The β-subunit of cGMP-phosphodiesterase (β-PDE) is a key protein in phototransduction expressed exclusively in rod photoreceptors. It is necessary for visual function and for structural integrity of the retina. β-PDE promoter deletions showed that the −45/−23 region containing a consensus Crx-response element (CRE) was necessary for low level transcriptional activity. Overexpressed Crx modestly transactivated this promoter in 293 human embryonic kidney cells; however, mutation of CRE had no significant effect on transcription either in transfected Y79 retinoblastoma cells or Xenopus embryonic heads. Thus, Crx is unlikely to be a critical β-PDE transcriptional regulator in vivo. Interestingly, although the β/GC element (−59/−49) binds multiple Sp transcription factors in vitro, only Sp4, but not Sp1 or Sp3, significantly enhanced β-PDE promoter activity. Thus, the Sp4-mediated differential activation of the β-PDE transcription defines the first specific Sp4 target gene reported to date and implies the importance of Sp4 for retinal function. Further extensive mutagenesis of the β-PDE upstream sequences showed no additional regulatory elements. Although this promoter lacks a canonical TATA box or Inr element, it has the (T/A)-rich β/T element located within the −45/−23 region. We found that it binds purified TBP and TFIIB in gel mobility shift assays with cooperative enhancement of binding affinity.

One of the key components of the phototransduction cascade that takes place in rod photoreceptors is the heterotetrameric (αβ)2 cGMP-phosphodiesterase (1). The gene encoding the β-subunit of the human enzyme (β-PDE)1 has been well characterized and consists of 22 exons encompassing ~43 kb of genomic DNA (2). Genetic defects in this gene have been linked to retinal degeneration in several animal species and human (3–9). There is increasing evidence that abnormalities in transcriptional regulatory components of different genes contribute significantly to or directly cause pathological phenotypes in the retina (10–13). Therefore, further studies on the transcriptional regulation of rod-specific β-PDE gene will identify additional genes important for retinal function and structural integrity and will ultimately help to establish the molecular mechanisms crucial for retina-specific expression of this and perhaps some other genes.

We recently reported our initial results on the transcriptional control mechanisms that take place in the human β-PDE 5′-flanking region (14). Mutational analysis of the β-PDE promoter tested both in vitro and ex vivo, and confirmed by the generation of transgenic Xenopus expressing mutant β-PDE promoter/green fluorescent protein fusion constructs in vivo, revealed a minimal promoter region, from −93 to +53, that supports high levels of rod-specific transcription (14). Two enhancer elements were localized within this minimal promoter, βAPI/NRE and β/GC, that interact with nuclear factors and activate transcription from the β-PDE promoter.

To continue the systematic analysis of the β-PDE promoter structure, we have now carried out extensive mutagenesis of the proximal promoter and the 5′-untranslated region. The presence of a consensus CRE sequence in the minimal rod-specific β-PDE promoter prompted us to test whether Crx (cone, rod homeobox), a member of the Otx family of homeodomain-containing transcription factors, is involved in transcriptional regulation of the β-PDE gene. Previously, Crx had been shown to be important for the transcriptional control of several retina-specific genes, including rhodopsin (15, 16). We report here that although Crx is capable of modest transactivation of the β-PDE promoter when overexpressed in 293 embryonic kidney cells, transfections in Y79 retinoblastoma cells and Xenopus embryonic heads showed that it is unlikely to be a major player in transcriptional regulation of the β-PDE gene. We also show that both purified TBP and TFIIB were able to bind to the β-PDE proximal promoter (−45/−16) with cooperative enhancement of binding. The interactions between the β-PDE promoter and the basal transcription factors were not completely disrupted by limited nucleotide substitutions in this region, which may be related to the complex, low affinity, basal transcription factor-promoter interactions over extended core promoter sequences described on other promoters (17, 18).

The functionally important β/GC element is homologous to the consensus GC box that binds members of the Sp family of transcription factors including Sp1, Sp3, and Sp4. These nuclear factors share similar structural features and have highly conserved DNA binding domains that allow them to bind with...
identical affinity to the consensus GC box (19). We have previously shown that Sp1 and Sp4 can interact with the β-PDE promoter (14). Our intriguing finding that the predominantly central nervous system-expressed Sp4 is also abundantly present in the adult retina prompted us to further test its activation properties on the rod-specific β-PDE promoter under defined conditions in direct comparison to Sp1 and Sp3. We report here that only Sp4, but not Sp1 or Sp3, is a strong activator of transcription from the β-PDE promoter. Thus, the rod-specific β-PDE gene is the first specific gene target for the Sp4 transcription factor described to date.

EXPERIMENTAL PROCEDURES

Cell Cultures and Transient Transfections—Y79 human retinoblastoma cells and 293 human embryonic kidney cells were obtained from the American Type Culture Collection (Manassas, VA). Y79 retinoblastoma cells were cultured in RPMI 1640 (Invitrogen) supplemented with 15% (v/v) fetal calf serum (Invitrogen) as described previously (20). 293 kidney cells were propagated in Dulbecco’s modified Eagle’s medium/ Ham’s F-12 (Invitrogen) supplemented with 10% fetal calf serum. These cells have been used previously for testing multiple retina-specific promoters and transcription factors including Crx (14, 15).

Calcium phosphate-mediated transient transfections as well as luciferase reporter and β-galactosidase assays were performed as described previously (20), except for the addition of a glycerol shock that improved the transfection efficiency of 293 kidney cells. For normalization of transfection efficiency, all transfection reactions included 5 μg of the pSV-β-galactosidase expression plasmid as an internal control. In cotransfection experiments, the ratios of the reporter vector to expression plasmid and transcription factors including Crx (14, 26). Recently, mutations in Crx genes (15, 26). Recently, mutations in Crx genes (15, 26) and the empty pGL2-Basic vector (Promega) as negative control. In cotransfection experiments, empty expression vectors were used to keep the promoter-less control (Fig. 1A).

Gel Mobility Shift Assays—Gel mobility shift assays (GMSA) were performed as described previously (23). Briefly, embryos at stages 24–45 (14). However, the −45 to +53 promoter construct carrying further deletion in cultured Y79 human retinoblastoma cells and then ex vivo in dissected Xenopus embryo heads. These human retina-derived cell culture and amphibian in situ transfection systems have been employed previously for studying the regulation of photoreceptor-specific gene expression, including that of β-PDE (14). Luciferase activities were measured and normalized to the β-galactosidase activities obtained with a control plasmid in Y79 cells or expressed per embryo and averaged statistically as described previously for Xenopus transfections (23). Further reduction in promoter activity was observed in both transfection systems when the −45 to −23 region was deleted (Fig. 1). The activity level of the −23 to +53 promoter was not significantly different from that observed with the promoter-less vector when tested in Y79 cells or Xenopus embryos. The +4 to +53 promoter construct carrying further 5′-end deletion past the major transcription start site (25) showed that luciferase activity remained low. High evolutionary conservation of the −45 to −23 region (25) that comprises the consensus CRE motif (~41/~36) and the T/A-rich β/TA sequence located at a consensus position for the TATA box is evident between mouse and human also suggesting its functional importance.

Overexpressed Crx Enhances β-PDE Transcription and Has Additive Effect with Nrl—The CRE motif (CT/GT/TAATC) interacts with Crx and plays an important regulatory role in the transcription of rhodopsin and several other retina-specific genes (15, 26). Recently, mutations in Crx have been linked to various forms of human retinal degeneration (10, 11). To investigate whether Crx is able to directly transactivate the β-PDE promoter, we transiently overexpressed Crx in 293 human embryonic kidney cells in cotransfections with different deletion mutants of the β-PDE promoter. These cells do not endogenously produce rod-specific phosphodiesterases includ-
ing β-PDE and have been used previously for transient transfections to study transcriptional regulation of the β-PDE gene (14, 15, 20, 27). Fig. 1B shows that although the uninduced activity of the –45 to +53 promoter was significantly lower than that of the –72 to +53 construct, overexpressed Crx caused similar (2-fold) transactivation of both promoters. In contrast, the –23 to +53 construct produced luciferase activity comparable with that of the promoter-less control and failed to show any transactivation potential when coexpressed with Crx. For comparison, we also tested the promoter region of the cone photoreceptor-specific α′-PDE gene that contains two sequences homologous to consensus CRE, one at position –95/–89 (TTAATCC) and the other at –118/–112 (GATTAG). Cotransfections of the –132 to +138 α′-PDE/luciferase reporter construct with the Crx expression plasmid resulted in an 8-fold increase in promoter activity compared with the uninduced promoter (Fig. 1B).

Since the –45 to –23 region was found to be important for the β-PDE promoter transactivation by overexpressed Crx, we tested whether the consensus CRE located within this region (–41/–36) was responsible for this transactivation. We also tested whether Crx-mediated transactivation of the β-PDE promoter had functional synergy with Nrl that had been previously shown to bind and activate this promoter (14). The activity of the wild-type –72 to +53 β-PDE promoter was compared with the CRE-mutant construct –41/–38m. Approximately 9–10-fold increase in luciferase activity by coexpressed Crx and Nrl was observed compared with the –4-fold increase caused by Crx alone and a 3-fold increase produced by Nrl alone (Fig. 1C). These results are consistent with an additive or a modest synergistic effect, which differs from the rhodopsin promoter that shows significant synergistic transactivation by the combination of Crx and Nrl (15).

Functional Analysis of the Consensus CRE, the Proximal Promoter, and the 5′-Untranslated Region in Retina-related Transfection Systems—Based on the results described above, we further investigated whether CRE and its flanking sequences were functionally relevant to the transcriptional regulation of the β-PDE promoter in vivo. A series of β-PDE promoter mutants carrying substitutions in the –45 to –23 region was transfected in Y79 retinoblastoma cells and then in Xenopus embryos maintained ex vivo (summarized in Fig. 2, top). Contrary to our initial expectations, the –41/–38m mutation that completely disrupted the consensus CRE had little effect on the β-PDE promoter activity in both transfection systems (Fig. 2A). In addition, no significant changes were seen with mutations in –37/–36, –35/–34, and –33/32. The –30/–27m mutant con-
taining nucleotide substitutions in positions 2–5 (GAAA–25 to TCCTCA) of the T/A-rich sequence also showed no significant effect on transcription.

Although neither the mutations in consensus CRE or β/TA affected promoter activity, a cooperative interaction of transcription factors at both sites was suggested by the results of the transient transfections. A double mutant containing nucleotide substitutions spanning the proximal 5′-flanking and the 5′-untranslated regions (Fig. 2) was tested in transient transfections of Y79 retinoblastoma cells. Promoter activity determined in these mutants ranged between −0.5- and 1.5-fold that of the wild-type control (Fig. 2B). A 3′-end deletion mutant (−72 to +4) lacking most of the 5′-UTR showed −3-fold reduction of promoter activity.

Taken together, these results suggest that the β-PDE promoter does not have well defined core elements responsible for basal transcription in Y-79 cells or Xenopus embryo heads. Rather, it appears that the transcription factors responsible for maintaining low level expression from this promoter do not require a rigid sequence for interactions, but can accommodate a range of nucleotides.

**TBP and TFIIB Bind the β-PDE Promoter**—Although the β/TA sequence located at −31/−25 of the β-PDE promoter is significantly different from the consensus TATA box, it has a high T/A content and is located in the proximity of the transcription start site with no other consensus promoter elements present in this gene. Thus, we tested whether the β/TA sequence was able to bind purified TBP separately or in complex with TFIIIB in GMSAs. As a control, we compared the binding of TBP, TFIIIB, and the TFIIB-TBP combination to the AdML promoter. Shifted bands were observed with the addition of either TBP alone or TFIIIB alone to the β/TA probe (Fig. 3).
Addition of the combination of TBP and TFIIB resulted in a slower migrating complex with about 3-fold increase in band intensity compared with TBP alone, producing a characteristic supershifted pattern described previously for the AdML promoter (18). These results suggest an enhanced cooperative binding by the TFIIB-TBP complex to the \( /H9252\)-PDE promoter compared with TBP alone. In contrast, when comparable protein concentrations were used, the AdML promoter interacted with TBP and TFIIB-TBP, but did not form a stable TFIIB-DNA complex in GMSA as demonstrated previously (Ref. 18 and data not shown). Although the addition of a 200-fold molar excess of the wild-type \( /H11002\)-\( /H11002\)/\( /H11002\)-\( /H11002\) competitor to the binding reaction prevented the shifted complex formation, the mutant \( /H11002\)-\( /H11002\) and \( /H11002\)-\( /H11002\) competitors also showed some competition with the wild-type sequence for TFIIB-TBP binding. These results further corroborate our functional transfection data that a well defined core promoter sequence could not be found in the \( /H9252\)-PDE 5'-flanking region.

**DISCUSSION**

Sequence analysis of the 5'-flanking region of the \( \beta\)-PDE gene showed that it has several sites homologous to known response elements (14, 28). These include an E box, an AP1/NRE–like sequence (\( \beta\)Ap1/NRE), a GC box–like site (\( \beta\)/GC), and a sequence identical to the consensus CRE. We recently demonstrated that \( \beta\)Ap1/NRE and \( \beta\)/GC were \textit{cis}-acting elements.
functionally important for \( \beta \)-PDE transcriptional regulation and that the E box seemed to have no significant role in \( \beta \)-PDE transcription (14, 28). To gain further insight into transcriptional regulation of this rod photoreceptor-specific gene, we performed a detailed mutagenic screen of the \( \beta \)-PDE promoter and the 5'-UTR. The functional relevance of the consensus CRE motif (−41/−36) was also investigated. In addition, we tested the effects of different members of the Sp family of transcription factors on activity of the \( \beta \)-PDE promoter that contains the functionally important GC element. Because the \( \beta \)-PDE gene does not have a TATA box, Inr sequence, or other known core promoter elements, we extended our studies to include the basal promoter region.

Crx has been shown to interact with the upstream region of the \( \beta \)-PDE gene in DNase I footprinting assays (15). We observed a modest increase in \( \beta \)-PDE promoter activity by cotransfected Crx that was significantly reduced after substituting CRE nucleotides with a wild-type sequence. Here we demonstrate the first natural target gene for Sp4. The \( \beta \)-PDE promoter luciferase transcription in 293 kidney cells. The \( \beta \)-PDE promoter luciferase transcription in 293 kidney cells and that the −41/−36 sequence functions as CRE.

However, in transfections of both Y79 retinoblastoma cells and \( \textit{Xenopus} \) embryos, \( \beta \)-PDE mutants with disrupted CRE (−41/−38m and −37/−36m) showed promoter activity comparable with that of the wild-type promoter. The lack of effect of an in vivo concentration of Crx on the \( \beta \)-PDE transcription in a retinal system differs from the transcriptional activation of the \( \beta \)-PDE promoter by cotransfected Crx in 293 kidney cells. The latter could be caused by Crx overexpression and, possibly, by the context of a non-retinal cell line that may contain additional cofactors interacting with Crx. Therefore, although Crx is involved in the regulation of several other photoreceptor-specific genes, our results suggest that the CRE-like sequence located in the \( \beta \)-PDE proximal promoter is unlikely to be a functional element important for the transcriptional activation of this gene in retinal cells. Nevertheless, under certain conditions, Crx may be able to modulate the effect of other transcription factors.

The possibility of an additional regulatory sequence(s) in the \( \beta \)-PDE basal promoter region or the 5'-UTR is suggested by the tight regulation of the transcriptional initiation site selection in this gene. There are only one major and one minor transcription start sites in both human and murine \( \beta \)-PDE genes (25). This indicates the assembly of the basal transcription machinery at a specific core promoter element rather than random binding to a variety of sequences. However, there are no consensus core promoter elements in the \( \beta \)-PDE gene. The T/G-rich A/T sequence located 25 bp upstream from the major transcription start site of the \( \beta \)-PDE gene (−31/−25) seemed to be a likely site for interactions with basal transcription factors, although the sequence (TGAAAGA) is not predicted from crystallographic studies to form a stable TBP-DNA complex (30). However, our protein binding studies suggest that the \( \beta \)-PDE promoter forms stable interactions in vivo in GMSA with purified TBP as well as with the TFIIB-TBP complex, with a cooperative enhancement of binding. Interestingly, a stable \( \beta \)-PDE promoter-TFIIB complex was also observed in the absence of TBP with a relatively modest concentration of TFIIB. Because the \( \beta \)-PDE promoter lacks the consensus BRE, (G/G/C)G/C/G/C/GCCG (30), proposed to be a binding site for TFIIB, it is likely that TFIIB interacts with an alternative DNA sequence in the \( \beta \)-PDE promoter. In addition, deletion of the −45/−23 region reduced the promoter activity virtually to the level of the promoter-less vector suggesting the presence of nucleotides critical for the \( \beta \)-PDE transcription. However, we observed no effect of a 4-nucleotide substitution in \( \beta \)TA (−30/−27m) on promoter activity in either Y79 retinoblastoma cells or \( \textit{Xenopus} \) embryos. Both −30/−27m and −35/−26m showed significant competition with the wild-type sequence for TFIIB-TBP binding in GMSA. These results suggest the lack of a well defined core element in this promoter necessary for basal transcription machinery binding and low level basal transcription.

The most significant finding of the present investigation was the demonstration of the functional involvement of members of the Sp family in transcriptional regulation of the \( \beta \)-PDE promoter. Interestingly, Sp1, Sp3, and Sp4 transcription factors showed differential effects on the \( \beta \)-PDE promoter activity. Sp4-mediated transactivation was significantly higher than that produced by Sp1 or Sp3, which suggests the importance of this transcription factor for the \( \beta \)-PDE gene transcription. Whereas Sp4 is predominantly restricted to the central nervous system and retina in vivo, it is expressed in many cell lines (19) including the 293 kidney cells. Sp1 and Sp3 are ubiquitous in mammalian cells. Therefore, all three proteins are expressed in 293 cells. Nevertheless, the difference between Sp4-mediated transactivation of the \( \beta \)-PDE and \( \textit{SV40} \) promoters was dramatic compared with Sp1 and Sp3.

Members of the Sp family bind GC-rich DNA sequences through three zinc finger motifs. The residues involved in the determination of the target site specificity and binding affinity are highly conserved between Sp1, Sp3, and Sp4. In fact, all of these transcription factors bind GC and GT boxes with equal affinity in vitro (19). Thus, a relative abundance of any one of the Sp proteins would lead to its increased competition with the others for the \( \beta \)-PDE promoter binding. However, DNA binding by single proteins may not be the key molecular basis to explain the Sp4, Sp1, and Sp3 functional differences in vivo. The \( \beta \)-PDE promoter contains other regulatory sequences. Thus, the differential Sp4-mediated stimulation of this gene transcription is likely to be dependent on its promoter context.

Sp4 has been the least characterized member of the Sp family partly because of its restricted pattern of expression in vivo. Here we demonstrate the first natural target gene for Sp4 that also seems to lack transcriptional regulation by Sp1 and Sp3. The fact that Sp4 was the only transcription factor to transactivate significantly the rod-specific \( \beta \)-PDE promoter supports our previous finding of this highly restricted protein, compared with Sp1 or Sp3, being abundantly expressed in retina (14). The lack of other known Sp4 targets combined with our finding of its regulation of a very specific rod-restricted \( \beta \)-PDE gene implies that this transcription factor functions in a relatively narrow promoter-specific manner.

In addition, Sp4 could have a more universal role in cell type-specific expression of certain genes in rods and possibly other retinal cell populations by interacting with different arrays of transcription factors. We have shown previously that another nuclear factor, Nrl, regulates transcription from the \( \beta \)-PDE promoter (14). Considering the additional \( \beta \)-PDE tran-

\[ \text{L. E. Lerner, Y. E. Gribanova, and D. B. Farber, unpublished observations.} \]
spatial mechanism described in this study, we can suggest that a unique combination of molecular interactions may be required for rod-specific transcription from this TATA- and Inr-less promoter (Fig. 5). This is consistent with the combinatorial model of transcriptional regulation of cell-specific gene expression.

Acknowledgments—We thank Branden S. Wolner for help with GMSAs using purified basal transcription factors TBP and TFIIIB.

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FIG. 5. Schematic model of the molecular events required for rod-specific transcription from the minimal −93 to +53 β-PDE promoter: a unique combination of transcription factor-DNA interactions. Functionally relevant DNA response elements in the β-PDE promoter are represented by tall graphic figures, and consensus binding sequences for known transcriptional regulators that do not affect transcription from this promoter are shown as narrow rectangles. All DNA sequences and their putative transcription factors are labeled. Potential protein-DNA interactions are shown as vertical arrows, and their functional effects on promoter activity are represented by semicircular arrows. Basal transcription factors TBP and TFIIIB may interact with the β-PDE promoter and their higher affinity cooperative binding is indicated as a hatched double arrow.
The Rod cGMP-phosphodiesterase β-Subunit Promoter Is a Specific Target for Sp4 and Is Not Activated by Other Sp Proteins or CRX
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J. Biol. Chem. 2002, 277:25877-25883.
doi: 10.1074/jbc.M201407200 originally published online April 9, 2002

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