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Type II Regulatory Subunit of Protein Kinase Restores cAMP-dependent Transcription in a cAMP-unresponsive Cell Line*

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cAMP-dependent protein kinase appears to play a role in cAMP-induced gene expression in mammalian cells. There exist two major types of cAMP-dependent protein kinase, type I and type II, which are distinguished by their regulatory subunits, RI and RII, respectively. We investigated the role of type I and type II protein kinase in the cAMP-induced gene expression by either stable or co-transfection of RI_α, RII_α, or RII_β gene in an expression vector together with somatostatin-chloramphenicol acetyltransferase (SS-CAT) fusion gene using a cAMP-unresponsive mutant pheochromocytoma cell line (A126-1B2). Introduction of the RII_β gene restored the capability of these cells to induce the SS-CAT gene expression in response to forskolin stimulus and induced a changed morphology which resembled that of wild type. The RII_α gene also induced SS-CAT gene expression but to a lesser degree than that achieved by the RII_β gene, whereas the RI_α gene had no effect. The induction of SS-CAT gene expression by the RII_β gene was specifically blocked by the 21-mer RII_β antisense oligodeoxynucleotide. These results show for the first time that type II but not type I regulatory subunit of cAMP-dependent protein kinase is essential for a cAMP-induced gene transcription.

In recent years, there has been remarkable progress in the identification and characterization of the promoter-regulatory regions (CRE)[1] of cAMP-regulated genes (1). However, little is understood about the mechanism responsible for the induction of these genes by cAMP. cAMP in mammalian cells acts through cAMP-dependent protein kinase. There are two types of cAMP-dependent protein kinase, type I and type II, which share a common catalytic (C) subunit but contain distinct regulatory subunits, RI and RII, respectively (2, 3). Four different regulatory subunits (RI_α (4), RI_β (5), RII_α (6), and RII_β (7)) have been identified at the gene/mRNA level. Two distinct C subunits (C_α (8) and C_β (9, 10)) have also been identified; however, preferential co-expression of either one of these C subunits with either type of protein kinase R subunit has not been found (10).

It was an intriguing observation (11) that the CRE-containing somatostatin gene is not inducible by cAMP in a mutant pheochromocytoma (PC12) line, A126-1B2 (12), which lacks type II cAMP-dependent protein kinase but contains the wild type level of type I protein kinase activity. Thus, the A126-1B2 cell line offers an experimental model in which the differential role of cAMP-dependent protein kinase isozymes in CRE transcription can be studied.

In the present study, by the use of gene transfection and antisense strategy, we examined the role of the regulatory subunits of protein kinase isozymes in the induction of the CRE-containing somatostatin gene in A126-1B2 cells. We also examined the effect of the introduction of the regulatory subunit gene of protein kinase on the cell morphology and biological response of cells to cAMP analogs.

EXPERIMENTAL PROCEDURES

Cell Lines—A-126-1B2 (12) (kindly provided by J. A. Wagner, Harvard Medical School and Dana Farber Cancer Institute, Boston, MA) and PC12 (American Type Culture Collection, Rockville, MD) cells were grown in Dulbecco's modified Eagle's medium containing 10% fetal calf serum, 5% horse serum, penicillin (100 units/ml), and streptomycin (100 μg/ml), and were fed every 3–4 days and passaged every 7 days (11).

Expression Vector Plasmids—The plasmid human RII_β ($hRII_\beta$) (kindly provided by T. Jahnsen, Institute of Pathology, Rikshospitalet, Oslo, Norway) is a 3.6-kb *Eco*RI fragment containing the full-length $hRII_\beta$ cDNA (13). A retroviral vector, OT1521 (14) (kindly provided by M. L. McGeady, National Cancer Institute, Bethesda, MD), which is derived from fpGV-1 (15, 16), the MSV-derived retroviral vector, contains the mouse metallothionein 1 (MT-1) promoter as an internal promoter and the neomycin resistance gene (G418) (Fig. 1). The vector MT-RII_β was constructed by inserting the 3.6-kb $hRII_\beta$ *Eco*RI fragment into OT1521 at an *Eco*RI site at the 3′ end of the MT-1 sequence, placing the $hRII_\beta$ gene under the transcriptional control of the MT-1 promoter (Fig. 1). The vector MT-RII_α was constructed in the same manner as the MT-RII_β vector by insertion of the 1.65-kb *Eco*RI fragment of human RII_α ($hRII_\alpha$) cDNA (17) (kindly provided by T. Jahnsen) into the OT1521 vector. The plasmid HL-REV RI_{wt} (18) (kindly provided by G. S. McKnight, University of Washington, Seattle, WA) contains the coding region of mouse RI_α which is under control of the long terminal repeat of the Ha-MSV.

Transfections and Transient Assays—Cells (10^6 cells/100-mm dish) were transfected with DNA consisting of 20 μg of somatostatin-chloramphenicol acetyltransferase fusion gene (Δ-71 CAT plasmid (11), kindly provided by M. R. Montminy, the Salk Institute, San Diego, CA) and 10 μg of calf thymus DNA carrier, with or without 10 μg of the expression vector plasmid (see above) of the regulatory subunit of protein kinase, by the calcium phosphate precipitation method (19). After 24 h, fresh medium was added, and the indicated cells were treated for 24 h with forskolin (10 μM) and/or $CdCl_2$ (2 μM) and then assayed for CAT activity. Cells were harvested and cell lysates were prepared as described by Gorman *et al.* (19). Lysates (75 μg of protein) were incubated with 1.0 μCi of [^{14}C]chloramphenicol and 0.2 mM acetyl-CoA in 150 mM Tris-HCl, pH 7.6, for 60 min at 37 °C. Under these conditions, CAT activity was linear with time. Reaction products were analyzed by thin-layer chromatography (19).

Production of Stable Lines—A126-1B2 cells (10^6 cells/100-mm dish) were transfected with 10 μg of MT-RII_β plasmid by the calcium phosphate precipitation method (19). 48 h after the transfection, the neomycin analog G418 was added to the medium, and the resistant colonies were isolated after 2–3 weeks of selection. Colonies were grown in the presence of $CdCl_2$ (2 μM) and were analyzed for produc-

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[1] The abbreviations used are: CRE, cAMP responsive element; kb, kilobase(s); MT-1, mouse metallothionein 1; CAT, chloramphenicol acetyltransferase; SS, somatostatin; 8-N_3-[^{32}P]cAMP, 8-azidoadenosine 3′:5′-mono[^{32}P]phosphate.

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tion of RII_β by photoaffinity labeling of cell extracts with 8-N_3-[^{32}P] cAMP followed by immunoprecipitation with anti-RII antiserum (kindly provided by S. O. Døskeland, University of Bergen, Bergen, Norway) as previously described (20, 21).

Oligodeoxynucleotides—We synthesized (Milligen Biosearch 8700 DNA synthesizer (Bedford, MA)) the 21-mer antisense oligodeoxynucleotides complementary to the human RI_α (22), human RII_α (17), or human RII_β (13) mRNA transcripts starting from the first codon. The oligomers had the following sequences: RI_α antisense, 5′-GGG-GGT-ACT-GCC-AGA-CTC-CAT-3′; RII_β antisense, 5′-CGC-CGG-GAT-CTC-GAT-GCT-CAT-3′; RII_α antisense, 5′-CGG-GAT-CTG-GAT-GTG-GCT-CAT-3′.

RESULTS

Construction of RII Expression Vectors—The absence of somatostatin gene transcription in a mutant PC12 cell line, A126-1B2, has been correlated with a deficiency in type II cAMP-dependent protein kinase activity (11, 12). In an attempt to restore the somatostatin gene transcription in A126-1B2 cells by manipulation of type II protein kinase activity, we constructed retroviral vectors for type II protein kinase regulatory subunits, RII_α and RII_β. The plasmids MT-RII_α and MT-RII_β were constructed by insertion of human RII_α (17) or RII_β (13) cDNA into the OT1521 retroviral vector (14) to obtain inducible expression of RII_α or RII_β. The plasmids contain the coding region of either RII_α or RII_β preceded by the metal ion (Cd or Zn)-inducible metallothionein promoter (Fig. 1). The plasmids also contain a gene coding for neomycin phosphotransferase, which confers G418 resistance and allows selection of stable transfectants (Fig. 1). OT1521 vector without RII gene was used as the control vector.

Stable Transfectants of RII_β Gene Restore Somatostatin Gene Transcription—We transfected A126-1B2 cells with either MT-RII_β or control plasmid, OT1521, which confers G418 resistance. Following selection with G418, we identified colonies that overexpressed RII_β by treatment of cells with $CdCl_2$ (2 μM) and analyzing RII_β protein levels in cell extracts with the photoaffinity labeling (8-N_3-[^{32}P]cAMP)-immunoprecipitation (anti-RII antiserum) method (20, 21). These transfectants (A126-RII_β) contained 3–5-fold increased levels of a 52-kDa protein that is antigenically related to the rat brain RII_β as compared with parent A126-1B2 cells (AV relative level ± S.D.: 4.5 ± 0.5 for A126-RII_β; 1.0 ± 0.1 for A126-1B2). In colonies carrying the OT1521 control vector, RII_β levels remained unchanged as compared with the parent A126-1B2 cells.

We examined whether these cells containing the RII_β gene are capable of somatostatin gene transcription. The parent A126-1B2 cells exhibited low basal levels of somatostatin-chloramphenicol acetyltransferase (SS-CAT) fusion gene transcription activity in the presence of forskolin (Fig. 2) (11). This basal activity varied from 0 to 0.8% as shown by the percent conversion of substrate (Fig. 2*B*). When A126-1B2 cells were stably transfected with the RII_β gene (A126-RII_β) there was a 56-fold induction of SS-CAT gene upon treatment of cells with $CdCl_2$ and forskolin over the basal activity (Fig. 2*B*). The A126-RII_β colonies that overexpressed 3–5-fold RII_β

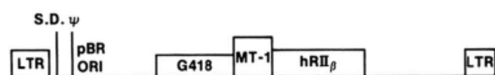

FIG. 1. **Schematic diagram of MT-RII_β retroviral vector plasmid.** OT1521 (14) containing the MT-1 promoter as an internal promoter, was derived from fbGV-1 (15, 16), the MSV retroviral vector. The hRII_β EcoRI fragment (13) was introduced into OT1521 at an *Eco*RI site at the 3′ end of the MT-1 sequence. *LTR*, long terminal repeat; *S.D.*, splice donor site; *ψ*, packaging site; *pBR ORI*, origin of replication from pBR322; *G418*, gentamicin-resistant gene; *MT-1*, mouse metallothionein-1 promoter gene; *hRII$_\beta$*, a 3.6-kb *Eco*RI fragment containing the full-length human RII_β cDNA.

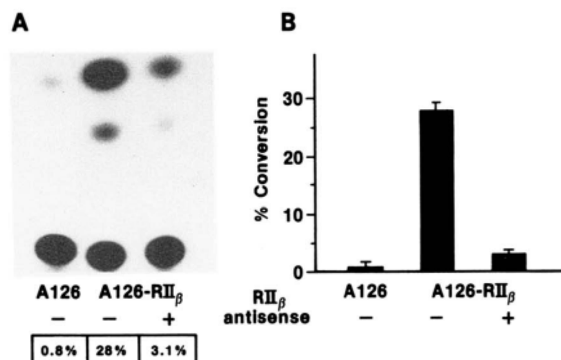

FIG. 2. **RII_β gene transfectants of A126-1B2 cells restore somatostatin gene transcription.** A126-1B2 cells and A126-RII_β cells (stable RII_β gene transfectants) (see "Experimental Procedures") were transfected with the SS-CAT (Δ-71 CAT) fusion gene, treated with $CdCl_2$ (2 μM) and forskolin (10 μM), and the CAT activity in cell extracts was analyzed by thin-layer chromatography to separate acetylated forms (*upper spots*) from unreacted chloramphenicol. −, +, lack of exposure or exposure to RII_β antisense (15 μM). Cells were treated with $CdCl_2$ (2 μM) and forskolin (10 μM) and exposed for the final 24 h of transection to the 21-mer RII_β antisense oligodeoxynucleotide. Similar results were obtained with 10, 20, and 40 μg of Δ-71 CAT plasmid. *A*, the results show CAT activity as measured by the percent conversion of chloramphenicol to acetylated forms; *B*, the data shown are the average ±S.D. of four experiments identical to *A*.

protein as compared with the parent A126-1B2 cells showed 35–95-fold induction of CAT activity. The SS-CAT gene induction in A126-RII_β cells was cAMP-dependent, since treatment of cells with $CdCl_2$ only without forskolin did not induce the CAT activity (average percent substrate conversion = 0.4%). The SS-CAT activity was not induced in cells stably transfected with OT1521 control vector (average percent substrate conversion = 0.4%).

Inhibition of Somatostatin Gene Transcription in RII_β Gene Stable Transfectants by RII_β Antisense Oligodeoxynucleotide—To provide direct evidence that the somatostatin gene transcription demonstrated above in A126-RII_β cells is due to the presence of RII_β gene, we used antisense strategy. Cells exposed to the 21-mer RII_β antisense oligodeoxynucleotide (15 μM) which specifically blocks RII_β production (21) exhibited a 90% reduction in SS-CAT transcription as compared with the control cells unexposed to the RII_β antisense oligomer (Fig. 2*B*). Neither RI_α antisense nor RII_α antisense oligodeoxynucleotide caused any reduction in the CAT activity (data not shown), indicating that the transfected RII_β gene was responsible for the somatostatin gene transcription in the stable transfectants, A126-RII_β cells.

Restoration of Wild Type Cell Morphology and Biological Response to cAMP Analogs by RII_β Gene—As shown in Fig. 3, A126-1B2 cells, when stably transfected with the RII_β gene, displayed an altered morphology which resembled that of wild type PC12 cells. Moreover, these RII_β stable transfectants exhibited the same sensitivity as PC12 cells in their biological response to cAMP; cells exhibited growth inhibition upon treatment with cAMP analogs as did the wild type PC12 cells, whereas the mutant A126-1B2 cells were refractory to the analog treatment (data not shown).

Overexpression of Type I Regulatory Subunit (RI_α) Does Not Induce Somatostatin Gene Transcription—We examined whether overexpression of RI_α gene could also induce the somatostatin gene transcription in A126-1B2 cells using a co-transfection assay that has been used extensively to study the effects of steroid receptors and oncogenes on specific gene expression (23, 24). We used the plasmid HL-REV-RI_{wt} which contains the Harvey sarcoma virus long terminal repeat pro-

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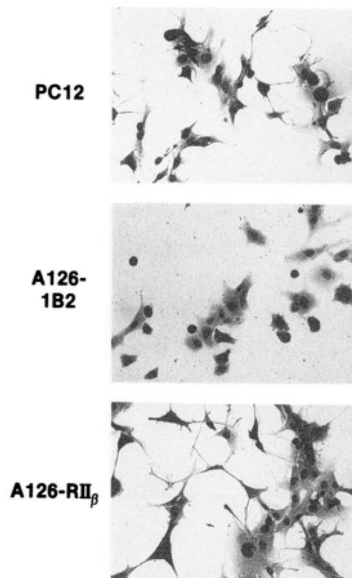

FIG. 3. **RII$_\beta$ gene induces wild type cell morphology in A126-1B2 mutant cells.** PC12, A126-1B2, and A126-RII$_\beta$ cells were seeded at 1×10^4 cells/1.0 ml onto four-chamber tissue culture slides and grown for 48 h. A126-RII$_\beta$ cells were grown in the presence of $CdCl_2$ (2 μM). Cells were fixed and stained by Wright's stain. × 75.

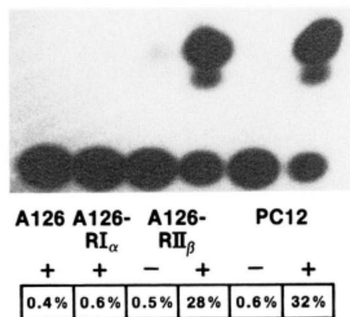

FIG. 4. **Overexpression of RI$_\alpha$ does not induce somatostatin gene transcription.** 20 μg of SS-CAT fusion gene was co-transfected into A126-1B2 cells with 10 μg of HL-REV-RI$_{wt}$ or MT-RII$_\beta$ plasmid. A126-1B2 and PC12 cells were also transfected with SS-CAT gene alone. +, treatment with both $CdCl_2$ (2 μM) and forskolin (10 μM) for the final 24 h of transection; −, $CdCl_2$ (2 μM) treatment only. The results show CAT activity as measured by the percent conversion of chloramphenicol to acetylated forms.

moter and allows strong constitutive overexpression of the mouse RI$_\alpha$ gene (18). The SS-CAT gene expression was not induced in cells co-transfected with the vector HL-REV-RI$_{wt}$ as in the control of A126-1B2 cells (Figs. 4 and 5). In contrast, cells co-transfected with the vector MT-RII$_\beta$ showed marked induction of the SS-CAT gene expression after stimulation with $CdCl_2$ and forskolin to the similar extent as that shown by wild type PC12 cells (Figs. 4 and 5). The failure of the RI$_\alpha$ gene to induce CAT activity was not due to low expression of RI$_\alpha$ protein; cells co-transfected with either a RI$_\alpha$ or RII$_\beta$ gene demonstrated a 4-fold overexpression of RI$_\alpha$ or RII$_\beta$ protein, respectively, as compared with the untransfected control cells (Fig. 5). Both A126-1B2 cells transfected with the RII$_\beta$ gene and PC12 cells exhibited a low basal activity percent conversion = 0–0.8%) of SS-CAT gene transcription in the absence of forskolin (Figs. 4 and 5), indicating that the somatostatin gene transcriptions in these cells were cAMP-dependent. Co-transfection with vector MT-RII$_\alpha$ also induced CAT activity in these cells but to a lesser degree than that by vector MT-RII$_\beta$. Thus, both type II regulatory subunits, RII$_\alpha$ and RII$_\beta$,

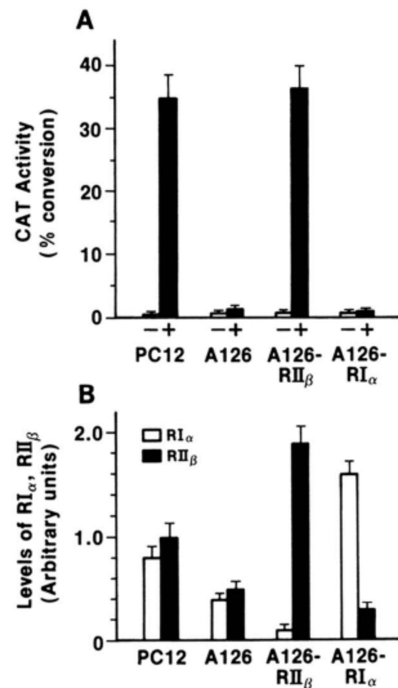

FIG. 5. **Failure of somatostatin gene transcription in RI$_\alpha$ gene transfectants is not due to the absence of functional RI$_\alpha$ protein.** *A*, the results are the average CAT activity (percent conversion) ±S.D. of seven experiments identical to those of Fig. 4. *B*, integrated densitometry data from the photoaffinity labeling-immunoprecipitation autoradiograms of RI$_\alpha$ and RII$_\beta$. The levels of RI$_\alpha$ and RII$_\beta$ are expressed relative to the levels of RII$_\beta$ in PC12 cells (arbitrary unit = 1.0). The data shown are the average ± S.D. of seven experiments identical to those of Fig. 4 but without forskolin treatment.

displayed positive effects on the somatostatin gene transcription, whereas the type I regulatory subunit, RI$_\alpha$, had no effect.

DISCUSSION

We reported here that introduction of the type II regulatory subunit gene of cAMP-dependent protein kinase converted cAMP-unresponsive A126-1B2 cells to cAMP-responsive cells. This conversion was detected at the level of somatostatin gene (CRE) transcription as well as in the biological response of these cells and their morphology. Our finding that overexpression of the RI subunit could not mimic the effect of the RII subunit in CRE transcription supports the specific role of RII in such transcription. Overexpression or suppression of one isoform of R subunits (RI or RII) results in a compensatory change in the amount of the other isoform of R subunit; the amount of C subunit; however, remains the same (25–29). Thus, the CRE transcription induced in the mutant A126-1B2 cells by the introduction of the RII gene may not be due to a change in the level of C subunit but rather to a change in the ratio of type I to type II cAMP-dependent protein kinase holoenzymes.

The role of the catalytic subunit of cAMP-dependent protein kinase has been described in the basal rather than the cAMP-induced expression of the CRE-containing genes (30, 31). Moreover, the role of the catalytic subunit of protein kinase has been shown in the transcription of both CRE (cAMP-responsive)- and AP-2 element (cAMP or phorbol ester-responsive)-containing genes (32, 33), indicating a lack of strict CRE specificity for the catalytic subunit effect. The induction of the somatostatin gene transcription by the RII gene that we have demonstrated here was cAMP-dependent. A recent report by Wu and Wang (34), who demonstrated

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cAMP-dependent and sequence-selective binding of purified preparations of RII to double helical DNA (CRE), supports the role of RII in CRE transcription. The experiments described here clearly demonstrate, although the mechanism of action is not known, the role of type II cAMP-dependent protein kinase in cAMP regulation of gene transcription.

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