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ARTICLES

Mediator Caused Induction of a Human Bradykinin B1 Receptor Minigene: Participation of c-Jun in the Process

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Abstract The bradykinin B1 receptor (BKB1R) gene is expressed in selected tissues such as lung and kidney. In these tissues it is expressed at a very low level until induced by inflammatory mediators. Our aim has been to understand the mechanism of this regulatory process. A human BKB1R minigene was constructed. It contained a 1.8 kb promoter, the entire exon I, 1.5 kb of intron I, the entire exon II and intron II, and the luciferase gene as a reporter. Transient transfection of the minigene into SV40-transformed IMR90 cells (IMRSV) resulted in a promoter activity which was activated by the mediators, lipopolysaccharide (LPS) and desArg^{10}-kallidin. In contrast, these mediators did not induce the activity of the 1.8 kb promoter construct alone. Thus, motifs exclusive of the promoter such as 5′-UTR and/or intron regions are required for mediator-induced expression of this gene. Promoter activities of both the minigene and the 1.8 kb promoter construct were enhanced in a dose-dependent manner upon cotransfection with c-Jun. Furthermore, cotransfecting c-Jun with the minigene achieved the maximal promoter activity with no further increase in response to mediators. Conversely, the induction of the minigene promoter activity by mediators was abolished upon cotransfection with a dominant negative mutant of c-Jun. Other experiments suggest that multiple AP-1 sites are interactive with the c-Jun upregulation of this gene. Taken together, these results point to c-Jun as a key intermediary in the activation of the expression of this gene by mediators. However, participation of motifs outside of the promoter are necessary to obtain this inducible expression. J. Cell. Biochem. 82: 163–170, 2001.

Key words: promoter activity; intron regions; lipopolysaccharide; des-arg^{10}-kallidin; inducible gene expression; AP-1 site; negative regulatory element; enhancer; TATA box; c-Jun dominant negative

The bradykinin B1 receptor (BKB1R) is normally expressed only minimally. However, BKB1R gene expression is induced markedly under many conditions such as arthritis, cystitis, UV irradiation, colitis, and hyperalgesia [Zuzack et al., 1995; Davis et al., 1996; Donaldson et al., 1997; Hall, 1997; Marceau et al., 1997; Rupniak et al., 1997]. Its ultimate expression is multilevel regulated, at points of transcription, mRNA degradation, and receptor maintenance [Zhou et al., 1998, 1999, 2000]. In vivo, inflammatory mediators such as lipopolysaccharide (LPS), interleukin-1β and even its own agonist, des-Arg^{10}-kallidin (DAK), activate the expression of the BKB1R gene [Ahluwalia and Perretti, 1996; Donaldson et al., 1997; Marceau et al., 1997; Sardi et al., 1997; Schanstra et al., 1998; Ni et al., 1998a]. However, the expression of this gene is very tissue and cell specific.

The 5′-flanking regulatory region of the human BKB1R gene has been studied by a few laboratories including ours [Schanstra et al., 1998; Yang et al., 1998; Ni et al., 1998a]. The promoter has a typical TATA-box, and is activated markedly by a cell type specific enhancer [Yang et al., 1998]. Promoter action is inhibited by negative regulatory elements upstream of the enhancer [Yang et al., 1998]. The minimal enhancer is a 100 bp element, located about 600 bp upstream of the transcription start site. The AP-1 site located within the enhancer region is essential for its activation [Yang et al., 1998]. In addition to its function in

Abbreviations used: BKB1R, bradykinin B1 receptor; BK, bradykinin; LPS, lipopolysaccharide; DAK, des-arg^{10} kallidin; IMRSV, SV40 transformed IMR90 cells; TK, thymidine kinase; adv, adenovirus.

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the BKB1R gene promoter, AP-1 transcription factors are important in the expression of a number of inducible genes, such as cyclooxygenase-2, urokinase-type plasminogen activator, matrix metalloproteinase family, and human inducible nitric oxide synthase [Bennow and Brinckerhoff, 1997; Guan et al., 1998, 1999; Marks-Konczalik et al., 1998; Ried et al., 1999]. The AP-1 family members have also been shown to cooperatively interact with other transcription factors, such as NF-κB proteins ETS factors, NFAT proteins and Smad family proteins [Bennow and Brinckerhoff, 1997; Chen et al., 1998; Liberati et al., 1999; Yang et al., 1999]. All three MAPK pathways, ERK, JNK, and p38 kinase, activate the AP-1 family proteins [Wisdom, 1999]. ERK and p38 MAP kinase pathways are known to be involved in the up-regulation of BKB1R gene expression [Larrivee et al., 1998; Campos et al., 1999; Naraba et al., 1999]. LPS has been shown to induce COX2 in mouse monocytes (72Mp16) and IL-8 in neutrophils (70M) through AP-1 activation [Roebuck, 1999; von Knethen and Brune, 2000]

Our efforts have been to decipher the mechanism(s) driving the inducible expression of the BKB1R gene. Unfortunately, attempts to define these inducible mechanisms by using promoter constructs have proven unsuccessful. Therefore, a minigene strategy which has been used successfully to determine cell-type specific and inducible expression mechanisms of other genes was employed [Kuncio et al., 1996; Hu et al., 1997; König et al., 1998]. We generated a minigene construct which mimics the native genomic structure of the BKB1R gene. With this minigene model we demonstrate induction of BKB1R promoter activity by LPS and DAK and subsequently investigate the mechanisms involved in the upregulated expression of this gene.

EXPERIMENTAL PROCEDURES

Plasmid Constructs

The minigene was generated by standard molecular biology techniques. It contains a 1.8 kb promoter, the entire exon I, 1.5 kb of intron I, the entire exon II and intron II, and the luciferase reporter gene. The pGl3-BKA-adv plasmid was generated with the pGL3-BKA plasmid as a template. To obtain this chimeric plasmid, the fragment from −384 to +89 of the BKA promoter in pGL3-BKA plasmid, was replaced by a 60 bp adenovirus promoter. Other plasmids used in this study were described in detail previously [Yang et al., 1998]. The pcDNA3/c-Jun and pcDNA3/c-$Jun^{D/N}$ were generous gifts from Dr. Michael J. Birrer in NIH. All of the oligonucleotides used in this study were purchased from Gibco. The cloning of the PCR products followed the TA-cloning protocol from Invitrogen Inc. All of the deletions and mutations were confirmed by automatic DNA sequencing (Applied Biosystem Inc. Model 370A) and detailed restriction enzyme digestion.

Cell Culture and Transfection

The IMRSV were seeded at a density of 40,000 cells/well onto 24-well plates in 0.5 ml of MEM with 10% FBS. After 24 h, the cells were cotransfected with 0.5 μg/well of target DNA and 25 ng/well of internal control plasmid (pRL-adv). As internal control we generated a new pRL-adv where the TK promoter was replaced with a 60 bp minimal adenovirus promoter. The modified pRL-adv proved a stable and reliable internal control plasmid. Transfections were performed with Profection Mammalian Transfection System (Promega). After 16 h, the medium was replaced with fresh growth medium. Six hours later, the cells were treated with or without 100 nM $desArg^{10}$-kallidin (DAK), or 10 μg/ml LPS. The cells were harvested 24 or 40 h later by lysis with passive lysis buffer (Promega). Dual luciferase activity was determined on TD-20/20 luminometer (Tunner Designs, Sunnyvale, CA) and reported as relative luciferase activity. At least three transfections, each run in triplicate, were performed. Data were expressed as mean ± S.D.

RESULTS

AP-1 Sites in the 1.8 kb Promoter Region

The 1.8 kb promoter construct (BKA) is depicted in Figure 1. A 100 bp enhancer segment is located at position (−505 to −484). An AP-1 site is situated within this enhancer. A TATA box is located at (−50 to −43). An AP-1 site is situated proximaly upstream of the TATA. The BKG construct is the minimal promoter (0 to −384) containing the TATA box and proximal the AP-1 site. The BKE construct (0 to −566) contains the two AP-1 sites and the enhancer region. The BKA construct spans the entire 1.8 kb of promoter region. In the

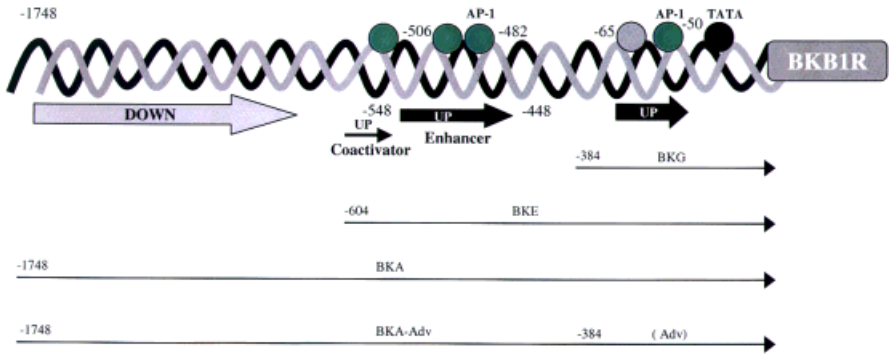

Fig. 1. Schematic of the promoter region. The specific locations of AP-1, TATA box, and enhancer are illustrated. The structures of BKA, BKE, BKG, and BKA-adv are also displayed. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

BKA-Adv construct a 60 bp adenovirus promoter was used to replace the (−384 to +89) promoter fragment thus eliminating the TATA box and its proximal AP-1 site.

Upregulation of the 1.8 kb Promoter by c-Jun

Previous results showed that the AP-1 site located within the BKB1R enhancer is crucial for its cell-type specific activation [Yang et al., 1998]. c-Jun, a trans factor interactive with the AP-1 elements upregulates the activity of the 1.8 kb promoter construct as illustrated in Figure 2. The BKA promoter construct linked to a luciferase reporter gene was cotransfected with 50 and 250 ng of pcDNA3/c-Jun plasmid into the IMRSV. A sizeable increase in luciferase activity is observed associated with the c-Jun cotransfection. Increasing c-Jun concentration resulted in increased promoter response. A dominant negative mutant of c-Jun (c-Jun^{DN}), where the transactivation domain is deleted, was used as a negative control. c-Jun^{DN} at 50 ng had no effect on the promoter activity of BKA.

Lack of Induction of Promoter Activity by LPS and DAK

The IMRSV were transfected with the BKA promoter. LPS 10 μg/ml or DAK (100 nM), were added to the cell culture 22 h after transfection. Luciferase activity was measured 24 h after addition of the mediators. As shown in Figure 3, neither LPS nor DAK induced BKA promoter activity. Response to either mediator remained at basal level.

Minigene Construct

A minigene was then constructed to determine whether other motifs within the gene would facilitate mediator caused induction when combined with the promoter. A diagram of the minigene construct is illustrated in Figure 4. In the construct, a luciferase reporter is driven by a 4.5 kb fragment of the human BKB1R gene. This fragment contains the 5′-flanking region (1.8 kb), exon I region (92 bp), 3′-end of intron I region (1.5 kb), exon II region (119 bp), and intron II region (0.9 kb) of the human BKB1R gene. In the promoter construct (BKA), the luciferase reporter gene is driven by a 1.9 kb fragment of the human BKB1R gene.

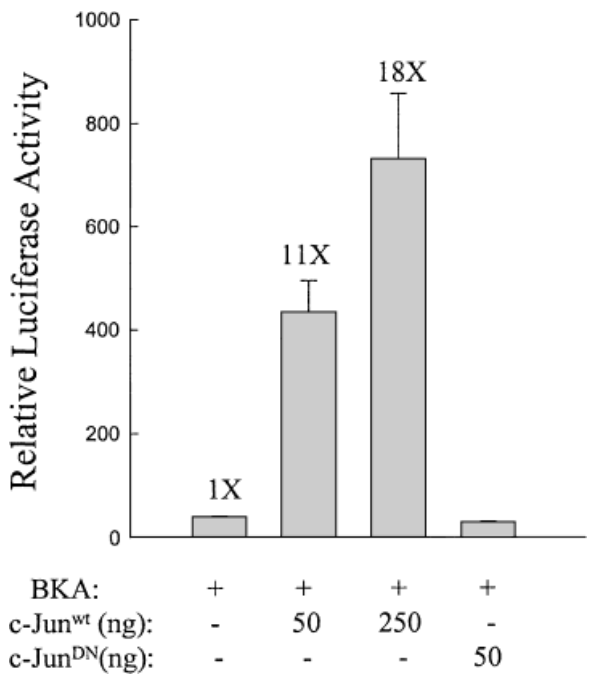

Fig. 2. c-Jun increases the promoter activity of BKA in a dose dependent manner. Values are shown as relative luciferase activities. The indicated values are from a representative experiment performed in triplicate. Each value is the mean±SD. Each experiment was repeated at least three times. Plasmid shown represents quantity/ml cotransfected.

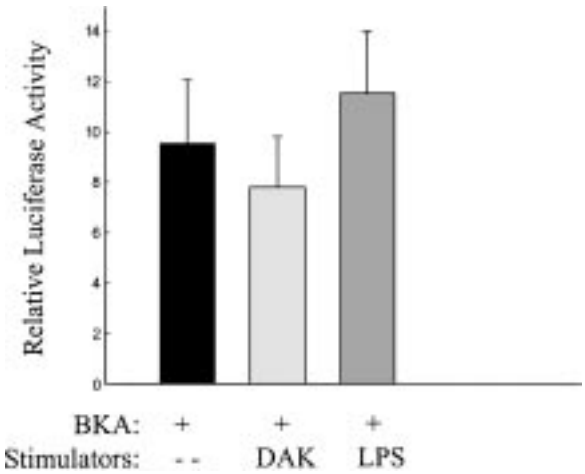

Fig. 3. Mediators fail to increase promoter activity of BKA. DAK = des-arg^{10}-kallidin, LPS = lipopolysaccharide. The detailed procedure is described in the methods section. No statistically significant differences in the luciferase values were found between un-stimulated and stimulated groups.

This fragment contains the 5′-flanking region (1.8 kb), and the 5′-end of the exon I region (89 bp) from the human BKB1R gene.

Induction of Minigene Promoter Activity

Unlike the 1.8 bp promoter, the minigene promoter activity proved to be mediator inducible (Fig. 5). The IMRSV were transfected with the minigene. LPS or DAK were added to the cell cultures 22 h later. At predetermined optimal concentrations (results not shown) both LPS (10 μg/ml) and DAK (100 nM) generated a statistically significant 4.0- and 2.6-fold increase in minigene promoter activity, respectively.

Effect of c-Jun and c-JunDN on Minigene Activity

Plasmids containing c-Jun and c-Jun^{DN} were then cotransfected with the minigene. As shown in Figure 6, transfection with the c-Jun plasmid up-regulated the promoter activity in a concentration dependent manner. c-Jun at 20 ng elevated minigene activity only slightly above basal. c-Jun at 50 ng elevated 3.8-fold above basal. At 80 ng c-Jun elevated minigene activity 4.8-fold above basal. c-Jun^{DN} at 50 ng brought the minigene activity to below basal.

Interaction of c-Jun With Mediators

c-Jun plasmid at 40 ng was used to increase promoter activity. This activation was within the range of that induced by the mediators, LPS and DAK. As seen in Figure 7A, 40 ng of the transfected c-Jun plasmid activated the reporter by about 3.5-fold. Following the transfection LPS 10 μg/ml or DAK (100 nM) displayed no further reporter activation. Conversly, c-Jun^{DN} ablated the stimulatory effects of both LPS and DAK Figure 7B.

AP-1 Site(s) Involved in the Inducible Expression of BKB1R

To clarify interaction of the two AP-1 site(s) with c-Jun (one within the enhancer and the other proximal to the TATA box), we examined the effect of c-Jun on promoter constructs which either contained the two AP-1 sites or lacked one of them. The configuration of these constructs is shown in Figure 1. As illustrated in Figure 8 the BKG construct which retained the proximal AP-1 site but lacked the enhancer and its AP-1 site retained the relative c-Jun induced response compared to basal. The BKA-adv construct which lacks the proximal AP-1 site but retains the enhancer located AP-1 site also retained the relative c-Jun induced response. Thus both AP-1 sites are c-Jun responsive and the presence of either upregulates promoter activity in response to c-Jun.

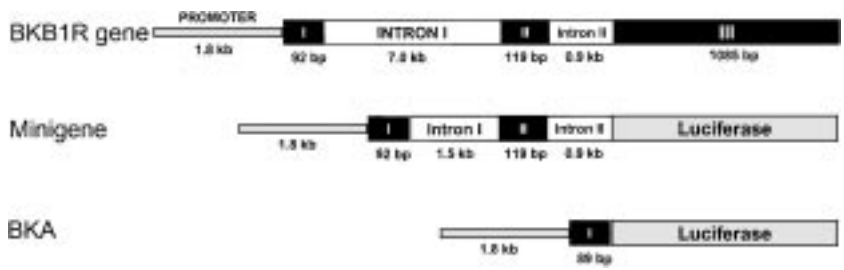

Fig. 4. Schematic depicting the minigene and other plasmid constructs. The black rectangles represent the exons of the BKB1R gene. The white rectangles represent the introns. The thin gray rectangles represent the 1.8 kb promoter. The big gray rectangle is the luciferase gene. The sizes of exons, introns, and promoters are specified.

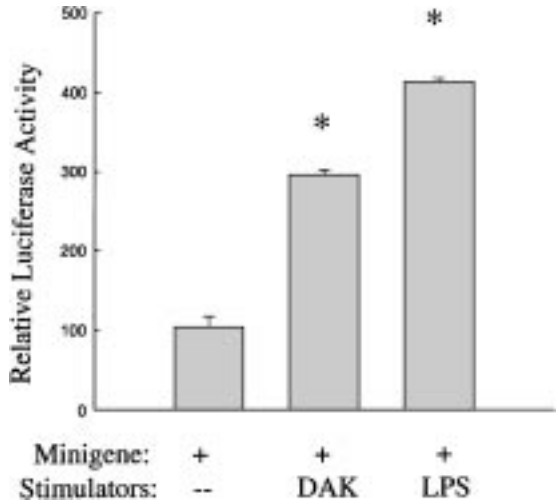

Fig. 5. Mediator induced minigene promoter activity. DAK = des-arg^{10}-kallidin, LPS = lipopolysaccharide. The detailed procedure is described in the methods section. *$P < 0.01$, for each stimulated group vs. control. Statistical analysis was carried out by one factor analysis of variance (ANOVA) followed by the Boferroni method.

It is interesting to note that these constructs displayed varied basal and c-Jun responsive activities, (Fig. 8). BKE which contains the enhancer region but is cut at position (−604), 5′ of the enhancer, displayed by far the greatest activity. The low activity of BKA, which is the total 1.8 promoter construct, is notable because it still contains the enhancer region. In presence of the region 5′ of the enhancer the basal and c-Jun responsive activities were reduced sizably

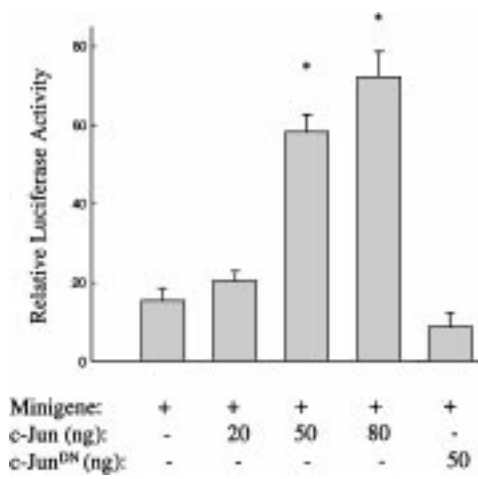

Fig. 6. Response of minigene to c-Jun at various plasmid concentrations. Values are shown as relative luciferase activity. The indicated values are from a representative experiment performed in triplicate. Each value is the mean±SD. Each experiment was repeated at least three times. c-Jun plasmid was transfected at 20, 40, and 60 ng/ml. *$P < 0.01$, for each group cotransfected with c-Jun plasmid vs. the c-Jun untransfecetd control. Statistical analysis was carried out by one factor analysis of variance (ANOVA) followed by the Boferroni method.

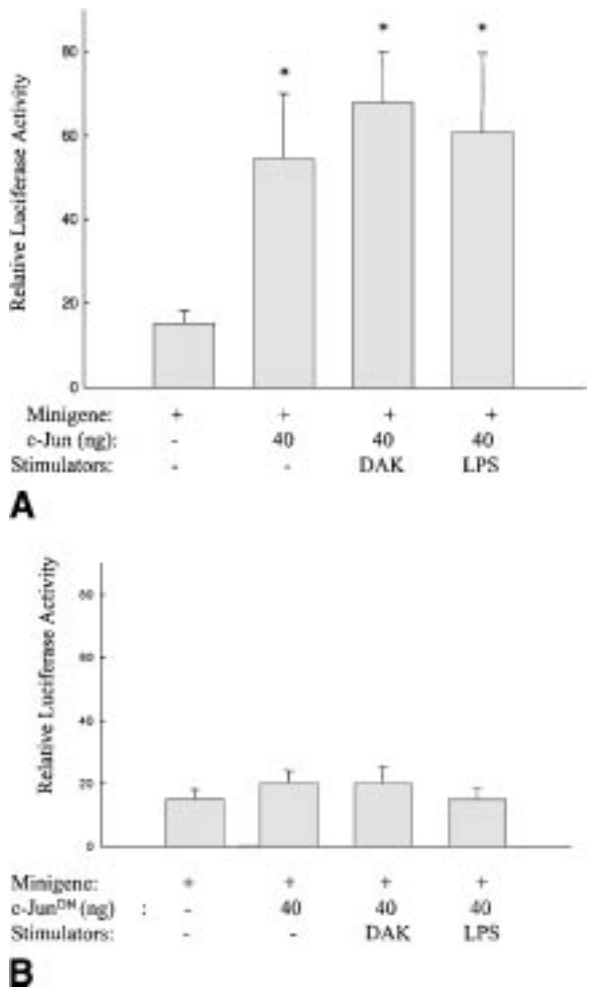

Fig. 7. **A:** Effect of c-Jun on inducibility of the minigene. DAK = des-arg^{10}-kallidin, LPS = lipopolysaccharide. The detailed procedure is described in the methods section. IMRV were cotransfected with minigene and c-Jun plasmids. A concentration of c-Jun plasmid was chosen which approximated maximal mediator caused increase in promoter activity. Statistical analysis was carried out by one factor analysis of variance (ANOVA) followed by the Boferroni method. No statistically significant differences in the luciferase values were found between the c-Jun transfected, DAK and LPS stimulated cells, and those only transfected with c-Jun but not stimulated. **B:** c-Jun^{DN} abolishes mediator induced increase in minigene activity. c-Jun^{DN} = the dominant negative of c-Jun. DAK = des-arg^{10}-kallidin, LPS = lipopolysaccharide. The detailed procedure is described in the methods section. Statistical analysis was carried out by one factor analysis of variance (ANOVA) followed by the Boferroni method. No statistically significant differences in luciferase values were found between the c-Jun^{DN} cotransfected cells including the DAK and LPS stimulated cells and those only transfected with the minigene.

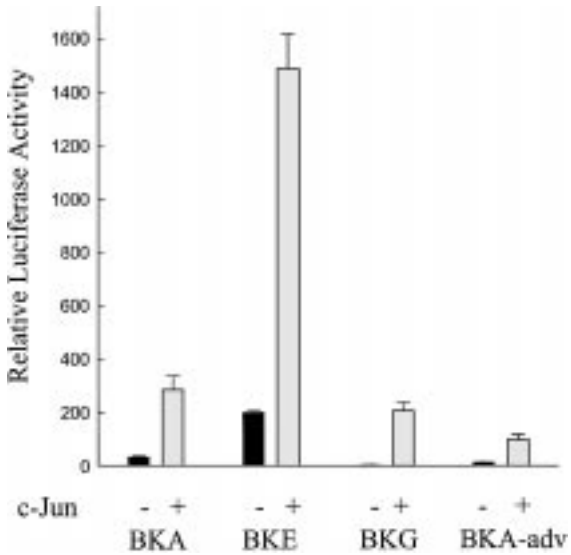

Fig. 8. Effect of c-Jun on activities of truncated promoter constructs. c-Jun represents the pcDNA3/c-Jun plasmid. BKA is a 1.8 kb promoter construct. BKE is a 693 bp promoter construct. BKG is a 473 bp promoter construct. These promoter constructs are described in detail elswhere [Yang et al., 1998]. BKA-adv = chimeric promoter construct with a 60 bp adenovirus promoter replacing fragment (−384 to +89) of BKA.Values are shown as relative luciferase activity. The indicated values are from a representative experiment performed in triplicate. Each value is the mean±SD. Each experiment was repeated at least three times.

affirming our previous report of the existance of a putative silencer 5′ of the enhancer [Yang et al., 1998].

DISCUSSION

We demonstrated previously that an AP-1 element within the enhancer region is essential for the action of the enhancer and the ultimate activity of the human BKB1R promoter [Yang et al., 1998]. Another AP-1 element proximal to the TATA box has been described and may be involved in the inducible expression of the BKB1R gene [Ni et al., 1998]. Critical roles for AP-1 sites within the promoter region in the upregulation of BKB1R gene expression have also been suggested by other studies [Larrivee et al., 1998; Naraba et al., 1999]. In this report we examined the effect of c-Jun, an AP-1 factor, on the promoter activity of the BKB1R gene. Cotransfection of the c-Jun plasmid with the 1.8 kb promoter construct, BKA, increased its reporter activity substantialy. The effect was c-Jun plasmid concentration dependent.

To separate the putative action of c-Jun on the AP-1 element located within the enhancer and the AP-1 element located proximal to the TATA box we examined the effect of c-Jun on variously sized promoter constructs. When the AP-1 site proximal to the TATA box was eliminated (BKA-adv) induction of promoter activity by c-Jun was retained. On the other hand, the BKG construct, where the enhancer region with its AP-1 site was eliminated, also displayed a strong response to c-Jun relative to basal. Thus, both AP-1 sites appear to be active targets for c-Jun.

However, the presence of the enhancer and its putative AP-1 proved very important to the total promoter activity. For example, when the region 5′ of the enhancer was removed the smaller construct containing the enhancer (BKE) displayed a greater activity. In turn further shortening of the promoter with the removal of the enhancer region (BKG) resulted in promoter construct activity well below that of the BKE construct and similar to that of the 1.8kb promoter construct (BKA). These results point to the importance of the enhancer and the presence of a negative regulatory element(s) upstream of the enhancer region [Yang et al., 1998]. It is important to note that it was the freeing of the enhancer from its negative control which resulted in sizable overall promoter activity. This freeing of enhancer's action may be a feature of this gene which leads to its ultimate upregulation by effectors.

Clearly, the promoter alone did not respond to mediator stimulation. Other motifs, outside of the 1.8 kb promoter region, appeared to be participating in the induction of BKB1R gene expression. To investigate this possibility we constructed a minigene which included the entire exon I, 1.5 kb of intron I, the entire exon II and intron II in addition to promoter region. Indeed, with this model, reliable and reproducible induction of the BKB1R gene was obtained. Thus certain elements, located either within the intron regions or the 5′-UTR are interacting with the promoter to produce a mediator responsive gene. This inductive action is separate from the observed effect of c-Jun on the activity of the promoter alone. With the minigene, cotransfection with the c-Jun plasmid at 40 ng/ml produced approximately the same increase in promoter response as the increase seen using LPS or DAK in absence of c-Jun. Combining transfection with c-Jun and stimulation with the mediators resulted in no

futher increase in minigene promoter activity compared to that of c-Jun alone. Additionally, transfection with c-Jun^{DN} ablated LPS and DAK inducibility of the minigene. c-Jun interaction with the AP-1 sites within the promoter itself are probably functioning interactively with other elements outside of the promoter region. These elements could be responsive to either c-Jun or other factors generated simultaneously during action by mediator. Further investigation is necessary to determine the mechanism of this interaction. One possibility is that mediator interaction with elements outside the promoter region causes a conformational change of the promoter secondary structure to free the enhancer from the negative regulatory element's inhibition. Interestingly, a second promoter located within the intron region was reported previously [Yang and Polgar, 1996]. Alone, this intron promoter exhibits much smaller activity than the 1.8 kb promoter discussed here. However the role of this promoter remains to be investigated and may prove important.

The minigene construct provides an excellent model to define the mechanisms regulating the inducibility of the BKB1R gene. The minigene mimics the native genomic structure of the BKB1R gene.

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