The transcriptional co-activators CBP and p300 Are Activated via Phenylephrine through the p42/p44 MAPK Cascade*

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The CBP and p300 co-activators play a key role in many aspects of gene regulation being recruited to the DNA via transcription factors that are targets for specific signaling pathways. It has previously been demonstrated that in neuronal cells the ability of CBP and p300 to activate transcription can be directly stimulated by nerve growth factor or calcium-activated signaling pathways. Here we demonstrate that, in cardiac cells, the activity of CBP and p300 is stimulated by phenylephrine (PE) treatment and that they are required for the activation of atrial naturetic factor (ANF) gene expression by PE. Activation of CBP/p300 by PE involves the p42/p44 MAPK pathway and targets primarily the N terminus of p300 and the C terminus of CBP, which are not homologous to one another. To our knowledge, this is the first report of a specific stimulus modulating the activity of CBP and p300 in cardiac cells and it suggests that these factors play an important role in the hypertrophic effect of PE.

The CBP1 co-activator protein was originally identified as a factor that interacts with the CREB transcription factor only following phosphorylation of CREB on serine 133 (for review see Ref. 1). Thus, following exposure to cAMP, the CREB factor, which is already bound to the cAMP-response element (CRE) in its target genes, is phosphorylated on serine 133 and can then recruit the CBP co-activator, resulting in cAMP-dependent activation of gene expression (1, 2).

Although originally identified in the cAMP pathway, it is now clear that CBP and the closely related p300 protein play a key role as co-activators for a wide variety of transcription factors involved in various different pathways, including the steroid/thyroid hormone receptors, AP1, STAT factors, and muscle-specific transcription factors such as MyoD and MEF2 (for review see Ref. 3).

As expected from this critical role in a variety of aspects of transcription factor regulation, loss of CBP is incompatible with survival of the organism. Indeed, even the loss of a single CBP gene (with a functional copy remaining) results in humans in the severe developmental disorder Rubinstein-Taybi syndrome (4). Interestingly, this disorder as well as its characteristic facial abnormalities and mental retardation can also result in cardiac disorders suggesting a role for CBP in the heart (5, 6). In the case of the closely related p300 protein, such a role has been directly confirmed by the finding that knockout mouse embryos lacking both copies of the p300 show abnormal heart development with reduced trabeculation of the ventricular chambers and weaker/less extensive heart contractions, which appear to be responsible for the death of the knockout embryos in utero (7).

Interestingly, the p300 knockout mouse embryos also show reduced expression of cardiac muscle structural proteins such as myosin heavy chain and α-actinin (8). This parallels previous findings that the expression of these genes could be inhibited in cultured cardiac cells by overexpression of the adenovirus E1A protein, which binds p300 and CBP and removes them from cellular transcription factors, thereby inhibiting the activity of these factors (8, 9). This potential key role for CBP and p300 in regulating cardiac cell-specific gene expression is supported by recent data that demonstrate that doxorubicin appears to promote transcriptional repression in cardiac cells by specifically mediating the degradation of p300 (10).

These effects of CBP and p300 on cardiac-specific gene expression are likely to be mediated via their ability to specifically interact with transcription factors involved in the regulation of gene expression in cardiac cells such as the MEF2 transcription factor, which is known to interact with p300/CBP and to play a key role in regulating cardiac-specific gene expression (10, 11). Similarly, CBP and p300 can also interact with transcription factors that have been shown to be involved in the hypertrophic response of the heart. Thus CBP/p300-interacting proteins include factors such as AP-1 and STAT-3, which are involved in the hypertrophic response to factors such as angiotensin II (12, 13) and cardiotoxin-1 (14, 15).

Hypertrophy is a response to overload in the heart, which initially results in an adaptive increase in muscle mass, based on the increased size of cardiac myocytes in the heart but ultimately is deleterious and results in heart failure (for review see Ref. 16). Evidently, an understanding of the processes involved in regulating cardiac gene expression during hypertrophy would be of considerable importance both in itself and in the development of novel therapies. In view of the interaction of...
CBP with transcription factors known to be involved in hypertrophy, we have studied the effect of hypertrophic agents on CBP and p300.

EXPERIMENTAL PROCEDURES

Materials—Urocortin (UCN), Phenytoin (PE), and Bt2cAMP were from Sigma Chemical Co. Cardiotrophin-1 (CT-1) was a kind gift from Dr. D. Pennica (Genentech). The adrenergic antagonists prazosin and propranolol were also obtained from Sigma. The specific MAPK inhibitor PD98059 (PD) was from New England BioLabs. The specific p38 MAPK inhibitor SB203580 (SB) was from Calbiochem. PKC inhibitor H-7 dihydrochloride was from Tocris and the PKA inhibitor H-89 dihydrochloride from Calbiochem. Cell culture media and fetal calf serum were from Invitrogen.

DNA Constructs—The following Gal4-CBP chimera constructs have been described previously: RSV pGal-CBP (227–460), pGal-CBP-(721–1679), pGal-CBP (1678–2441), pGal-(1678–2441), pGal-CBP (1678–2441–2179), pGal-(2173–2288), pGal-CBP (2288–2441), and pGal-CBP (full-length (17)). The pGal-p300 chimeras Gal-p300 (1–743), Gal4-p300 (242–1737), Gal4-p300 (964–1922), Gal4-p300 (1514–1922), Gal4-p300 (1737–2414), Gal4-p300 (1945–2414) and Gal4-p300 full-length have also been described previously (18). The reporter plasmid 5xGal4-E1B (2192–2614) was a kind gift of Dr. R. H. Goodman (21). The ANF-luciferase reporter construct (–3003 to +62) of the ANF rat gene was a kind gift of Dr. K. Knowlton (22). The CBP antisense vector was constructed by cloning CBP full-length (1–7326) into the BamHI site of Bluescript KS (Stratagene) in the reverse orientation and subsequently excising the insert with NotI and SalI and inserting it into a pBl-G expression vector (CLONTECH). The plasmid containing a dominant negative mutant of p300 (lacking the CHI domain, amino acids 348–412) under the control of the CMV promoter was obtained from Upstate Biotechnology.

Cardiac Cell Culture—Ventricular myocytes were isolated from the hearts of neonatal rats (Sprague-Dawley) less than 2 days old and were cultured as described previously (23). Cardiac myocyte cell suspension was transferred to 24-well (1-cm diameter) gelatin-coated plates at a density of 10^6 cells/well in Dulbecco’s modified Eagle’s medium supplemented with 15% fetal calf serum. After 24 h the cardiac cultures could be seen to beat in synchrony.

Transfection and Assay of Luciferase Activity—Transient transfections of rat neonatal cardiac myocytes were performed using the calcium phosphate procedure as described by Gorman (24). The amounts of expression vectors used are indicated in the figure legends. For each transfection, cells were incubated for 20 h in media containing 15% fetal calf serum. Cells were then treated with UCN, PE, CT-1, and cAMP for 26 h in media supplemented with 1% fetal calf serum. In some experiments, cells were pretreated with different protein kinase inhibitors for 10 min before addition of PE. Cells were then harvested and assayed for luciferase activities according to the manufacturer’s directions (Promega). Results were normalized to protein content as determined by Bradford protein assay (25).

Western Blotting—Protein extracts were run on a 10% acrylamide gel, transferred to Hybond C membrane (Amersham Biosciences, Inc.), probed with relevant antibody and enhanced chemiluminescence (Amersham Biosciences, Inc.) was used to visualize labeled bands by exposure to photographic film. Monoclonal antibodies against phosphorylated or total p42/p44 were obtained from Santa Cruz Biotechnologies. 

Statistics—Values are given as percent activity relative to the luciferase in unstimulated cells (set at 100%). Values are expressed relative to the level of luciferase control, untreated transfected rat neonatal cardiac myocytes (set at 100%) and are the means of three independent transfection experiments whose standard error is indicated by the bars. * p < 0.05 versus control.

RESULTS

To analyze the effect of hypertrophic agents on the CBP transcriptional co-activator, we made use of constructs in which the DNA sequences encoding CBP have been fused to sequences encoding the DNA binding domain of the yeast Gal4 transcription factor (17). Co-transfection of these constructs with a reporter construct containing Gal4 DNA binding sites upstream of a heterologous promoter allows DNA binding mediated via the Gal4 portion of the molecule and transcriptional activation via the CBP molecule. Hence the effect of any stimulus on the ability of CBP to activate transcription can be assessed without any complications arising from it being recruited to the DNA via interaction with a DNA-bound transcription factor that may itself be modulated by the stimulus. We have previously used this system to determine that nerve growth factor stimulates the transcriptional activating ability of CBP and that this effect is dependent upon the p42/p44 MAPK pathway (26).

The Gal4/CBP constructs were therefore transfected into neonatal cardiac cells together with the reporter luciferase construct, and the cells were either left untreated or exposed to the hypertrophic agents PE, UCN, or CT-1. In these experiments, a significant enhancement of promoter activity was observed in the cells transfected with constructs containing full-length CBP when the activity in untreated cells was compared with that observed in PE-treated cells (Fig. 1). In contrast, a much smaller up-regulation was observed with UCN and virtually no enhancement was observed with CT-1 or cAMP. PE produced no enhanced activity when a construct containing the isolated DNA binding domain of Gal4 alone was transfected, indicating that these effects are mediated via the CBP or p300 portion of the construct (data not shown). A similar up-regulation of activity with PE to that seen with full-length CBP was observed with a Gal4 construct containing the C-terminal activation domain of CBP (amino acids 1678–2441). In contrast, no enhancement with PE was observed when a construct containing the N-terminal activation domain of CBP (amino acids 1–460) was used, indicating that this effect was specific to the C-terminal activation domain (Fig. 1). The construct containing the C-terminal activation domain was, therefore, used in our subsequent mechanistic experiments.

These experiments demonstrate therefore that the hypertrophic agent PE is able to enhance the transcriptional stimulating ability of CBP in cardiac cells acting via the C terminus of CBP. In view of this and the much weaker or no effect noted with UCN or CT-1, we decided to analyze the effect of PE.
Initially to confirm that this effect was mediated via PE-mediated activation of α-adrenergic receptors, we used the α-adrenergic antagonist prazosin and, for comparison, the β-adrenergic agonist propranolol (20 μM). Values are expressed relative to the level of luciferase in control, untreated transfected rat neonatal cardiac myocytes (set at 100%) and are the means of three independent transfection experiments whose standard error is indicated by the bars. * , p < 0.05 versus control; + , p < 0.05 versus PE alone.

To investigate the mechanisms mediating the effect of PE, the experiments were repeated in the presence or absence of the inhibitors PD, which specifically inhibits the activity of the p42/p44 MAPK pathway, and SB, which inhibits the activity of the p38 MAPK pathway. In these experiments (Fig. 3) the up-regulation of CBP activity by PE was unaffected by addition of SB, indicating that it does not involve the p38 MAPK pathway. In contrast, addition of PD resulted in a significant fall in the basal activity produced by the CBP and p300 constructs in the absence of PE and prevented any stimulatory effect of PE on this transcriptional activity. This suggests therefore that in cardiac cells the ability of PE to stimulate the transcriptional activity of CBP involves the p42/p44 MAPK pathway.

As expected, Western blotting with an antibody specific for active phosphorylated p42/p44 MAPK showed a clear activation of both p42 and p44 by PE. Moreover, this effect was not observed when PE and PD were added together (Fig. 4).

It has previously been shown that activation of p42/p44 MAPK in cardiac myocytes requires activation of protein kinase C but not protein kinase A (27). To test this in our system, we examined the effect of the PKC inhibitor H-89 on the ability of PE to activate CBP. As indicated in Fig. 3B, H-7 was indeed able to block activation by PE whereas H-89 had no effect, confirming the role of PKC.

To confirm our experiments with the chemical inhibitor PD, we used a dominant negative mutant of the p42 MAPK enzyme that contains a single amino acid substitution replacing tyrosine with phenylalanine and acts as a dominant negative mutant. In these experiments (Fig. 5A) transfection of an expression vector encoding this mutant was able to block the ability of PE to enhance CBP transcriptional activity, whereas transfection of a control expression vector lacking any insert failed to produce this effect. This therefore confirms our conclusion that CBP is activated by PE via this pathway and provides further evidence that PE acts via this pathway and hence does not further stimulate transcription in the presence of active p42 MAPK. In agreement with this, a plasmid (SS/DD) encoding a constitutively active form of MEK-1, the upstream activator of p42/p44 MAPK, was also able to stimulate the activity of the CBP construct in the absence of PE (Fig. 5B).

Interestingly, transfection of a plasmid encoding wild type p42 resulted in enhanced transcription activating ability of CBP, which was of similar extent to that produced by PE and which was not further enhanced by the addition of PE. This provides further evidence that PE acts via this pathway and hence does not further stimulate transcription in the presence of active p42 MAPK. In agreement with this, a plasmid (SS/DD) encoding a constitutively active form of MEK-1, the upstream activator of p42/p44 MAPK, was also able to stimulate the activity of the CBP construct in the absence of PE (Fig. 5B).

In our previous experiments (26) we demonstrated that the ability of NGF to stimulate the transcription activating ability
of CBP was also dependent on the p42/p44 MAPK pathway and was observed with constructs containing two small independent regions at the C terminus of CBP. To determine whether a similar effect could be observed in the case of PE, we transfected a wide variety of constructs containing different N-terminal and C-terminal regions of CBP linked to the Gal 4 DNA binding domain and analyzed their response to PE. In these experiments (Fig. 6) a strong response to PE of over 5-fold was observed with the construct containing the region of CBP from amino acids 1961 through 2039, and smaller responses of approximately 2-fold were observed with other C-terminal regions. This suggests that multiple regions at the C terminus of CBP can mediate the response to PE, but that a single short region produces the strongest effect.

To determine whether this short region showed a similar dependence on the p42/p44 MAPK pathway for its transcriptional activation by PE, we carried out experiments in which the effect of PE on this region was assayed in the presence or absence of PD or of the dominant negative p42 MAPK pathway. In these experiments (Fig. 7) the strong up-regulation of transcription activity by PE was prevented by the addition either of PD or of the dominant negative p42 MAPK construct, and the activity of this region was enhanced by the construct encoding wild type p42. Hence, as with the entire C terminus of CBP can mediate the response to PE, but that a single short region produces the strongest effect.

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Evidently, all our experiments investigating the effect of PE on CBP use Gal4/CBP fusion proteins, and this approach has been criticized, because of the artificial nature of the constructs used (21). To confirm our results, we therefore used a mutant form of the CREB transcription factor, which has been altered so that it constitutively binds CBP without the need for phosphorylation of serine 133 of CREB (21). Hence, any effect of a specific agent when this mutant is used cannot reflect enhanced recruitment of CBP via phosphorylation of CREB. When a target promoter containing a CREB-binding cAMP response element (CRE) was co-transfected into cardiac myocytes with this mutant form of CREB, transcription was stimulated by PE (Fig. 8) consistent with PE targeting the transcriptional activity of CBP under conditions where any effect on its recruitment is eliminated.

To further extend these studies, we wished to test the role of CBP in the activation of a natural promoter by PE. To do this...
we used the promoter of the atrial natriuretic factor (ANF) gene, which is known to be activated during cardiac hypertrophy and to be stimulated by PE (22, 28). The activation of this promoter by PE was abolished by co-transfection of a construct expressing full-length CBP in an antisense orientation (Fig. 9A). As expected, the antisense CBP construct also inhibited the response of the SS-CRE promoter to cAMP, indicating that it was able to prevent a well characterized effect of CBP (Fig. 9B).

In view of the close relationship of CBP and p300, we wished to determine whether PE could also affect the ability of p300 to stimulate transcription. To do this we used constructs in which different regions of p300 had been linked to the DNA binding domain of Gal4 (18). In these experiments (Fig. 10) a small non-statistically significant effect of PE was observed with constructs containing the C-terminal activation domain of p300 (amino acids 1737–2414 or 1945–2414), which is homologous to that found at the same position in CBP (for review see Refs. 3, 29).

Interestingly, however, the strongest stimulation by PE, which was comparable to that observed with full-length p300, was observed with the N-terminal activation domain of p300 (amino acids 1–743) even though no effect of PE was observed with constructs containing the C-terminal activation domain of p300 (amino acids 1737–2414 or 1945–2414), which is homologous to that found at the same position in CBP (for review see Refs. 3, 29).

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Interestingly, however, the strongest stimulation by PE, which was comparable to that observed with full-length p300, was observed with the N-terminal activation domain of p300 (amino acids 1–743) even though no effect of PE was observed with the homologous region of CBP (compare Figs. 1 and 10). Despite this distinction, activation of the N-terminal domain of p300 by PE was mediated via p42/p44 MAPK activation, because it was blocked by PD (Fig. 11A) and by the dominant negative mutant of p42 MAPK as well as being activated by overexpression of wild-type p42 (Fig. 11B).

As in the case of CBP, the role of p300 in the response to PE could be demonstrated with a natural promoter. Thus, a dominant negative mutant of p300 (lacking amino acids 348–412) was able to block the activation of the ANF promoter by PE (Fig. 12) in a similar manner to that observed with the antisense CBP construct.

**DISCUSSION**

Considerable evidence suggests that activation of the p42/p44 MAPK pathway is critical for the hypertrophic response of cardiac cells. Thus, for example, stimuli that induce hypertrophy such as mechanical load and angiotensin II have been shown to induce activation of this pathway (30, 31). Moreover, a recent study has demonstrated that overexpression of a constitutively active form of MEK1 (which is an upstream activator of the p42/p44 MAPK enzymes) in transgenic mice results in a significant hypertrophic response in the myocardium (32).
in compensated cardiac hypertrophy providing direct evidence that activation of this pathway can induce a hypertrophic response (32).

In the case of PE, initial studies demonstrated that treatment of cardiac cells with this factor was associated with activation of the p42/p44 MAPK pathway (27, 33). Moreover, such activation appears to be necessary for the hypertrophic response induced with this system (21). Moreover, we have used an antisense CBP construct to block the effect of PE on a natural target promoter, that of the ANF gene. Hence, in our case, the effect of PE has been demonstrated using three distinct systems, two of which rely on endogenous CBP rather than Gal4/CBP constructs.

Interestingly, a dominant negative mutant of p300 was also able to block activation of the ANF promoter by PE indicating that the role of p300 in the PE response could also be demonstrated by inhibiting endogenous p300. It is possible that the ability to block the PE response of the ANF promoter by blocking either CBP or p300 reflects distinct functions for these two factors in the stimulation of the promoter, with inhibition of either factor therefore blocking the response. It is more likely, however, that this effect reflects a dependence of the response on the maintenance of the normal total level of functional CBP and p300. Hence, inhibition of either factor reduces the total level of these two closely related factors and therefore inhibits the response. This effect has been observed, for example, in knockout mice where CBP/p300 double-heterozygote animals show a similar lethal phenotype to that observed with the homozygous knockout of either factor alone (for review see Ref. 39).

In our studies, other hypertrophic agents such as UCN and CT-1 did not induce significantly increased activity of CBP. Both these agents have been shown to activate the p42/p44 MAPK cascade.
MAPK pathway (40–42). However, unlike the case of PE, inhibition of p42/p44 MAPK activation does not affect the ability of UCN or CT-1 to induce hypertrophy (14, 42). Hence the ability of PE to induce strong enhancement of the transcriptional activation ability of CBP and p300 via the p42/p44 MAPK pathway correlates with the essential role of this pathway in its ability to induce hypertrophy.

These findings suggest therefore the possibility that enhanced transcriptional activity of CBP and p300 may be involved in the induction of hypertrophy by PE. Interestingly, a number of factors involved in the hypertrophic response such as AP-1 and the STAT factors have been shown to associate with CBP and p300 (12, 13). Recent studies of the activation of endothelin-1 (ET-1) gene expression by PE have shown that the transcription factor GATA-4 is phosphorylated by the p42/p44 MAPK pathway following PE treatment and plays a critical role in the activation of ET-1 gene expression, which is required for hypertrophy (43). Moreover, it has been demonstrated that CBP enhances the activation of BNP by GATA-4 and YY1 (44) whereas p300 associates with GATA-4 and inhibition of p300 activity by overexpression of E1A prevents GATA-4 stimulation of ET-1 activity (45).

It is likely therefore that CBP and p300 play a critical role in the process of cardiac hypertrophy and, in particular, in its induction by PE. Initial studies of the CBP/CREB system showed that signaling pathways produced phosphorylation of the CREB factor leading to the recruitment of CBP to the DNA and transcriptional activation (1, 2). Studies of this type led to the idea that DNA-bound transcription factors such as CREB represented the primary targets for signaling pathways that induce transcriptional activation with co-activators such as CBP and p300, which in turn recognize the consequences of these signaling pathways acting on the DNA-bound transcription factors rather than being targets themselves for such signaling pathways.

A variety of recent data, however, suggests that CBP and p300 themselves are targets for specific signaling pathways. Thus, for example, in our previous work (26) we demonstrated that NGF was able to enhance the ability of CBP-Gal 4 fusion proteins to activate transcription and that this effect was dependent upon the ability of NGF to activate the p42/p44 MAPK pathway. Similar activation of CBP by calcium-stimulated signaling pathways has been observed in neuronal cells (37, 38, 46). The work presented here extends these studies to show that activation, of p42/p44 MAPK in cardiac cells by PE, similarly results in an enhancement of the transcriptional activation ability of CBP and p300. This indicates that the activity of CBP can be directly targeted by specific signaling pathways in cardiac as well as neuronal cells and identifies PE as an agent able to produce this effect. Moreover, it suggests that, during the hypertrophic response, CBP and p300 are not simply passive partners being recruited to the DNA via phosphorylation.
of DNA-bound factors such as GATA4. Rather they represent targets for these signaling pathways and will induce enhanced transcription activation following PE treatment.

Interestingly, the predominant effect of PE involves the C-terminal domain of CBP and the N-terminal domain of p300 even though these regions are non-homologous to one another (for review see Refs. 3, 29). In contrast, the C-terminal region of p300 was only weakly activated by PE whereas PE had no effect at all on the activity of the N-terminal region of CBP. Hence, the same signaling pathway can target two different regions of these closely related molecules to enhance their transcriptional activating ability.

It is likely that the enhanced transcriptional activating ability of p300 and CBP is mediated via phosphorylation induced by the p42/p44 MAPK pathway. Evidently, the putative phosphorylation sites targeted by the p42/p44 MAPK pathway are within the region 1891–1900 of DNA-bound factors such as GATA4. Rather they represent one of two regions at the C terminus of CBP involved in its transcriptional activating ability following PE treatment. This indicates that a small C-terminal region of CBP acts as a phosphorylation site targeted by the p42/p44 MAPK pathway. Evidently, the putative phosphorylation sites targeted by the p42/p44 MAPK pathway are on at least two sites in vitro by the p42/p44 MAPK pathway. Evidently, the putative phosphorylation sites targeted by the p42/p44 MAPK pathway are within the region 1891–1900 of DNA-bound factors such as GATA4. Rather they represent two different regions at the C terminus of CBP involved in its transcriptional activating ability following PE treatment.

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