A cis-Acting DNA Element Located between TATA Box and Transcription Initiation Site Is Critical in Response to Regulatory Sequences in Human Angiotensinogen Gene*

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The promoter of the human angiotensinogen (hAG) gene functioned in its own core promoter context but not when replaced with simian virus 40 (SV40) core promoter, suggesting the presence of a transcriptionally important cis-acting sequence. Electrophoretic mobility shift assays demonstrated that a ubiquitously expressed nuclear factor, AGCF1, bound to AGCE1 (hAG core promoter element 1; positions –25 to –1) located between the TATA box and transcription initiation site. Substitution mutation in AGCE1 which disrupted AGCF1 binding affected the promoter activity more severely than a nonsense mutation of the hAG TATA sequences did. When AGCE1 was placed at the downstream of SV40 core promoter, the responsiveness to hAG upstream region was significantly restored. Furthermore, mutation and in vivo competition experiments suggested that AGCF1 acts as a critical regulator of hAG transcription by mediating the activity of the hAG upstream and downstream enhancer elements. DNase I footprinting and UV cross-linking analyses showed that AGCF1 with apparent molecular masses of 31, 33, and 43 kDa as the components protected the region from –26 to –9 which partially overlapped with the TATA box consensus sequences. These findings indicate that AGCE1 in addition to the TATA box plays a key role in mediating the hAG regulatory elements.

A number of transcriptional DNA control elements, such as upstream and core promoter elements, have been identified as being important in affecting promoter activity of eukaryotic genes transcribed by RNA polymerase II. These elements direct the action of two classes of transcription factors, sequencespecific regulatory factors and general transcription factors, the former regulates the rate of transcription initiation and the latter is essential for initiating a basal level of transcription (1–3). Although core promoter elements have been considered to be important for general reaction of transcription initiation, several studies have indicated that these elements play a key role in determining the characteristic pattern of gene expression. For example, a muscle-specific enhancer activates transcription when fused to the myoglobin core promoter but has no influence upon the transcription from SV40 early core promoter (4). A 15-bp1 core promoter region that includes the TATA box of the growth hormone gene has been shown to regulate its expression through the pituitary-specific transcription factor GHF-1 (5). Moreover, the degree of transcriptional stimulation by activating transcription factor is dependent upon the context of core promoter elements (6). Therefore, these observations provide evidence that each core promoter element would have intrinsic differences dependent upon its promoter context.

Angiotensinogen is the precursor of angiotensin II that acts as a physiologically important regulator of blood pressure and electrolyte homeostasis as well as a growth factor of cardiac myocytes (7–10). Genetic linkage analyses proposed association between essential hypertension and molecular variants of the human angiotensinogen (hAG) gene (11–13). Our previous studies have shown that cis-acting elements located at nucleotide positions –1222 to –44 are sufficient for the hAG gene expression in transiently transfected human hepatoma HepG2 cells and in the liver and the neuroectodermal tumor of the transgenic mice (14–17). In particular, the removal of the DNA element located at –16 to –44 of the transcription start site led to the dramatic reduction of its transcriptional activity, suggesting the presence of a core promoter with a functional importance for transcription (14). Furthermore, we recently identified several regulatory elements of the hAG gene including the downstream enhancer elements (18–20), but it is still unknown how these cis-acting sequences activate the hAG promoter. In the present study, to examine the putative hAG core promoter function and the mechanism of action of hAG transcriptional elements, we have analyzed the core promoter element and identified a ubiquitously expressed nuclear factor, AGCF1 (hAG core promoter binding factor 1) that bound to AGCE1 (hAG core promoter element 1; nucleotide positions –25 to –1), which plays a major role in mediating the hAG enhancer function.

Experimental Procedures

Plasmid Constructions—The hAG promoter-chloramphenicol acetyltransferase (CAT) hybrid genes, 13cat (positions –1222 to +44), DM10cat (–106 to +44), and DM12cat (–32 to +44), were constructed as described previously (16). 13–36cat was constructed by inserting 1187-bp (–1222 to –36) hAG3-deletion fragment at the BhIII/HindII sites of pUCSVcat (16). 13ATcat and 13STcat were constructed by inserting 76-bp (–32 to +44) hAG core promoter fragment and 114-bp Ncol/HindII SV40 core promoter fragment derived from SV3cat (16) at 1

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1 The abbreviations used are: bp, base pair; CAT, chloramphenicol acetyltransferase; hAG, human angiotensinogen; AGCF1, hAG core promoter binding factor 1; hASR, hAG Sp-1 and RFB-1-like element; AGCE1, hAG core promoter element 1; EMSA, electrophoretic mobility shift assays; C/EBP, CCAAT enhancer-binding protein; CREB, cyclic adenosine monophosphate response element-binding protein; ATF, activating transcription factor.
Human Angiotensinogen Core Promoter

the downstream of hAG 3′-deletion fragment of the 13–36cat, respectively. 13ST1cat was constructed by inserting two copies of AGCE1 fragments at the downstream of SV40 core promoter fragment of the 13STcat. The unique 5′ BglII or 3′ BamHI site of 13cat was used as the insertion site for B2 fragment (+1399 to +2230) in forward or reverse orientations to reconstitute the hAG gene. DM12d61-2 (–), DM12med61-2 (–), and DM12ME (–) were described as described previously (18, 19). The hASRDMD12cat and ALEDM12cat were constructed by inserting four copies of HASR fragments (–344 to –313) and ALE fragments (–103 to –87) at the upstream of the hAG core promoter fragment of the DM12cat (20), respectively. A competitive plasmid, pUC-AGCE1, was constructed by fusing the eight head-to-tail tandem repeats of AGCE1 (pUC-119) with 5′-GATGCCCTAGATC-3′, and cloned into the 5′-GATCTAGGGC-3′ fragment of the DM12cat (20), respectively. The hAG core promoter and heterologous SV40 core promoter, SV40 core promoter sequences (114-bp NcoI/HindIII fragment containing TATA box and initiation site), wild-type TATA box, and SV40-type TATA box whose base substitutions are indicated below the box, respectively. Right, Hep2 cells were transfected with 3 μg of the indicated CAT vectors and 1 μg of β-galactosidase expression plasmid (pCH110) as an internal control for transfection efficiency. After 48 h of culture, β-galactosidase activities were measured, and extracts containing equivalent amounts of β-galactosidase activities were used for CAT assays. The CAT activity of 13cat is designated as 100 and each value of CAT activity represents the mean ± S.E. for at least four independent experiments. N.D., not detected.

RESULTS

In order to examine the functional significance of putative hAG core promoter (nucleotide positions –32 to +44) responsible for its upstream DNA region (positions –1222 to –36), we first constructed a series of mutant promoters linked to the CAT reporter gene and analyzed their promoter activities in transiently transfected Hep2 cells (Fig. 1). Substitution of SV40 core promoter for hAG core promoter 13STcat did not produce the CAT activity at all, as observed in 13–36cat that lacks hAG core promoter. In contrast, the addition of hAG core promoter below the oval box conferred the CAT activity to the levels similar to those found in the wild-type promoter, 13cat, although hAG core promoter alone represented little activity (data not shown). These two core promoters had TATA box and CAP site but no consensus initiator sequence (25) and apparent differences in the sequences of their TATA boxes. 13STcat with substitution mutation of hAG TATA box sequence (TATAAAT) to SV40-type sequences (TATTTAT) in the upstream region by EMSA using the dissected DNA fragment that covers the core promoter region (Fig. 1). Incubation of AGCE1 fragment with the nuclear extracts prepared from Hep2 cells produced retarded complexes, AGCF1 (Fig. 2B), which represented a sequence-specific interaction between AGCE1 fragment and a
Identification of a novel nuclear factor and effect of various mutations on its binding activities. A, oligonucleotides comprising wild-type (AGCE1) and mutant AGCE1 (Am1, Am2, Am3, and Am4) are shown. The positions of base substitutions are underlined and numbered. The mutations are indicated by boxed nucleotides. Double-stranded versions of the indicated sequences were used in competition experiments. B, EMSA. The indicated double-stranded oligonucleotides were end-labeled with T4 polynucleotide kinase using [γ-32P]ATP. Five micrograms of HepG2 nuclear extracts were incubated with 0.5 ng of 32P-labeled probes in a competition assay. 5-, 50-, 100-, and 200-fold molar excess of the unlabeled oligonucleotides, as indicated for each lane, were added to the reaction mixture. Binding reactions were resolved by 4.5% acrylamide, 1 x TBE electrophoresis. AGCF1 are indicated. 

Fig. 2. Identification of a novel nuclear factor and effect of various mutations on its binding activities. A, oligonucleotides comprising wild-type (AGCE1) and mutant AGCE1 (Am1, Am2, Am3, and Am4) are shown. The positions of base substitutions are underlined and numbered. The mutations are indicated by boxed nucleotides. Double-stranded versions of the indicated sequences were used in competition experiments. B, EMSA. The indicated double-stranded oligonucleotides were end-labeled with T4 polynucleotide kinase using [γ-32P]ATP. Five micrograms of HepG2 nuclear extracts were incubated with 0.5 ng of 32P-labeled probes in a competition assay. 5-, 50-, 100-, and 200-fold molar excess of the unlabeled oligonucleotides, as indicated for each lane, were added to the reaction mixture. Binding reactions were resolved by 4.5% acrylamide, 1 x TBE electrophoresis. AGCF1 are indicated. 

nuclear factor, since the formation of this complex was specifically reduced with molar excess of unlabeled competitors (Fig. 2B, lanes 1-6). Moreover, double-stranded oligonucleotides containing the consensus binding sequences for C/EBP, ATF, Sp1, AP-1, AP-2, AP-3, and NF-1/CTF failed to compete with AGCF1-binding activity (Fig. 2B, lane 7, and data not shown). The DNA-protein complex formed by AGCF1 binding to AGCE1 was, however, inhibited by molar excess of nonlabeled AGCE1, Am2, and Am3 (Fig. 2, A and B). Although Am1 could partially prevent this complex formation, Am4 did not compete for this binding at all (Fig. 2B, lanes 8-14). 

To evaluate the role of AGCE1 in the native promoter context, the Am4 mutations that abolished AGCF1-binding activity were introduced into the hAG promoter. The DM10cat, which could supply a sufficient CAT activity in our previous experiments (16), was used as the wild-type promoter for the convenience of constructions. As shown in Fig. 3A, DM10Am4cat with the Am4 mutation decreased the transcription activity to 10% of the wild-type construct, whereas DM10Tmcat with a nonsense TATA box (TATGGAT) reduced the activity by 50%. To examine whether AGCE1 provides the functional differences between hAG and SV40 core promoters in addition to TATA box, we reconstituted the chimeric core promoters by fusing SV40 core promoter with AGCE1 and assayed their promoter activities (Fig. 3B). As expected, AGCE1 could significantly restore the core promoter activity under the control of hAG upstream DNA region. Taken together, these findings suggested that AGCE1 in addition to TATA element is critical for the efficient hAG promoter activity.

To define the contribution of AGCE1 to hAG transcription in the whole gene context, we reconstituted the hAG gene containing its 1.3-kilobase promoter (13 fragment) and the downstream enhancer (B2 fragment) that is composed of the three enhancer core elements, d6l-2, GM, and ME (18, 19) (Fig. 4A). When the Am4 mutation was introduced into the 13 fragment, the mutated promoter activity decreased to 40% as compared with that of the wild-type sequence (Fig. 4B, 13cat and 13Am4cat). Furthermore, the transcriptional activity dramat-ically dropped by the Am4 mutations in the reconstituted hAG gene even when the three sets of enhancer core elements are included (Fig. 4B). These results indicated that AGCE1 is an authentic regulatory element for hAG transcription.

We have previously identified hASR in the upstream region (20) and the three enhancer core elements in the downstream region (18, 19) as hAG regulatory elements. Recently, we found...
another upstream element, ALE (ATF-Like Element), of which deletion reduced the hAG promoter activity by 50% and the binding of multiple factors including CREB/ATF family and novel ones to ALE.2 Therefore, we next examined the mechanism of action of AGCE1 in response to these hAG regulatory elements (Figs. 4A and 5). When hASR was placed in front of a native or Am4-mutated hAG core promoter fragment, it functioned efficiently in both the core promoter contexts. In contrast, the degrees of stimulation by ALE, d61-2, GM, and ME dramatically decreased upon the Am4 mutations. To confirm the functional importance of AGCF1, we performed in vivo competition experiments (Fig. 6). The various amounts of pUC-AGCE1, which included eight tandem copies of AGCE1 in pUC119, were cotransfected with DM12d61–2(−) or SV3c3at. The CAT activity derived from DM12d61–2(−) decreased with sequential titration of AGCF1 binding, although the activity driven from a positive control, SV3c3at, was little influenced. These results suggested that the responsiveness of hAG core promoter to the activation by factors bound to ALE and the hAG downstream enhancer core elements are largely dependent upon AGCF1, whereas the factors bound to hASR function independently of AGCF1.

We decided to delineate the AGCF1 binding site more thoroughly, since this location between the TATA box and transcription initiation site is very unique. DNase I footprinting using 40% saturation ammonium sulfate precipitation of HepG2 nuclear extracts showed a protected region from −26 to −9 (Fig. 7A, denoted by bracket). Interestingly, the protected region partially overlapped with the consensus sequences of the TATA box (TATAAAT). Finally, UV cross-linking was performed to determine the molecular masses of the nuclear factors involved in AGCF1 (Fig. 7B). Ten micrograms of HepG2 nuclear extracts were incubated with 5-bromodeoxyuridine-substituted AGCE1 probe in the absence or presence of the unlabeled oligonucleotides. The mixtures were UV cross-linked, digested with DNase I, and analyzed on a 12.5% SDS-polyacrylamide gel. Factors corresponding to apparent 31, 33, and 43 kDa were identified as the major components of AGCF1 (Fig. 7B, lane 1), since these factors were specifically eliminated by the molar excess of unlabeled AGCE1 fragment (lane 2) but not by that of unlabeled C/EBP fragment (lane 3).

DISCUSSION

In the present study, we have analyzed hAG core promoter region and found that hAG core promoter but not SV40 early core promoter responds to hAG upstream region (Fig. 1). This functional difference was likely due to the major action of hAG core promoter element. We identified a potential DNA element, AGCE1 (nucleotide positions −25 to −1), that interacted with a nuclear factor, AGCF1 (Fig. 2). Mutation analyses and reconstitution experiments combined with CAT assays suggested that AGCE1 in addition to TATA element plays a key role in maintaining the hAG promoter activity (Fig. 3). Furthermore, AGCF1 acts as an authentic regulator of hAG transcription (Fig. 4) by mediating the responsiveness to one of the upstream elements, ALE, and the downstream enhancer core elements (Figs. 5 and 6). DNase I footprinting and UV cross-linking experiments indicated that AGCF1 with apparent molecular masses of 31, 33, and 43 kDa protected the region from −26 to −9 that partially overlapped with the consensus sequences of the TATA box (Fig. 7).

It has been reported that the functional diversity of multiple classes of TATA sequences plays an important role in responding to the regulatory elements. For example, the sequence differences between myoglobin TATA motif and SV40 early TATA element are responsible for the differential response to muscle-specific enhancer (4). In another instance, heat shock protein 70 and EIIa TATA elements confer high activity on the ATF site whereas the SV40 early TATA motif hardly responds to it (6). In contrast to these observations, a conversion of hAG TATAAAT sequence to SV40 TATTTAT in the hAG promoter context resulted only in the moderate reduction of the promoter activity, although hAG core promoter but not SV40 early core promoter responds to hAG upstream region (Fig. 1).

Several lines of evidence have demonstrated that the first step in preinitiation complex assembly involves binding of a multiprotein complex TFIID to the promoter via sequence-specific interactions between the TATA box and TFIID at TATA-containing promoters (27–30). TFIID complex is proposed to be recruited by a “tethering factor,” such as Sp1, which could function as a substitute for TATA box via protein-protein interactions between the Sp1 and TFIID elements conferring high activity on the ATF site whereas the SV40 early TATA motif hardly responds to it (6). In contrast to these observations, a conversion of hAG TATAAAT sequence to SV40 TATTTAT in the hAG promoter context resulted only in the moderate reduction of the promoter activity, although hAG core promoter but not SV40 early core promoter responds to hAG upstream region (Fig. 1).

A positive regulatory element located around or downstream of the TATA box has recently been identified and discovered to...
possess an intrinsic function for cell type-specific regulation. The human gastrin gene fragment from 217 to 157 shows a considerable cell type specificity in transfection experiments (37). The cell type specificity determinant of the peripherin gene is localized to a region overlapping the TATA box, whereas

FIG. 5. The mechanism of action of AGCE1 in responsiveness to the hAG regulatory elements. Left, thick lines, open boxes, and vertical lines represent the wild-type promoter sequences, wild-type TATA box, and AGCE1 mutations whose base substitutions are indicated in Fig. 2A, respectively. Boxes marked hASR, ALE, d61–2, GM, and ME represent the upstream elements, hASR and ALE, and downstream enhancer core elements, d61–2, GM, and ME, respectively. Right, HepG2 cells were transfected with the indicated CAT vectors, and CAT assays were performed as described in Fig. 1. The CAT activity of DM12cat is designated as 1.0, and each value of CAT activity represents the mean ± S.E. for at least four independent experiments.

FIG. 6. In vivo competition analysis of the AGCE1. A competitive plasmid, pUC-AGCE1, containing eight head-to-tail tandem repeats of the AGCE1 fragment was used in this experiment. Two micrograms of reporter plasmids (SV3cat or DM12d61–2(-)) were cotransfected with 1, 2, or 4 μg of pUC-AGCE1. Total amounts of DNA were adjusted to 6 μg by pUC119. After a 48-h culture, the protein concentration was measured, and aliquots of cell extract containing equal amounts of total protein (40 μg) were used in CAT assay. The CAT activity of each reporter plasmid, cotransfected with 4 μg of pUC119, is designated as 100, and each value of CAT activity represents the mean ± S.E. for at least four independent experiments.

FIG. 7. Identification AGCF1-binding site and determination of the molecular masses of AGCF1. A, DNase I footprinting. The hAG proximal promoter fragment (−106 to +44) was labeled on the coding strand. The probe (approximately 20,000 cpm) was incubated with 2 μg of poly(dI:dC) in the absence or presence of 40% saturation ammonium sulfate precipitation of HepG2 nuclear extracts and then subjected to DNase I digestion. DNA separation was done on an 8% polyacrylamide, 8M urea sequencing gel. Bracketed and boxed sequences represent the protected sequences and TATA box, respectively. B, UV cross-linking. Ten micrograms of HepG2 nuclear extracts were incubated with 4 ng (approximately 250,000 cpm) of 5-bromodeoxyuridine-substituted AGCE1 probe and 1 μg of poly(dI:dC) in the absence or presence of 300-fold molar excess of the unlabeled oligonucleotides for AGCE1 or C/EBP (18) as indicated. After incubation for 20 min at 20 °C, the mixtures were UV cross-linked, digested with DNase I, and analyzed on a 12.5% SDS-polyacrylamide gel. Molecular size markers are shown on the right. The three major bands (solid arrows) represent proteins of 31, 33, and 43 kDa. The minor bands are indicated by hatched arrows.
elements determining the strength of the promoter are localized upstream (38). Interestingly, the core promoter (−36 to +12) of the myelin basic protein gene is shown to direct brain-specific in vitro transcription (39). In addition to the above elements that interact with cell-specific nuclear factors, other examples of core promoter regions have been reported including the pro-opiomelanocortin gene (−18 to +6) that bind to widely distributed nuclear factors (40). Despite the positions between the TATA box and transcriptional initiation site, there was no extensive homology between AGCE1 and the DNA sequences of those previously identified core promoter elements (data not shown).

Our striking finding in the present study is that AGCE1 plays a critical role in activating hAG transcription by one of the upstream elements, ALE, or the downstream enhancer core elements, but not by another upstream element, hASR (Figs. 3–5). In other words, AGCF1 can mediate the transcriptional activating function of ALE- and downstream core element-binding factors. In the case of the latter factors, at least in part, this notion is supported by the sequential titration of AGCF1 binding by means of the in vivo competition (Fig. 6). On the other hand, other core promoter elements, for example TATA-box sequences of those previously identified core promoter elements, may be needed for hASR function. Taken together, we now hypothesize that the cis-acting sequences of hAG gene selectively activate its transcription through the diversity of core promoter elements. Further study will be necessary to define, by means of purifying AGCF1 and cloning its cDNA, the molecular mechanism by which it can respond to the upstream or downstream regulators of the hAG gene. Such investigations are now in progress in our laboratory.

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Human Angiotensinogen Core Promoter