The Transcriptional Co-activators CREB-binding Protein (CBP) and p300 Play a Critical Role in Cardiac Hypertrophy That Is Dependent on Their Histone Acetyltransferase Activity*

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The CBP and p300 proteins are transcriptional co-activators that are involved in a variety of transcriptional pathways in development and in response to specific signaling pathways. We have previously demonstrated that the ability of both these factors to stimulate transcription is greatly enhanced by treatment of cardiac cells with the hypertrophic agent phenylephrine (PE). Here, we show that inhibition of either CBP or p300 with antisense or dominant negative mutant constructs inhibits PE-induced hypertrophy as assayed by atrial naturetic protein production, cardiac cell protein: DNA ratio and cell size. Furthermore, we show that overexpression of CBP or p300 can induce hypertrophy and that this effect requires their histone acetyltransferase (HAT) activity. Moreover, we show that PE can directly enhance CBP HAT activity and that artificial enhancement of HAT activity is sufficient to induce hypertrophy. Hence, CBP and p300 play an essential role in hypertrophy induced by PE, and this effect is mediated via PE-induced enhancement of their HAT activity. This is the first time a role for these factors, and their HAT activity, in hypertrophy has been directly demonstrated.

The CBP transcriptional co-activator protein was initially identified as a factor that interacts with the CREB1 transcription factor only following phosphorylation of CREB on serine 133 (for review see Ref. 1). Such recruitment of CBP to DNA-bound CREB results in transcriptional activation, because CBP links CREB to the basal transcriptional complex stimulating transcriptional activity and has histone acetyltransferase (HAT) activity allowing it to produce a more open chromatin structure compatible with transcription (for reviews see Refs. 2 and 3). Although initially discovered via its association with CREB, it has subsequently been shown that CBP and the related p300 factor interact with a wide variety of transcription factors and play a key role in a number of different aspects of cellular signaling and gene regulation during development (for reviews see Refs. 2–4). Factors that interact with CBP and/or p300 include, for example, the steroid/thyroid hormone receptors, the hypoxia-inducible factor HIF-1, and a number of factors important in gene regulation in cardiac muscle, including, for example, MEF-2 and GATA-4 (5–7).

As expected from this critical role in a variety of aspects of transcription factor function, loss of CBP or p300 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 (8), which as well as characteristic facial abnormalities and mental retardation can result in cardiac disorders (9–11). This indication that these factors may play a role in regulating gene expression in the heart has been directly confirmed in the case of p300, where knockout mice lacking both copies of the p300 gene show abnormal heart development with reduced trabeculation of the ventricular chambers and weaker/less extensive heart contractions (12). Similarly, these embryos show reduced expression of cardiac muscle structural proteins such as myosin heavy chain and α-actinin (12). Moreover, inhibition of p90Raf with E1A also inhibits cardiac-specific gene expression (13).

As well as being involved in the development of the heart, it appears that CBP and p300 are also involved in the process of cardiac hypertrophy in which the heart increases in size in response to increasing demand, leading ultimately to heart failure. Indeed, CBP and p300 can interact with transcription factors such as AP-1 and STAT-3, which are involved in the hypertrophic response of cardiac cells to factors such as angiotensin II (14, 15) and cardiotrophin-1 (16, 17). Moreover, it has been shown that the activation of the brain natriuretic peptide gene during hypertrophy involves the interaction of CBP with the transcription factors GATA-4 and YY1 (5), whereas the interaction of p300 with the GATA-4 transcription factor has been shown to be responsible for the stimulation of endothelin-1 activity following treatment with PE (18, 19).

The interaction of CBP and p300 with transcription factors involved in hypertrophy, is of considerable interest, because this initially adaptive increase in muscle mass is ultimately deleterious and results in heart failure (for review see Ref. 20). Hence, an understanding of the gene regulatory mechanisms mediating this response could be of potential importance.

To analyze these mechanisms and provide evidence for an involvement of CBP and p300, we previously used constructs in which the DNA binding domain of the Gal-4 transcription factor had been fused to either CBP or p300. We demonstrated that the ability of these constructs to stimulate transcription

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from a reporter gene containing Gal-4 DNA binding sites was strongly stimulated by the hypertrophic agent PE but not by other hypertrophic agents such as uroctin (21). Hence, a hypertrophic agent can enhance the ability of CBP and p300 to stimulate transcription following recruitment to the DNA via a heterologous DNA binding domain. Moreover, inhibition of CBP or p300 (using an antisense or dominant negative mutant approach) was able to block the ability of PE to activate a construct containing the promoter of the gene encoding ANP (21), which is known to be activated during cardiac hypertrophy and to be stimulated by PE (22, 23).

Although these findings suggest a role for CBP and p300 in PE-induced cardiac hypertrophy, they do not directly prove that this is the case. We have therefore tested the effect of specifically inhibiting CBP and p300 on the ability of PE to induce hypertrophy in cultured cardiac cells using a variety of different assays. Furthermore, we have attempted to probe the mechanisms by which CBP and p300 can induce hypertrophy, and in particular to relate them to their known HAT activities.
(1% fetal calf serum) for 48 h. Cells were harvested by trypsinization, washed in PBS without calcium to prevent cell aggregation, and fixed in 4%. Cells were again washed in PBS and resuspended in block buffer (10% fetal calf serum, 0.05% sodium azide in PBS) to block nonspecific sites of antibody adsorption. Cells were permeabilized in 0.05% saponin in block buffer for 15 min at room temperature. Primary CBP antibody was added to each sample for 1 h at 4°C and washed in PBS, and nonspecific sites were blocked in blocking buffer for 15 min at room temperature. Secondary anti-mouse IgG1:RPE (phycoerythrin) was added for 30 min at room temperature. Cells were washed in PBS, and the samples were read on a Coulter EPICS XL using Epo2 software to detect GFP-positive cells at 525 nm and RPE at 575 nm.

**ANP Measurement**—Cells were incubated in serum-free media in the presence or absence of PE for 48 h. The concentration of immunoreactive ANP in cell culture supernatants was determined by radioimmunoassay by competition between labeled 125I-rat ANP and unlabeled ANP peptide. The amount of ANP in each unknown sample was calculated from a standard curve prepared with purified rat ANP.

**Measurement of Protein and DNA Content**—Cells were incubated in maintenance media in the presence or absence of PE. After 48 h, cells were harvested by trypsinization, washed in PBS (without calcium) to prevent cell aggregation, and resuspended in ice-cold 70% ethanol in PBS. Cells were fixed at 4°C, resuspended in 100 µl of fluorescein isothiocyanate (FITC) stain (0.1 µg/ml FITC, 50 µg/ml RNase A, in PBS), and stained for 2 h. Cells were washed twice in PBS and resuspended in 400 µl of propidium iodide (PI) buffer (50 µg/ml PI, 0.1% trisodium citrate, 0.1% Triton X-100, in dH2O). Cells were passed through a fine needle to prevent cell aggregation and analyzed on a Beckman Coulter Elite FACS machine. The mean fluorescence from 10,000 cells was measured for FITC (protein) at 525 nm and PI (DNA) at 620 nm, and the mean ratio of protein to DNA was calculated for cells positive for CFP at 424 nm.

**Measurement of Cell Size**—Cells were incubated in serum-free media for 24 h and treated for a further 48 h in the absence or presence of PE. Cells were rinsed with PBS, fixed in 4% paraformaldehyde, washed in PBS, and observed under phase-contrast microscopy. Planimetry was performed using Zeiss AxioVision image analysis software to measure GFP-positive cells.

**Histone Acetylation Activity**—Cells were incubated in serum-free media in the presence or absence of PE for 48 h. Cells were then harvested in ice-cold Hanks’ balance salt solution, and the protein concentration of each sample was determined by the Bradford protein assay (28) and re-suspended in immunoprecipitation lysis buffer (10 mM Tris-HCl, pH 8.0, 0.5% Nonidet P-40, 150 mM NaCl, complete protease inhibitor mixture). CBP was isolated by immunoprecipitation, using mouse CBP antibody. An indirect enzyme-linked immunosorbent assay kit was used to detect acetyl residues according to the manufacturer’s instructions (Upstate Biotechnology). The HAT activity in each un-
known sample was determined on a plate reader at a wavelength of 450 and 550 nm and calculated from a standard curve prepared with acetylated histone H4 peptide.

**Statistics**—Values are expressed as mean ± S.E. of n experiments. Values are given as percent activity relative to the activity in unstimulated cells (set at 100%). Statistical analysis was performed by the two-tailed Student’s t test for unpaired data. Analysis of variance was used to look for differences in cell size between treatment groups, and Bonferroni tests were performed post-hoc to test for significant difference between specific treatments. Significance was determined at the level of p < 0.05.

**RESULTS**

In our previous experiments (21) we utilized a construct containing the full-length CBP sequence in an antisense orientation and a construct encoding a dominant negative mutant of p300 to, respectively, inhibit CBP and p300 and to show that this blocks the ability of PE to stimulate an ANP promoter-reporter gene construct. To further validate these constructs, they were co-transfected with constructs containing the Gal-4 DNA binding domain linked to either a C-terminal fragment of CBP or full-length p300. The activity of these constructs has previously been shown to be stimulated by PE, whereas constructs containing, for example, other regions of CBP linked to the Gal-4 DNA binding domain are unaffected by PE treatment (21).

In accordance with our previous results (21), treatment with PE stimulated the ability of these constructs to activate a reporter construct containing Gal-4 DNA binding sites when the constructs were co-transfected into cardiac cells together with empty expression vector (Fig. 1). In contrast, however, when the empty expression vectors were replaced with the vector encoding antisense CBP (Fig. 1A) or dominant negative p300 (Fig. 1B), stimulation by PE was either abolished or reduced to non-significant levels. Hence, the antisense CBP or dominant negative p300 constructs can indeed interfere with the ability of CBP or p300 to respond to PE when delivered to the DNA via the Gal-4 DNA binding domain. Furthermore, basal transcription induced by Gal-CBP-(1678–2441) alone in the absence of PE was also inhibited by antisense CBP (data not shown).

In parallel experiments, cardiac cells transfected with the antisense CBP construct showed a dramatic decrease in the expression of endogenous CBP (Fig. 2), further confirming that the antisense construct is capable of inhibiting both the expression of endogenous CBP and the activation of Gal4-CBP constructs.

Having established that the constructs were able to block CBP or p300, we wished to test whether they could inhibit hypertrophy induced by PE as assayed by various parameters. In particular, because induction of ANP expression by PE is characteristic of its hypertrophic effect (22, 23), we wished to determine whether transfection of cardiac cells with antisense CBP or dominant negative p300 would result in reduced endogenous ANP release following PE stimulation. As illustrated in Figs. 3A and 4A, enhanced levels of ANP were clearly assayable in the medium of cultured cardiac cells treated with PE, compared with untreated controls. However, in cells trans-
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Fig. 5. Effect of wild type E1A and E1AΔ on PE-induced ANP-luciferase reporter activity (A) and cell area (B) and cell length (C) in neonatal cardiac myocytes. To measure ANP promoter activity (A), cells were incubated in 100 μM PE for 48 h in serum-free media following transfection of 2.5 μg of wild type E1A and E1AΔ and 2.5 μg of ANP-luciferase reporter. To measure area (B) and cell length (C), cells were incubated in 100 μM PE for 48 h in serum-free media following transfection with 5 μg of GFP and 5 μg of wild type E1A or E1AΔ. Values are expressed relative to the level of luciferase in control, untreated transfected rat neonatal cardiac myocytes (set at 100%) and are the mean of three independent experiments whose standard error is shown by the bars. *, p < 0.05 versus control or versus the same construct without treatment; n/s, no significant difference versus control or versus the same construct without treatment.

Fig. 6. Relative luciferase activity in neonatal cardiac myocytes co-transfected with 2.5 μg of a promoter-reporter construct containing Gal4 DNA binding sites upstream of the luciferase gene and constructs containing either functional CBP (CBP HAT WT) or a mutant lacking HAT activity (CBP HAT WY) linked to the DNA binding domain of Gal4. Cells were either left untreated or treated with PE (50 μM) for 24 h in maintenance media. Values are expressed relative to the level of luciferase in control, untreated transfected rat neonatal cardiac myocytes (set at 100%) and are the mean of three independent experiments whose standard error is shown by the bars. *, p < 0.05 versus control; n/s, no significant difference versus control.

It is likely that in the transfected cells inhibition of CBP or p300 function produces complete inhibition of PE-mediated stimulation of ANP production.

Having established the effect of inhibiting CBP and p300 on a PE-induced gene, which is activated during hypertrophy, we wished to test the effect on other aspects of the hypertrophic response. Initially, therefore, we measured the effect of antisense CBP or dominant negative p300 on the increase in protein:DNA ratio, which occurs in hypertrophy when cells increase in size without any increase in DNA content. To do this, cells were transfected with antisense CBP or dominant negative p300 and a marker gene encoding cyan fluorescent protein (CYP) to mark the successfully transfected cells. Cells were then gated in a FACS analyzer for CFP-positive cells and assayed for protein or DNA content. Treatment with PE produced a clear, statistically significant increase in the protein:DNA ratio of cells transfected with empty expression vector alone (Figs. 3B and Fig. 4B). In contrast, no such PE-induced increase was observed in the cardiac cells transfected with antisense CBP (Fig. 3B) or dominant negative p300 (Fig. 4B). Hence, antisense CBP or dominant negative p300 can indeed prevent PE-induced hypertrophy as assayed by the enhanced protein:DNA ratio.

To further confirm the effect of antisense CBP or dominant negative p300 on hypertrophy, we also measured their effect on PE-induced increases in cell area or cell length, as measured by microscopy of the transfected cells. As indicated in Figs. 3C, 3D, 4C, and 4D, PE induced increases in both cell area and cell length in the cells transfected with empty expression vector alone. However, these increases were abolished in the cells transfected with antisense CBP (Fig. 3C and 3D) or dominant negative p300 (Fig. 4C and 4D). Hence, inhibition of CBP or p300 activity can block PE-induced hypertrophy as assayed by cell length or cell area.

To confirm these results by using another means of inhibiting CBP and p300, we transfected cultured cardiac cells with an expression vector encoding the adenovirus E1A protein. Thus, both CBP and p300 bind to E1A and are therefore removed from their cellular targets upon E1A overexpression (3, 4). This method has therefore been widely used to inhibit CBP and p300 activity and in particular has been used to demonstrate the role of these factors in the regulation of...
myosin heavy chain and α-actinin gene expression in cardiac cells (13, 29).

In these experiments, overexpression of E1A abolished the ability of PE to induce the ANP promoter (Fig. 5A) or to induce enhanced cell area (Fig. 5B) or cell length (Fig. 5C). In contrast, an E1A mutant that does not interact with CBP or p300 (24) did not inhibit the action of PE (Fig. 5) indicating that the effect of wild type E1A was indeed mediated via CBP/p300.

To determine whether the histone acetyltransferase (HAT) activity of CBP has any role in the effect of PE-induced hypertrophy, we utilized a construct (25) in which full-length CBP containing a mutation (WY), which completely abolishes its HAT activity, has been linked to the DNA binding domain of Gal-4. As illustrated in Fig. 6, this construct was incapable of inducing enhanced promoter activity in response to PE, whereas this was observed as before with a construct containing full-length wild type CBP linked to Gal4. Hence, a mutant CBP lacking HAT activity also fails to respond to PE in terms of enhanced transcription activating ability.

We next wished to determine the effect of such inactivation of HAT activity on the ability of CBP to induce hypertrophy itself. However, all our previous experiments have involved the inhibition of CBP or p300, resulting in inhibition of hypertrophy induced by PE. To provide a means of analyzing specific mutations for their effects on hypertrophy, we therefore tested whether overexpression of wild type CBP or p300 would be sufficient to induce hypertrophy even in the absence of PE. In this experiment, we were indeed able to observe a statistically significant increase in ANP production (Fig. 7A), cell protein:DNA ratio (Fig. 7B), cell area (Fig. 7C) or cell length (Fig. 7D) in the cardiac cells transfected with full-length active CBP.

Hence, the ability of CBP to induce hypertrophy is indeed dependent upon its HAT activity.

To extend these results to p300, we similarly transfected cardiac cells with a full-length p300 expression vector and measured cell area, cell length, and protein:DNA ratio in the transfected cells. In these experiments, p300, like CBP, was able to induce hypertrophy as assayed by all three parameters
However, no induction of hypertrophy was observed with the p300 WY mutation (Fig. 8), which completely abolishes p300 HAT activity, 1.8% of control (25). Similarly, the DGV mutation reduces HAT activity to 70% of control (25) and produced a reduced induction of hypertrophy compared with wild type p300 (Fig. 8). Hence, overexpression of both CBP and p300 can induce hypertrophy, and this effect is dependent on their HAT activity.

In view of the key role of CBP/p300 in PE-induced hypertrophy, we tested whether PE could enhance the HAT activity of CBP. Indeed, in experiments where CBP was immunoprecipitated from PE-treated cardiac cells, we observed a significant increase in its HAT activity compared with untreated cells (Fig. 9), demonstrating that a hypertrophic agent can enhance the HAT activity of the CBP co-activator.

The essential role of HAT activity in the hypertrophic effect of CBP and p300 suggested that an increase in histone acetylation levels might be sufficient to induce hypertrophy. To test this possibility, we used the histone deacetylase inhibitor TSA and determined whether it could induce hypertrophy. As illustrated in Fig. 10, TSA was indeed able to induce hypertrophy as assayed by enhanced cardiac cell protein:DNA ratio (Fig. 10B) as well as increased cell area (Fig. 10C) or cell length (Fig. 10D). Indeed, the effect of TSA was similar in extent to that observed with PE. Interestingly, however, TSA did not enhance...
ANP production (Fig. 10A). Hence, other effects of TSA in addition to enhanced histone acetylation must be required for this aspect, although the HAT activity of CBP and p300 is required for their ability to induce enhanced ANP production (see Figs. 7A and 8A).

We next wished to determine whether CBP and/or p300 were involved in the hypertrophic effect of TSA. Interestingly, we observed that the dominant negative mutant of p300 specifically blocked the ability of TSA to induce hypertrophy as measured by enhanced cell area (Fig. 11A) or cell length (Fig. 11B). In contrast, however, the antisense inhibition of CBP had no effect on the ability of TSA to induce hypertrophy (Fig. 11A, C and D), although it blocked the effect of PE, showing that the antisense vector was indeed having an effect. Hence, p300 activity is required for the hypertrophic effect of TSA, whereas CBP activity is not essential.

**DISCUSSION**

The data presented here demonstrate for the first time that inhibition of either of the transcriptional co-activators CBP or p300 blocks hypertrophy of cardiac cells induced by PE, that overexpression of either factor alone induces hypertrophy, and that these hypertrophic effects are dependent on the HAT activity of p300 and CBP, which is enhanced by PE.

The modification of the N termini of histone molecules by acetylation plays a critical role in the regulation of chromatin structure (for reviews see Refs. 30 and 31). In turn, such acetylation of histones is a key target for cellular regulatory processes, with transcriptional activation being accompanied by acetylation of histones inducing a more open chromatin structure compatible with transcription, whereas, conversely, transcriptional repression is accompanied by histone deacetylation resulting in a more tightly packed chromatin structure incompatible with transcription.

Interestingly, however, most transcriptional activators and repressors, which act by binding to specific DNA sequences and interacting with the basal transcriptional complex, do not possess HAT or deacetylation activity. Rather, they recruit non-DNA binding co-activators or co-repressors that have such activity (for reviews see Refs. 32 and 33). A prime example of this effect is provided by CBP and p300, which bind to a number of DNA-bound transcriptional activators and thereby play a key role in a variety of different cellular regulatory processes (for reviews see Refs. 2–4). Thus, both these factors have been shown to possess HAT activity (34), and this activity has been shown to be essential for their ability to modulate processes as diverse as the G1–S phase transition in the cell.
cycle (26) and to function as a co-activator for the GATA-4 transcription factor (35).

In this report, we have demonstrated that the HAT activity of CBP and p300 is essential for their ability to induce cardiac hypertrophy. In addition to the findings that both CBP and p300 are essential for hypertrophy induced by PE as demonstrated by inhibition of either CBP or p300, we show that overexpression of either factor in cardiac cells can induce hypertrophy. Assays of ANP production, protein:DNA ratio, and cell size in cardiac cells were used as markers of hypertrophy. As well as demonstrating that CBP and p300 can induce hypertrophy in the absence of any other signal, this system also allowed us to demonstrate that the induction of hypertrophy by these factors requires their HAT activity, because mutations that abolish or reduce such activity correspondingly abolish or reduce the ability to induce hypertrophy, as assayed by all three parameters.

Interestingly, we have previously demonstrated that the key role of CBP and p300 in PE-induced hypertrophy is accompanied by an enhanced ability of CBP and p300 to stimulate transcription following exposure of cardiac cells to PE (21). Here, we demonstrate that this effect is dependent on the HAT activity of CBP, because inactivation of such activity within a construct containing CBP linked to the Gal-4 DNA binding domain abolishes enhanced activity in response to PE.

The HAT activity of CBP is contained within the central HAT domain of the molecule located between amino acids 1200 and 1600 (25). In contrast, we previously demonstrated that the enhanced transcriptional activating ability of CBP following PE treatment is dependent on a more C-terminal region located between amino acids 1961 and 2039 (21). This region is a target for p42/p44 MAPK activation, which is essential for the enhanced transcriptional activating ability of CBP in cells.

![Graphs A and B: Mean cell area and length](image)

![Graphs C and D: Mean cell area and length](image)

**Fig. 11.** Mean cell area (A and C) and mean cell length (B and D) in transfected neonatal cardiac cells either left untreated or treated with 100 μM PE or 300 nM TSA for 48 h in serum-free media following co-transfection with 5 μg of GFP and 5 μg of antisense CBP (A and B) or dominant negative p300 (C and D). All values are the mean of three independent experiments whose standard error is shown by the bars. *, p < 0.05 versus the same construct untreated; n/s, no significant difference versus the control or the same construct untreated.
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Hypertrophy, although this effect can also be achieved by cell cycle-dependent kinases (37). Hence, it is likely that PE-induced phosphorylation of the C-terminal region by p42/p44 MAPK results in a corresponding enhancement of HAT activity of CBP, leading to enhanced ability to activate transcription.

Hence, the HAT activity of CBP and p300 appears to be essential both for their ability to enhance hypertrophy and for their enhanced transcriptional activating ability following exposure to PE, which itself induces enhanced CBP HAT activity. This key role for the HAT activity of the factors is paralleled by our finding that the histone deacetylase inhibitor TSA can itself induce hypertrophy in cardiac cells as assayed by enhanced cardiac cell protein:DNA ratio, cell area, and cell length. This indicates that the balance between histone acetylation and histone deacetylation is critical for controlling the hypertrophic response of cardiac cells. Interestingly, however, enhanced production of the ANP factor, a marker of hypertrophy, is not induced by TSA. Therefore, although the HAT activity of CBP and p300 is essential for ANP production, unlike the other tested parameters of hypertrophy, enhanced histone acetylation alone is not sufficient for ANP induction.

The enhanced cell area and cell length induced by TSA is dependent upon the activity of p300, because it can be blocked by a dominant negative mutant of this factor. In contrast, however, the hypertrophic effect of TSA appears to be independent of CBP, because it cannot be blocked by antisense inhibition of this factor even though such inhibition blocks the hypertrophic effect of PE. Furthermore, these results suggest that the antisense CBP construct is specific to CBP expression and does not block p300 expression.

This suggests, that there are specific targets that must be acetylated by p300 for hypertrophy to occur in response to the decreased deacetylation, which occurs in the presence of TSA. Such targets appear to be specific for p300, because this cannot be achieved in cells where CBP is active but p300 is inactive. This is in contrast to the situation with PE where CBP and p300 appear to be independently required for hypertrophy to occur. This could be because these two factors have distinct targets, with acetylation of both sets of targets being required for hypertrophy. Alternatively, PE-induced hypertrophy may simply be sensitive to the total level of CBP and p300 that is present in the cells so that inhibition of either factor alone reduces the total level of these factors and therefore inhibits the response. This effect has been observed, for example, in knock out mice where CBP/p300 double-heterozygote animals show a similar lethal phenotype to that observed with homozygous knock out of either factor alone (for reviews see Ref. 4).

Whatever the case, the data presented here show for the first time that both CBP and p300 play a key role in the PE-induced hypertrophic response with inhibition of either of these factors blocking this response as assayed by ANP protein production, protein:DNA ratio, or cell area/cell length and that the balance between HAT activity and deacetylation of histones plays a key role in controlling the hypertrophic response of cardiac cells. Thus, inhibition of histone deacetylation using TSA can induce hypertrophy, although this effect can also be achieved by enhanced histone acetylation achieved either by the overexpression of CBP or p300 or by the specific enhancement of CBP HAT activity by PE. These findings raise the possibility, therefore, that drugs that modulate HAT activity in the heart may ultimately be useful therapeutically in the control of human heart failure caused by cardiac hypertrophy.

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