributed to both transcriptional and post-transcriptional regulation. To test the possibility that there was a component of post-transcriptional stabilization of COX-2 mRNA in response to low salt or low chloride medium, cTALH cells were stimulated by low salt medium for 2 h, and then actinomycin D was added with or without the specific p38 inhibitor, SB203580. p38 inhibition led to an increased decay rate of COX-2 mRNA (from 68 to 18 min, n = 4–7, p < 0.05) (Fig. 7), suggesting that p38 activity may also regulate COX-2 mRNA stability with low salt stimulation.

DISCUSSION

In vivo, dietary salt restriction increases COX-2 expression in the macula densa and the surrounding cTALH cells (5, 6). Macula densa/cTALH regulate renal renin expression and renal hemodynamics in response to alterations in tubular luminal chloride concentration (15). Macula densa sensing of luminal chloride is dependent on net apical transport, mediated by the luminal Na+/K+/2Cl− co-transporter, BSC-1 (28–30). Na+/K+/2Cl− co-transporter has a high affinity for Na+ and K+ but a lower affinity for Cl− (in the 30–50 mmol/l range), resulting in sensitivity to physiologic changes in luminal chloride (31). The potential role of prostaglandins in mediation of macula densa function has prompted further studies to investigate the signals mediating this increased COX-2 expression.

In our previous studies utilizing primary cultured cTALH cells, we determined that immunoreactive COX-2 expression increased significantly when medium NaCl was decreased without alterations in extracellular osmolality or following administration of the Na+/K+/2Cl− co-transport inhibitor, bumetanide. Selective substitution of chloride led to increased COX-2 expression, whereas selective substitution of sodium had no effect (16). Similarly, it has been reported recently that low chloride stimulates prostaglandin E2 release and COX-2 expression in MMDD1 cells, which are derived from mouse macula densa (32). These studies suggested that decreased extracellular [Cl−] initiates the overexpression of COX-2 observed in vivo in response to salt restriction.

The present studies indicate that a lessened extracellular chloride-mediated increase in p38 activity stimulates COX-2 expression in cTALH and macula densa by transcriptional regulation via an NF-κB-dependent pathway and by post-transcriptional increases in mRNA stability. In other systems, different members of the mitogen-activated protein kinase super-
family have been shown to increase COX-2 expression, including extracellular signal-regulated kinase (33, 34), c-Jun N-terminal kinase (34–36), and p38-dependent pathways (33–35, 37–39) (40). Our previous study indicated that activation of p38 occurred in cultured cTALH cells incubated with either low salt or low chloride medium and preceded increases in COX-2 protein expression; the increased COX-2 expression was prevented by specific p38 inhibitors (16). Similar findings were observed in MMDD1 cells (32). In addition, in vivo, increased pp38 immunoreactivity was detected in macula densa and cTALH in response to dietary sodium deprivation (16). The current study showed that p38 specific inhibitors abolished low salt-induced increase in COX-2 promoter-mediated luciferase p38 inhibition and also led to a decreased half-life of COX-2 mRNA. Therefore, the p38 pathway mediates both transcriptional and post-transcriptional regulation of COX-2 in cTALH induced by low salt/chloride.

Transcriptional regulation of COX-2 expression appears to involve diverse mechanisms in different cell types and conditions (41–46), and transcription factors, such as NF-κB (19, 47–50), CREB and E-box promoter elements (51), and AP-1 (52, 53), have all been determined to mediate COX-2 expression. In the present studies, the NF-κB inhibitor BAY 11–7082 (26) partially reversed increased luciferase activity in response to decreased NaCl or chloride, and selective deletion or mutation of a putative NF-κB binding site in the murine COX-2 promoter completely inhibited NaCl or chloride-mediated stimulation, suggesting a predominant role for NF-κB in the transcriptional regulation. EMSA confirmed stimulated nuclear NF-κB binding activity in response to alterations in extracellular ionic content. Furthermore, the inhibition of NF-κB activity by the p38 inhibitor SB203580 indicated that the p38 pathway mediates NF-κB activation.

CREB promotes recruitment of the transcriptional co-activator CBP and p300. It has been shown to function as a classic intracellular second messenger in glucose homeostasis, growth factor-dependent cell survival, and involvement in learning and memory (54). Although NF-κB activation appears to be absolutely necessary for low salt-mediated increases in COX-2 transcription, our luciferase activity and EMSA data also suggest the possibility of an additional role for CREB. In this regard, in activated macrophages both CREB and NF-κB, as well as C/EBP β and δ, have been identified as key factors in coordinately orchestrating COX-2 transcription (55).

NF-κB is a heterodimer composed of p50 and RelA/p65 subunits. Its inactive form is found in cytoplasm associated with IκBα and IκBβ. In response to agonist stimulation, IκB is phosphorylated at two critical serine residues by IκB kinase and degraded, resulting in the release of NF-κB, which translocates to the nucleus to activate transcription of responsive genes (56–61). Although some previous studies in other systems had not found that p38 mediated NF-κB nuclear translocation (62, 63), recent studies have suggested such an interaction (64, 65). In the present studies, increased levels of phosphorylated IκB and decreases in level of immunoreactive IκB, both of which were inhibited by p38 inhibitors, suggested that decreased medium NaCl or chloride activated IκB phosphorylation in cTALH through a p38-dependent pathway.

In addition to the transcriptional induction of COX-2, stabilization of the COX-2 mRNA at the post-transcriptional level is important for maximal expression (66–68). A crucial role for
AU-rich sequence elements in the COX-2 3′-untranslated region to stabilize COX-2 mRNA expression has been shown in human lung fibroblast cells (66), HeLa-To cells (68), and murine macrophage-like cells (69). Further studies will be required to determine whether p38 activation by decreased extracellular chloride increases COX-2 mRNA stability by a similar mechanism. In summary, these studies indicate that p38 stimulates COX-2 expression in cultured cTALH by transcriptional regulation predominantly via a NF-κB-dependent pathway and by post-transcriptional increases in mRNA stability.

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Cyclooxygenase-2 Expression in Cultured Cortical Thick Ascending Limb of Henle Increases in Response to Decreased Extracellular Ionic Content by Both Transcriptional and Post-transcriptional Mechanisms: ROLE OF p38-MEDIATED PATHWAYS

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J. Biol. Chem. 2002, 277:45638-45643.
doi: 10.1074/jbc.M206040200 originally published online September 16, 2002

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