IJKD KIDNEY DISEASES

Regulation of Cyclic Adenosine Monophosphate Response Element Binding Protein on Renin Expression in Kidney Via Complex Cyclic Adenosine Monophosphate Response Element-Binding-Protein-Binding Protein/P300 Recruitment

Pei Li,[1] Jing Zhang,[1] Yuanfang Zhu,[2] Ming Liu,[1] Xuan Jin[1]

[1]Center of Assisted Reproduction, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China
[2]Department of Obstetrics and Gynecology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China

Original Paper

Keywords. cyclic AMP response element-binding protein, renin, kidney

Introduction. Renin synthesis and release is the rate-limiting step in the renin-angiotensin system, because cyclic adenosine monophosphate (cAMP) has been identified as dominant pathway for renin gene expression, and cAMP response element-binding protein (CREB) is found in the human and mouse renin promoter. This study aimed to evaluate the role of CREB in expression of the renin gene.

Materials and Methods. We created conditional deletion of CREB in mice with low-sodium diet, specifically in renin cells of the kidney. To assess the effect of CREB on renin expression, immunostaining of renin was used in samples from wild-type mice and mice with gene knock-down of CREB. Cyclic AMP response element-binding-protein-binding protein (CBP) and p300 were measured in cultured renin cells of the mice, and RNA detection was done with real-time polymerase chain reaction.

Results. With low-sodium diet, renin was expressed along the whole wall of the afferent glomerular arterioles in wild-type mice, while there was no increase or even decrease in renin expression in CREB-specific deletion mice; RNA level of renin in cultured cells decreased by 50% with single knock-down of CREB, CBP, or p300, and decreased 70% with triple knock-down of CREB, CBP, and p300.

Conclusions. This study found that CREB was important for renin synthesis and the role of CREB can be achieved through the recruitment of co-activators CBP and p300.

IJKD 2015;9:440-8
www.ijkd.org

INTRODUCTION

The plasma renin-angiotensin system (RAS) plays a central role in the regulation of blood pressure and electrolyte and volume homeostasis, and a functional RAS is required for normal mammalian renal development.[1] Renin is a protease that initiates an enzymatic cascade. Renin secretion has been recognized the first and rate-limiting step in the activity of the entire system.[2] Transcription of renin genes is tissue-specific and developmentally regulated.[3]

Kidney is the major source of active circulating renin. In the mouse kidney, renin expression is first detected at 14.5 days of gestation in the earliest developing arteries, and then in the newly forming arterial branches, subsequently restricted to smaller arterials and arterioles, until in the adult, whose renin is stored and released by juxtaglomerular granular (JG) cells. The rate of renin granule exocytosis determines the level of activation of

the RAS. In addition to the JG area in the kidney, renin gene is also expressed in some other tissues including the ovaries, adrenal glands, brain, and anterior prostate.[4] Renin is encoded by 1 gene in humans and in C57BL/6 strain mice, but in J129 strain mice, there are 2 renin genes (*Ren1d and Ren2*), which share 97% of their amino acid identity. Ren1 protein is the major source of circulating renin.[3]

Renin production from the JG cells is regulated by a variety of factors, and these factors are of particular interest and importance in understanding the physiology of the RAS as well as therapeutic targets for a myriad of cardiovascular diseases. Cyclic adenosine monophosphate (cAMP) is a second messenger used for intracellular signal transduction of a diverse range of biologic processes and is also suggested to be the central stimulator of renin gene expression.[5,6] Factors that increase the levels of cAMP have a stimulating effect on renin expression in cultured JG cells.[7,8] Through cAMP response elements (CRE) located in target gene promoters, cAMP signals interact with members of the activating transcription factor-1/cAMP response element-binding protein (CREB)/cAMP response element modulatory protein basic leucine zipper transcription factor family. Several binding sites of CREB have been identified in the human and mouse renin promoter.[9-15] Intracellular delivery of cAMP in signal JG cell elicits exocytosis of renin depends on protein kinase A activity.[16-18] Cyclic AMP binds to the regulatory subunit of protein kinase A to free the catalytic subunit, which enters the nucleus and phosphorylates CREB, and finally results in the recruitment of ubiquitous co-activators cAMP response element-binding-protein-binding protein (CBP)/p300 to promote gene transcription.[19-22] These ubiquitous co-activators were originally identified as binding partner to the CREB and the adenovirus early-region 1A, respectively.[23] The CBP/p300 share several conserved regions, which constitute many overlapping functions and henceforth be referred to as the CBP/p300. They have interchangeable roles during embryonic development and maintain cellular homeostasis in many processes.[24,25] The CBP/p300 functions as a transcriptional cofactor for proteins involved in cell viability or proliferation; aberrant CBP/p300 activity has been observed in various human diseases.[26,27] They also play essential roles in renin cells and primordial germ cells.[8,28]

To define the role of CREB and CBP/p300 in renin synthesis and release, we used a conditional deletion approach in which floxed CREB, CBP, and p300 mice were crossed with mice expressing *cre recombinase (cre)* in renin cells, as well as RNA interference method in cultured renin cells.

MATERIALS AND METHODS

Animals

Housing and experimental use of the mice conformed to the guiding principles in the care and use of animals approved by the Animal Care and Use Committee of Jiangxi Province. The conditional deletion of the activator CREB in renin cells was derived from crossing 2 strains of animals: mice with Ren1dcre,[29] which express cre in renin cells, and mice with floxed alleles of the activator CREB (CREB flox) as previously described.[8,30] All mice used in this study were offspring of compound heterozygotes (Ren1d+/Cre/CREB+/fl). Experiments were performed in wild-type mice and renin cell-specific CREB knock-out mice. Any mouse carrying a Ren1dcre allele also has a Ren2 allele since the targeting to produce this mouse was done in embryonic stem cells containing both *Ren1d* and *Ren2*.[29] To obtain recruitment of renin-expressing cells, 5-week-old wild-type and renin cell-specific CREB knock-out mice were administered a low-sodium diet (0.05%, Harlan, Madison, WI, USA) plus captopril (Sigma, St Louis, MO, USA) in the drinking water for 12 days (6 control animals and 8 treated animals).

Preglomerular Arteriolar Smooth Muscle Cells Culture

Mouse preglomerular arteriolar smooth muscle cells (SMCs) were isolated according to the methods described previously, using the kidneys of 2 to 4 mice (6 to 8 weeks old) for 1 preparation of SMCs.[31] After the differential plate being generated for 2 or 3 passages, the cultures had the highest proportion of SMCs. The cells maintained their identity for at least 25 passages.

RNA Interference with Small Interfering RNA

Cells were transfected with SMART-pool CREB small interfering RNA (SiRNA), SMART-pool CBP SiRNA, and SMART-pool p300 SiRNA, separately (Dharmacon, Lafayette, CO, USA), or nontargeting SiRNA pool (Dharmacon) as negative control. Small interfering RNA was complexed with DharmaFECT

SiRNA transfection reagent (Dharmacon), according to the manufacturer's instructions. The transfection efficiency was evaluated by SiGlo (Dharmacon). Twenty-four hours before cells were harvested, SMCs were treated with forskolin (10 µmol/L of forskolin and 100 µmol/L of 3-isobutyl-1-methylxanthine) to stimulate renin expression. The transfection per se had no effect on the cell growth or fate, and the transfection efficiency was evaluated by SiGLo (Thermo Fisher Scientific, Waltham, MA, USA) was close to 90%.

RNA Extraction and Reverse Transcription Polymerase Chain Reaction

Cells were lysed and tissues were ground in Tri-Reagent (Molecular Research Center, Cincinnati, OH, USA). Total RNA was extracted according to the manufacturer's instructions. The complementary DNA was prepared from 2 µg of RNA using Moloney murine leukemia virus reverse transcriptase (Life Technologies, Grand Island, NY, USA) and an oligo(dT)15 primer according to the manufacturer's instructions. Polymerase chain reaction was performed on 2 µL of the reverse transcription reaction as a template using *Taq* DNA polymerase (Promega, Madison, WI, USA). The primer sequences for all the genes examined are listed in the Table.

Primers Used for Reverse Transcription and Real-Time Polymerase Chain Reaction

Gene	Primer Sequence
CBP	
Forward	5' AGAGAACAGTTCGAACGACACAGC
Reverse	5' TCTAGAGTTGGCATAAGTGCCTGG
CREB	
Forward	5' AACATACCAGATCCGCACAGCACC
Reverse	5'GTTCTTCATTAGACGGACCTCTCTCTTCCG
GAPDH	
Forward	5' GTCATCATCTCCGCCCCTTC
Reverse	5' GTCCACCACCCTGTTGCTGTAG
P300	
Forward	5' AATTCACCTTCTCCTGTTCCTAGCCG
Reverse	5' AGGTGTTGGAATTGCTGTTGCTGG
Renin	
Forward	5' ATGCCTCTCTGGGCACTCTT
Reverse	5' GTCAAACTTGGCCAGCATGA

Immunohistochemistry

The sections were incubated with the primary antibodies specific for renin and CREB (abCAM, Hong Kong), respectively, in 10% goat serum, and then biotinylated secondary antibody and horseradish peroxidase-conjugated strepavidin, normal immunoglobulin G instead of the primary antibody, was served as the negative controls.

Statistical Analyses

Values for continuous variables were shown as the mean ± standard error of mean. The 1-way analysis of variance test was used for comparisons between groups. *P* values less than .05 were considered significant.

RESULTS

Figure 1 shows the expression pattern and distribution of renin and CREB in the kidney. Renin

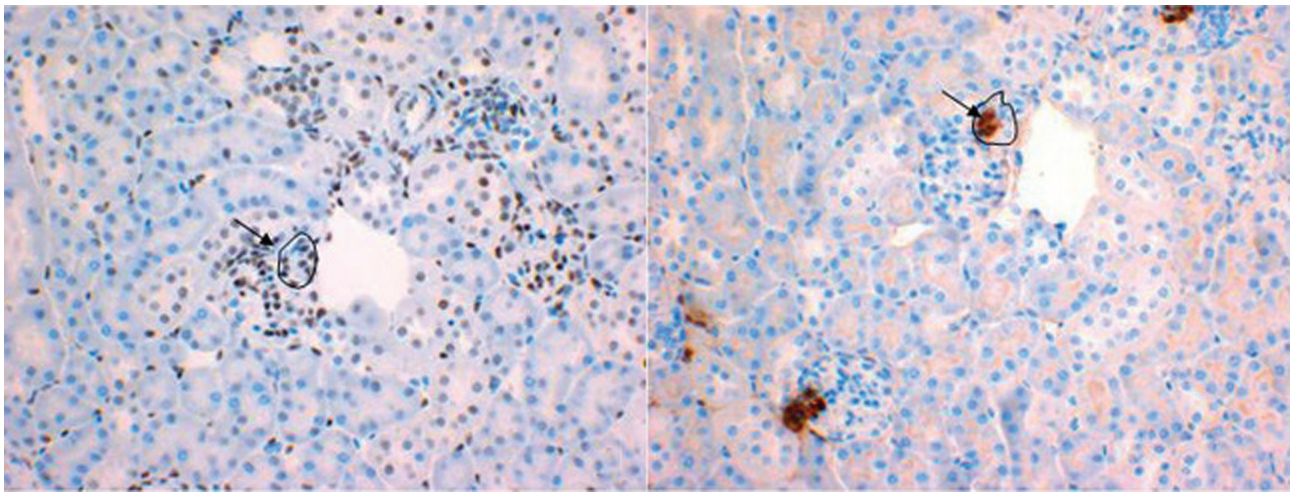

Figure 1. Left, Immunostaining for cyclic AMP response element-binding protein in consecutive sections of kidneys. **Right,** Immunostaining for renin in consecutive sections of kidneys. Nuclear staining for cyclic AMP response element-binding protein (brown) is present in nearly all cells, including juxtaglomerular cells (arrow). Renin staining (brown) is present in juxtaglomerular area (arrow).

immunostaining was found in the kidney cortex in juxtaglomerular location, associated with renin expression. In serial sections, CREB was detected in juxtaglomerular cells where renin was expressed, as well as tubules and glomeruli.

Figure 2A shows immunostaining for CREB in wild-type mice in nearly all cells, including JG cells, arterioles, and tubules. While in CREB*fl*/

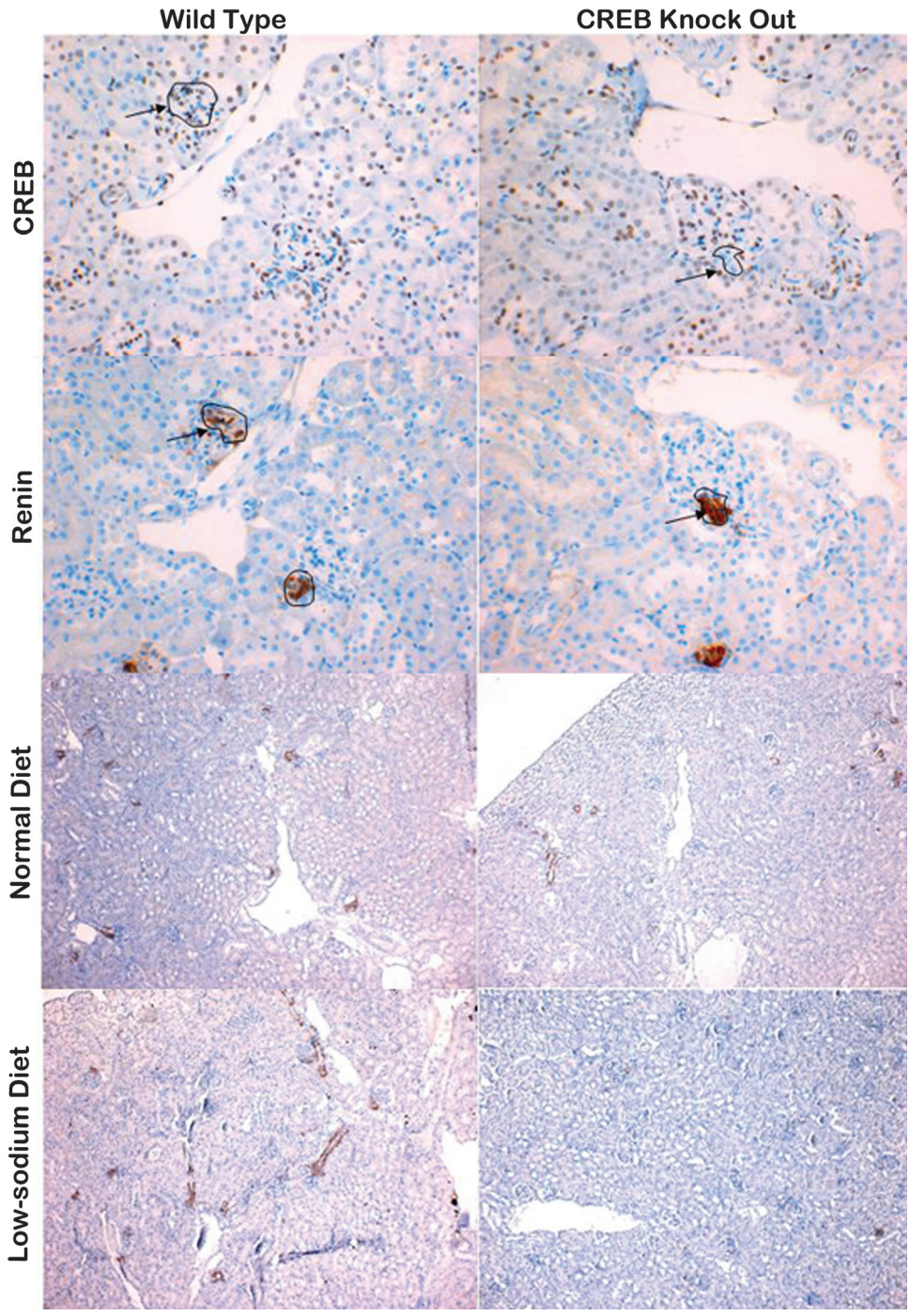

Figure 2. Deletion of cyclic AMP response element-binding protein (CREB) in renin cells does not alter basal renin expression in adult kidney, but influence renin recruitment in low-sodium diet mice kidney. Top two rows are immunostaining for renin and CREB in consecutive sections of kidneys from wild type and *CREB* gene knock out mice, respectively. In wild type kidney, renin cells are positive for CREB (brown nuclei), but in *CREB* knock out kidney, CREB is absent (blue nuclei). Bottom two rows are immunostaining for renin in wild type and *CREB* knock out mice with normal and low-sodium diet, respectively. In wild type mice, renin staining increased in low-sodium diet kidney compared with normal diet. By contrast, in *CREB* knock out mice renin staining did not increase or even decreased in low-sodium diet kidney.

fl;Ren*cre*/+ mice, CREB was absent in the nuclei of the JG cells, and expression of CREB in other kidney structures, such as tubules, was still obvious, which means CREB was knock-out by *cre* recombinase specifically in the JG cells. Interestingly, deletion of CREB did not affect the expression of renin, compared with wild-type mice, in consecutive sections of CREB knock-out kidney. There was no apparent alternation in the distribution of renin (Figure 2B). However, when the mice got low-sodium diet, no increase or even decrease of renin expression was found in CREB specific deletion mice. In contrast, immunostaining of renin in wild-type mice increased significantly, and renin was expressed along the whole wall of the afferent glomerular arterioles (Figure 2C).

Harvesting mRNA from the preglomerular arteriolar SMCs in culture, CREB, CBP, and p300 expression was detected by reverse transcription polymerase chain reaction (Figure 3A). The transfection per se had no effect on the cell growth or fate, and the transfection efficiency was close to 90% (Figure 3B). To evaluate the influence of CREB on the renin mRNA expression, CREB was knocked-down by transfection with 200 nmol/L of specific SiRNA in cultured SMCs treated with forskolin. Nontarget SiRNA was used as negative control to transfect SMCs treated with forskolin. After 48 hours in the presence of the specific SiRNA, CREB mRNA expression was significantly decreased as compared with the control cells (Figure 3C). The changes in CREB abundance in SiRNA-treated cells were paralleled by decrease of renin mRNA compared with negative control in response to forskolin treatment (Figure 3D). Similar results were seen in the SMCs with CBP, p300 knock-down separately. The diminished expression of CBP and p300 was associated with significant decrease of renin mRNA compared with the negative control, as shown in Figures 3C and 3D by the end-point reverse transcription polymerase chain reaction. The forskolin-untreated cells did not express renin mRNA.

In SMCs with triple knock-down (200 nmol/L of siRNA for each gene), the level of CREB, CBP, and p300 mRNA was effectively downregulated. Expression of CREB showed a 50% reduction in comparison to the control group, and CBP and p300 mRNAs were drastically reduced to a remaining level of 10% to 15% of the control (Figure 4A). The

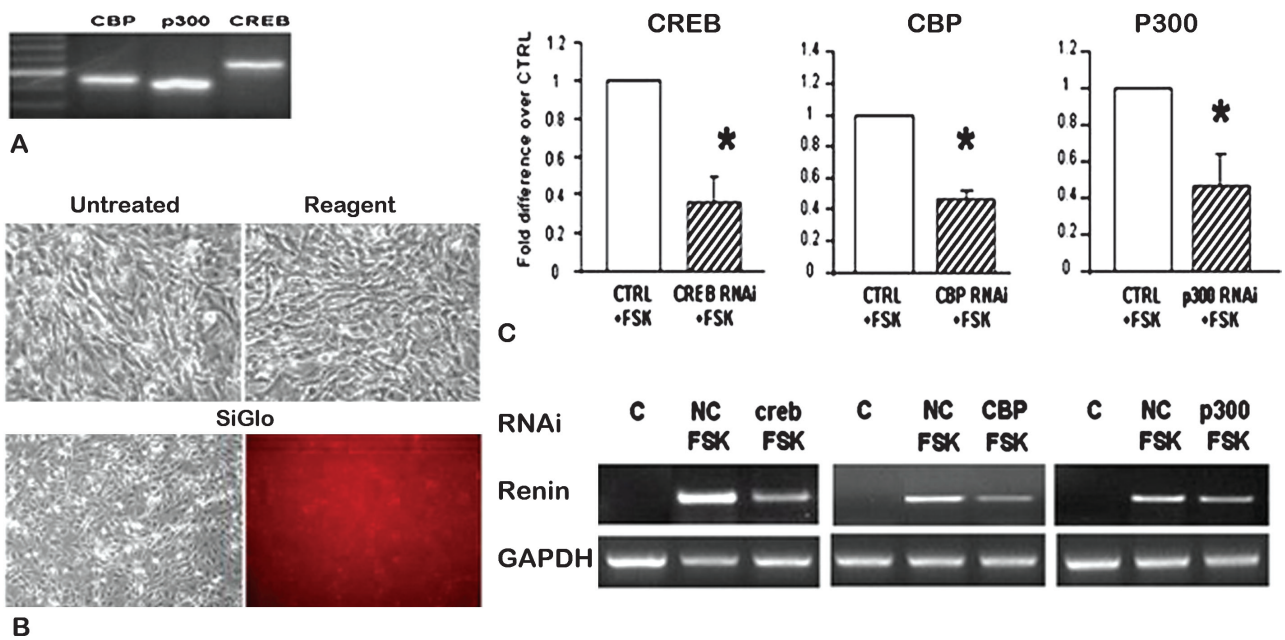

Figure 3. Cyclic AMP response element-binding protein (CREB)/CBP/P300 involved in the regulation of renin mRNA expression in cultured renin cells. A, Polymerase chain reaction from cultured renin cells cDNA show the presence of CREB mRNA, CBP mRNA, and P300 mRNA. B, Forty-eight hours in transfection reagent, cultured cells grow as full confluence as that of untreated group, and transfection of SiGlo shows the efficiency is 90%. C and D, Single knock down of CREB, CBP, and P300 in cultured renin cells. Quantitative real-time polymerase chain reaction shows that the level of CREB, CBP, and P300 reduced separately significantly ($P < .05$), and renin mRNA decreased correspondingly as the band of PCR shown.
*$P < .05$

loss of CREB, CBP, and p300 was associated with a lower level of renin mRNA in the triple knock-down (renin mRNA expression was reduced by 70% compared to the negative control) than in the single gene knock-down (reduced by around 40% compared to the negative control; Figure 4B). The remarkable influence of triple-gene knock-down on renin expression showed a synergistic effect.

As shown in Figure 4C, about 50% decrease was seen for the mRNA expression of CBP and p300, same as previously observed in the single knock-down. The renin level in the double knock-down was reduced in similar proportion to the single knock-down (Figure 4D).

The partial recovery of CBP, p300, and renin expression in the double knock-down compared to the triple gene knock-down suggested a strong involvement of CREB in this system of a direct action on CBP and p300 expression. As shown in Figure 4E, the level of CBP and p300 expression was impaired by CREB knock-down with only 20% and 40% of the remaining expression for CBP

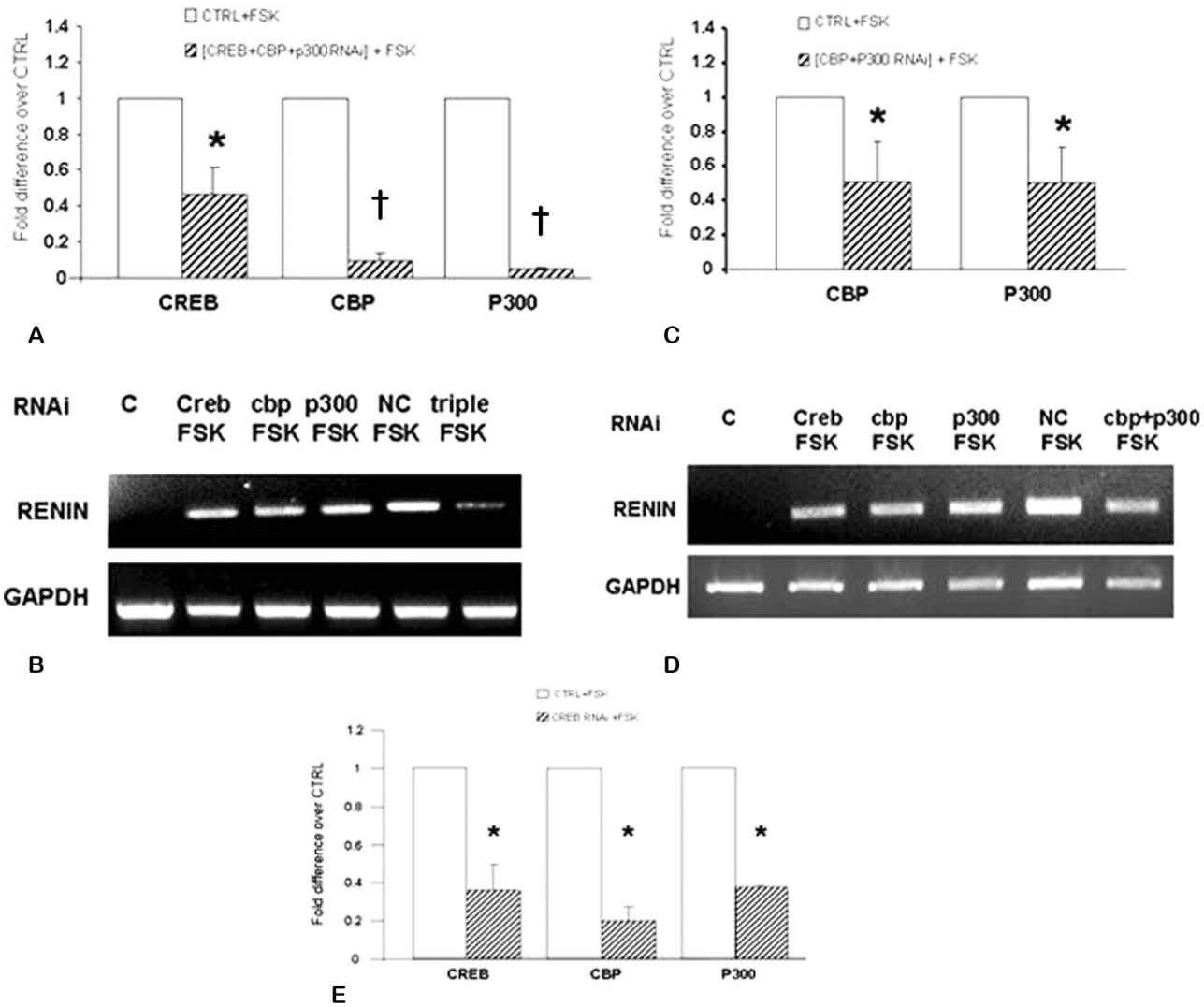

Figure 4. Cyclic AMP response element-binding protein (CREB)-regulated renin gene expression in cultured cells via CBP/P300 recruitment. A and B, Combined triple gene deletion of CREB, CBP, and P300 in cultured renin cells results in renin mRNA severely reduced, as well as CREB mRNA decreased, and CBP mRNA and P300 mRNA decreased drastically. C and D, Combined double gene deletion of CBP and P300 in cultured renin cells. Quantitative real-time polymerase chain reaction shows the level of CBP and p300 mRNA decreased, and the band of polymerase chain reaction shows renin mRNA decreased similar as that in cells transfected with single gene SiRNA of CBP or P300. E, Quantitative real-time polymerase chain reaction shows the level of CBP and p300 mRNA decreased in the cells treated with CREB RNA interference, CREB mRNA decreased too. FSK indicates forskolin.
*$P < .05$
†$P < .01$

and p300, respectively, in the control group. These results suggested a direct effect of CREB on CBP and p300 gene expression.

DISCUSSION

Renin synthesis in renal JG cells is regulated by many neural and humoral factors.[32-34] There are multiple transcription factors identified to date that are linked to the regulation of renin gene expression, CREB was reported to be one of these factors.[16] Our immunostaining result shows that there was CREB gene expression in JG area where renin produced. However, different from the result of Pan and colleagues that showed CREB controlled renin transcription under basal conditions,[11] no change of renin expression was found at JG cells where homozygous CREB gene were specifically deleted compared with wild-type mice in our study. When an adult animal is subjected to a challenge to homeostasis, such as reduced blood pressure and sodium depletion, circulating renin would increase to regain the normal blood pressure and sodium homeostasis. Among the physiological and pathological factors that influence renin production from JG cells, tubular sodium chloride load is the most important one.[35-37]

We treated the mice with a diet low in sodium chloride combined with captopril to address whether CREB null mutant in renin cells of mice would be capable of responding to the threats when more renin is needed to reestablish homeostasis with an increase in the number of renin-expressing cells called recruitment. Renin extended throughout the length of the afferent arteriole in the kidney of wild type mice as we expected. In contrast to the increase of the number of renin-expressing cells and raised renin expression in wild-type mice, no increase of renin expression happened in CREB deletion mice. The present study shows CREB gene is important to the animal responding to the stimulus when homeostasis is threaten and can normalize the homeostasis by renin cells recruitment. Because the need of circulating renin increased when the body under the threat, the reserve of renin protein in the kidney was exhausted and no renin cells were recruited to produce more renin in the CREB null mutant mice, and the stain of renin protein in JG area could even decreased.

To identify the molecular events regulating a gene expression, a suitable in vitro cell culture model has always been used. We isolated SMCs from the glomerulus and made culture in vitro to address the questions about the mechanism of modulating renin synthesis and release. When SMCs are freshly purified and placed in culture, renin synthesizing is stopped. However, stimulating the cells with agents that increase intracellular cAMP levels, such as forskolin, can force them to express renin again.[36,38] As we expected, JG cells cultured began to express renin when treated with forskolin, and RNA silencing experiments indicated that CREB was important for the renin gene transcription. Furthermore, the effect of CREB on a specific gene transcription is always through the coactivator CBP/p300,[38] which have specific areas for interaction with a wide array of transcription factors. Phosphorylation of the transcription factor CREB modulates its interaction with CBP when hormones can induce the binding of CBP/p300 to nuclear receptors.[39] These proteins can stimulate diverse functions of certain transcriptional regulatory proteins.[24,25] The RNA interference-mediated knock-down of CBP and p300 in immortal HeLa cells results in cell death.[40] Mutations of the *P300* gene have been detected in human epithelial tumors.[41,42] Of importance is also the role of CBP and p300 in the regulation of renin expression. Weihua and coworkers have shown that both CREB and CBP are present on the CRE element when the renin gene is active by using ChIP studies in AS4.1 cells.[19] With transgenic mice, under control of the human renin promoter p300 stimulated mouse renin mRNA transcription.[43] Those previous studies have demonstrated that CBP and p300 play essential roles in renin expression, which has been confirmed by our RNA interference on CBP or p300 experiment too. Renin transcription has been inhibited by either of SiRNA-mediated depletion of CBP or p300. In addition, we found that CREB could recruit cofactors CBP/p300 when CREB played its function on renin transcription. As the data of Figure 4 show, CBP and p300 gene mRNA level decreased concurrently when CREB was knocked down. A similar result was shown in triple gene (CREB/CBP/p300) RNA silencing experiment; CBP and p300 mRNAs were drastically reduced to a remaining level of 10% to 15% of the control compared with 50% reduction in the CBP or p300 single knock-down group. Renin mRNA was also decreased considerably when CREB/CBP/

p300 was silenced at the same time. In contrast, we did not find the synergistic reducing effect on CBP or p300 mRNA expression when the double gene was knocked down simultaneously. Therefore, CBP/p300 might act as a bridging factor between CREB and specific genes, like renin, to mediate the transcriptional activation. Also, CBP/p300 acts as a scaffold for the formation of multicomponent complexes containing transcription factors and cofactors, by providing the platform for the assembly of transcription regulatory protein, and increases the relative concentration of the factors in the local transcriptional environment.[23] This way, the complex of CREB/CBP/p300 plays its important role in the mechanisms involved in transcription of renin.

CONCLUSIONS

We know that CREB is one of the factors which involved in the control of renin transcription. Our study has shown that *CREB* gene is important to the animal responding to the stimulus when homeostasis is threaten and can normalize the homeostasis by renin cells recruitment. Furthermore, CBP and p300 also play essential roles in renin expression. On the other hand, CREB can recruit cofactors CBP/p300 when CREB plays its function on renin transcription, and CBP/p300 might act as a bridging factor between CREB and renin, to mediate the transcriptional activation. This way, the complex of CREB/CBP/p300 plays its important role in the mechanisms involved the transcription of renin.

FINANCIAL SUPPORT

The research was supported by National Natural Science Foundation of China (30940045, 31160246), Scientific Grant of Department of Education in Jiangxi Province (GJJ10322), Scientific Grant of Health Department in Jiangxi Province (20121038), and Natural Science Foundation of Jiangxi Province (20114BAB205011).

CONFLICT OF INTEREST

None declared.

REFERENCE

1. Nishimura H, Ichikawa I. What have we learned from gene targeting studies for the renin angiotensin system of the kidney? Int Med. 1999;38:315-23.
2. Lum C, Shesely EG, Potter DL, Beierwaltes WH. Cardiovascular and renal phenotype in mice with one or two renin genes. Hypertension. 2004;43:79-86.
3. Signund CK, Gross KW. Structure, expression and regulation of murine renin genes. Hypertension. 1991;18:446-57.
4. Li P, Kenneth WG. Transcriptional regulation of renin. Hypertension. 2005;45:3-8.
5. Matsushita K, Morello F, Wu YJ, et al. Mesenchymal stem cells differentiate into renin-producing juxtaglomerular (JG)-like cells under the control of liver X receptor-α. J Biol Chem. 2010;285:11974-82.
6. Bader M, Ganten D. Regulation of renin: new evidence from cultured cells and genetically modified mice. J Mol Med. 2000;78:130-9.
7. Sequeira Lopez MLS, Gomez RA. Novel mechanisms for the control of renin synthesis and release. Curr Hypertens Rep. 2010;12:26-32.
8. Gomez RA, Pentz ES, Xuan J, Cordaillat M, Sequeira Lopez ML. CBP and P300 are essential for rennin cell identity and morphological integrity of the kidney. Am J Physiol Heart Circ Physiol. 2009;296:1255-62.
9. Bjorn N, Katharina M, Min C, et al. Development of vascular rennin expression in the kidney critically depends on the cyclic AMP pathway. Am J Physiol Renal Physio. 2009;296:1006-12.
10. Adams DJ, Head GA, Markus MA, et al. Renin enhancer is critical for control of rennin gene expression and cardiovascular function. J Biol Chem. 2006;281:31753-61.
11. Pan L, Black TA, Shi Q, et al. Critical roles of a cyclic AMP responsive element and an E-box in regulation of mouse rennin gene expression. J Biol Chem. 2001;276:45530-8.
12. Pan L, Gross KW. Transcriptional regulation of rennin: an update. Hypertension. 2005;45:3-8.
13. Ying L, Morris BJ, Sigmund CD. Transactivation of the human rennin promoter by the cyclic AMP/protein kinase a pathway is mediated by both cAMP-responsive element binding protein-1 (CREB)-dependent and CREB-independent mechanisms in Calu-6 cells. J Biol Chem. 1997;272:2412-20.
14. Zhou X, Davis DR, Sigmund CD. The human rennin kidney enhancer is required to maintain base-line rennin expression but is dispensable for tissue-specific, cell-specific, and regulated expression. J Biol Chem. 2006;281:35296-304.
15. Klar J, Sandner P, Muller MW, Kurtz A. Cyclic AMP stimulates rennin gene transcription in juxtaglomerular cells. Pfluegers Arch. 2002;444:335-44.
16. Vladimir TT, Simon V, Jurgen F, et al. Role of CREB1 and NFkB-p65 in the down-regulation of rennin gene expression by tumor necrosis factorα. J Biol Chem. 2005;280:24356-62.
17. Ulla GF, Jane S, Torben RU, et al. Prostaglandin E2 EP2 and EP4 receptor activation mediates cAMP-dependent hyperpolarization and exocytosis of rennin in juxtaglomerular cells. Am J Physiol Renal Physiol. 2005;289:989-97.
18. Friis UG, Jensen BL, Sethi S, Andreasen D, Hansen PB, Skott O. Control of rennin secretion

from rat juxtaglomerular cells by cAMP-spefific phosphodiesterases. Circ Res. 2001;90:996-1103.

19. Weihua Y, Wei P, Juan K, et al. 1,25-Dihydroxyvitamin D3 suppresses rennin gene transcription by blocking the activity of the cyclic AMP response element in the rennin gene promoter. J Biol Chem. 2007;282:29821-30.
20. De Cesare D, Fimia GM, Sassone-Corsi P. Signaling routes to CREB and CREB: plasticity in transcriptional activation. Trends Biochem Sci. 1999;24:281-5.
21. Montminy M. Transcriptional regulation by cyclic AMP. Annu Rev Biochem. 1997;66:807-22.
22. Andrisani OM. CREB-mediated transcriptional control. Crit Rev Eukaryot Gene Expr. 1999;9:19-32.
23. Michalis VK, Panagiotis AK, Athanasios GP. Roles of CREB-binding protein (CBP)/P300 in respiratory epithelium tumorigenesis. Cell Res. 2007;17:324-32.
24. Goodman RH, Smolik S. CBP/P300 in cell growth, transformation, and development. Genes Dev. 2000;14:1553-77.
25. Chan HM, La Thangue NB. P300/CBP proteins: HATs for transcriptional bridges and scaffolds. J Cell Sci. 2001;114:2363-73.
26. Ling W, Yong T, Philip AC, Ronen M. Structure and chemistry of the p300/CBP and Rtt109 histone acetyltransferases:implications for histone acetyltransferase evolution and function. Curr Opin Struct Biol. 2008;18:741-7.
27. David CB, Lawryn HK, Tomofusa F, Paul KB. Target gene context influences the transcriptional requirement for the KAT3 family of CBP and p300 histone acetyltransferases. Epigenetics. 2010;5:9-15.
28. Elliott A, de Miguel MP, Rebel VI, Donovan PJ. Identifying genes differentially expressed between PGCs and ES cells reveals a role for CREB-binding protein in germ cell survival. Dev Biol. 2007;311:347-58.
29. Chen L, Kim SM, Oppermann M, et al. Regulation of renin in mice with Cre recombinase-mediated deletion of G protein Gsalpha in juxtaglomerular cells. Am J Physiol Renal Physiol. 2007;292:27-37.
30. Chen M, Gavrilova O, Liu J, et al. Alternative Gnas gene products have opposite effects on glucose and lipid metabolism. Proc Natl Acad Sci USA. 2005;102:7386-91.
31. Ellen Steward P, Maria Luisa SL, Magali C, Gomez RA. Identity of the renin cell is mediated by cAMP and chromatin remodeling: an in vitro model for studying cell recruitment and plasticity. Am J Physiol Heart Circ Physiol. 2007;294:699-707.
32. Todorov V, Muller M, Schweda F, Kurtz A. Tumor necrosis factor-alpha inhibits rennin gene expression. Am J Physiol Regul Integr Comp Physiol. 2002;283:1046-51.
33. Muller MWH, Tdodrov V, Kramer BK, Kurtz A. Angiotensin II inhibits rennin gene transcription via the protein kinase C pathway. Pflugers Arch. 2002;444:499-505.
34. Bader M, Ganten D. Regulation of rennin: new evidence from cultured cells and genetically modified mice. J Mol Med. 2000;78:130-9.
35. Maria Luisa SSL, Ellen SP, Takayo N, Oliver S, Gomez RA. Renin cells are precursor for multiple cell types that switch to the rennin phenotype when homeostasis is threatened. Dev Cell. 2004;6:719-28.
36. Gomez RA, Norwood VF. Developmental consequences of the rennin-angiotensin system. Am J Kidney Dis. 1995;26:409-31.
37. Gomez RA, Maria Luisa SSL, Jin X, Magali C, Ellen SP. Renin cell identity and homeostasis. The local Cardiac Renin-Angiotensin Aldosterone System. New York, NY: Springer Science+Business Media, LLC; 2009. p. 101-6.
38. Lundblad JR, Kwok RP, Laurance ME, Harter ML, Goodman RH. Adenoviral E1A-associated protein p300 as a functional homologue of the transcriptional co-activator CBP. Nature. 1995;374:85-8.
39. Johannessen M, Delghandi MP, Moens U. What turns CREB on? Cell Signal. 2004;16:1211-27.
40. Stauffer D, Chang B, Huang J, Dunn A, Thayer M. P300/CREB-binding protein interacts with ATR and is required for the DNA replication checkpoint. J Biol Chem. 2007;282:9678-87.
41. Lyer NG, Ozdag H, Caldas C. P300/CBP and cancer. Oncogene. 2004;23:4225-31.
42. Ionov Y, Nowak N, Perucho M, Markowitz S, Cowell JK. Manipulation of nonsense mediated decay identifies gene mutations in colon cancer cells with microsatellite instability. Oncogene. 2004;23:639-45.
43. Fukamizu A, Sagara M, Sugiyama F, Yagami K, Murakami K. Tissue-specific trans-activation of renin gene by targeted expression of adenovirus E1A in transgenic mice. Biochem Biophys Res Commun. 1994;199:183-90.

Correspondence to:
Jin Xuan, MD, PhD
The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, China
Tel: +86 791 8869 3296
Fax: +86 791 8869 3296
E-mail: jinxuan725@163.com

Pei Li and Jing Zhang contributed equally to this work as first authors.

Received January 2015
Revised July 2015
Accepted July 2015