FEBS Letters 469 (2000) 118–122 FEBS 23392

Retinoic acid stimulates HIV-1 transcription in human neuroblastoma SH-SY5Y cells

Juan A. Recio[1], Jorge Martínez de la Mata[1], José Martín-Nieto, Ana Aranda*

Instituto de Investigaciones Biomédicas 'Alberto Sols', Consejo Superior de Investigaciones Científicas and Universidad Autónoma de Madrid, Arturo Duperier 4, 28029 Madrid, Spain

Received 1 February 2000

Edited by Jesus Avila

Abstract Although the brain is an important target for the human immunodeficiency virus type 1 (HIV) and viral infection causes neuronal degeneration and dementia, the mechanisms responsible for HIV transcription in neuronal cells are largely unknown. We show here that retinoic acid (RA) stimulates HIV transcription in human neuronal SH-SY5Y cells. The steroid receptor coactivator 1 (SRC-1) enhances the transcriptional response to RA, and the viral protein Tat cooperates with RA and SRC-1 to induce a strong transactivation. These results suggest that retinoid receptors could play an important role as activators of viral gene expression in the human brain.

Key words: Retinoic acid; Neuronal cell; Human immunodeficiency virus type 1 transcription; Tat; Nuclear receptor coactivator

1. Introduction

Human immunodeficiency virus type 1 (HIV) causes infections in the brain, leading to massive neuronal damage and to AIDS dementia complex [1]. Although microglial cells appear to be the major target brain cells for the virus, infection of neuronal cells appears to cause neuronal loss and dysfunction [2,3]. It is therefore important to understand the regulation of HIV-1 gene expression in neuronal cells, which appear to possess the machinery responsible for HIV transcription [4–6].

The retinoic acid (RA) receptors are members of the steroid/thyroid hormone receptor superfamily which act as ligand-inducible transcription factors by binding to responsive elements (HREs) normally located in regulatory regions of target genes [7]. Upon ligand binding, the receptors undergo conformational changes which facilitate recruitment of coactivators responsible for gene activation [8,9]. The steroid hormone receptor coactivator 1 (SRC-1/NCoA1) [10] is one of such coactivators. A HRE located between nucleotides −352 and −320 in the HIV long terminal repeat (LTR) binds retinoid receptors (RARs and RXRs) [11,12]. However, depending on the cell type it has been found that RA can either stimulate or inhibit the activity of the HIV LTR [13–17].

The human neuroblastoma cell line SH-SY5Y, which differentiates in the presence of RA, provides an excellent model to analyze the effect of retinoids on neuronal cells. In this study we show a strong activation of the HIV LTR by RA in SH-SY5Y cells. This activation is enhanced by the coactivator SRC-1 and the viral transactivator Tat. Surprisingly, activation by RA is only slightly reduced in an LTR construct in which the HRE had been mutated. Furthermore, sequences within the core promoter bind RAR–RXR heterodimers and are sufficient for RA-dependent HIV LTR stimulation. These results show that the HIV LTR contains multiple binding sites for retinoid receptors and that retinoids could play a role in the regulation of HIV LTR activity in neurons and during progress of the neurological damage in AIDS patients.

2. Materials and methods

2.1. Plasmids

The plasmid −453HIV-Luc contains HIV-1 LTR sequences from −453 to +80 fused to luciferase, and in −453ΔNF-κBHIV–Luc the GCG motif of both NF-κB binding sites located at −104/−76 was mutated to TCT [18]. Deletion mutants extending to nucleotides −453, −104, −76 and −28 of the HIV LTR were previously described [12]. To construct plasmid −453ΔHREHIV-Luc, site-directed mutagenesis by PCR was performed using the oligonucleotide 5′-CCAGGA**TCT**AGATATCCACTG**TG**CTTTGG-3′ in which both hemisites of the HRE located between nucleotides −356 and −320 were mutated. The expression vector for Tat has been cloned in pcDNA3, which contains the cytomegalovirus (CMV) promoter. The truncated receptor RARΔAF-2 contains amino acids 1–419 of human RARα; and RXRΔAF-2 contains amino acids 1–445 of human RXRα [19]. Expression vector for SRC-1 [20] has been previously described.

2.2. DNA transfection

SH-SY5Y cells were transiently transfected by the calcium phosphate method with 4 μg of reporter constructs as previously described [12]. The cells were incubated for 48 h with RA or tumor necrosis factor α (TNFα), and luciferase activity determined. Each treatment was performed in triplicate cultures that normally exhibited less than 10–15% variation and each experiment was repeated at least three times with similar differences in regulated expression. The data are shown as the mean ± S.D.

2.3. Protein preparations

The glutathione *S*-transferase (GST) fusion proteins, GST–RAR, GST–TR, GST–VDR and GST–RXR [21,22] were expressed in the bacterial strain BL21(DE3) and purified by standard techniques. The expression of correctly sized proteins was monitored by SDS–PAGE.

2.4. Gel mobility shift assays

Electrophoretic mobility shift assays were performed using either recombinant receptors or 5 μg of SH-SY5Y nuclear extracts as previously described [12]. The κB oligonucleotides used were: 5′-CAAGGGACTTTCCGCTGGGGACTTTCCAGG-3′ corresponding to sequences −104 to −76 of the HIV-1 LTR containing the two κB binding sites, 5′-CAA**TCT**ACTTTCCGCTG**TCT**ACTTT-CCAGG-3′ in which both binding sites were mutated. The oligonucleotide 5′-AGGGAGGCGTGGCCTGGGCGGGACTGGGGAGT-CCC-3′ corresponds to the HIV LTR Sp1 sites from −75 and −44.

*Corresponding author. Fax: (34)-91-5854587.
E-mail: aaranda@iib.uam.es

[1] Both authors have contributed equally to this work.

PII: S0014-5793(00)01249-7

Oligonucleotides containing nuclear receptor binding sites were: 5′-CCAGGGGTCAGATATCCACTGACCTTTGG-3′ encompassing the HRE present in the HIV LTR, and the mutated oligonucleotide described above. Different labeled promoter fragments (−109/+89; −78/+89; −35/+89; +31/+89 and −35/+30) obtained by PCR were also used as probes in gel retardation assays. The antisense oligonucleotides used were: 5′-GCCAAGCTTTATTGAGGC′-3′ (+72/+89) and 5′-CTCAGATCTGGTCTAACC-3′ (+13/+30). The sense oligonucleotides were the following: 5′-GTTACAAGGGACTTTCGCG-3′ (for −109); 3′-AGGGAGGCGTGGCCTGG-3′ (for −78); 5′-AGATGCTGCATATAAGCAGC-3′ (for −35); and 5′-CCTGGGAGCTTTTCTGGC-3′ (for +31).

3. Results

As shown in Fig. 1, incubation of SH-SY5Y cells with RA significantly increased the activity of −453HIV–Luc. This activation was similar in its extent to that caused by TNFα, a potent inducer of the LTR (data not shown). Removal of the LTR sequences from −453 to −104 reduced by about 50% basal promoter activity. However, a significant response to RA was observed with the −104HIV–Luc construct, which does not contain the previously identified HRE. These results suggest that elements additional to the HRE contribute to HIV activation by RA. The core HIV promoter contains two binding sites for NF-κB (nucleotides −104 to −81) in close proximity to three binding sites for the transcription factor Sp1 (nucleotides −77 to −46), and a cooperative interaction between both factors is required for activation of the virus in non-neuronal cells [23]. An LTR fragment extending

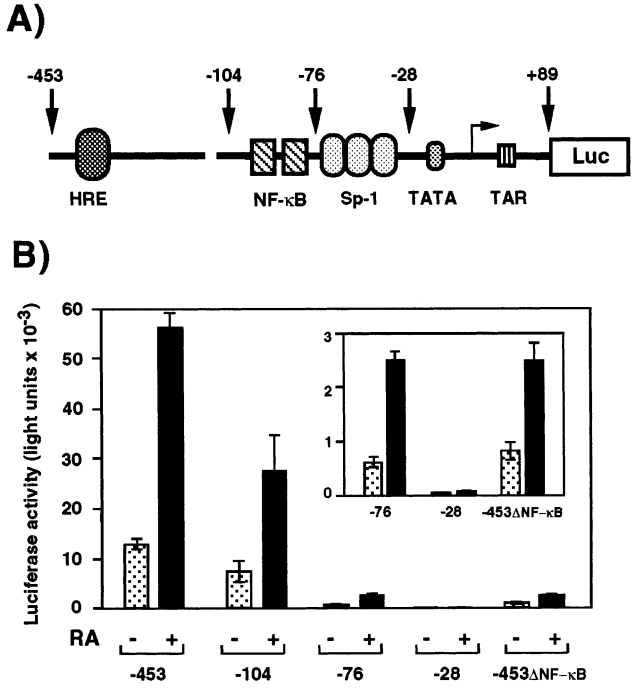

Fig. 1. Elements of the HIV LTR mediating regulation by RA. A: Schematic representation of the HIV LTR. The positions of the arrows indicate the deletion mutants of the LTR which were used. B: Constructs extending to −453, −104, −76 and −28, as well as a construct in which the NF-κB sites have been mutated in the context of the −453 plasmid (−453ΔNF-κB), were transfected into SH-SY5Y cells. Luciferase activity was determined in untreated cells and in cells treated with 1 μM RA for 48 h. The inset represents a magnification of the luciferase values obtained in the plasmids showing low basal activity.

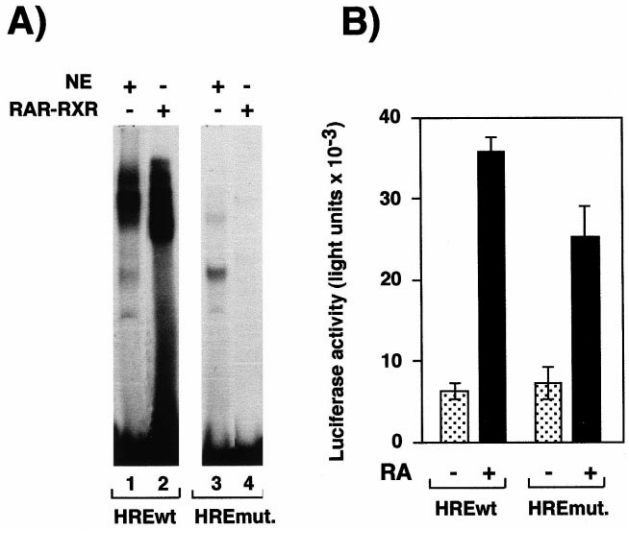

Fig. 2. Role of the HRE located between −352 and −320 on RA-mediated activation. A: Nuclear extracts (NE) from cells treated with RA from 24 h, as well as recombinant RAR–RXR (100 ng) were subjected to mobility shift assays with the wild-type HRE oligonucleotide (HREwt) or with an oligonucleotide in which both hemisites of the HRE had been mutated (HRE mut.). B: SH-SY5Y cells were transfected with 4 μg of −453HIV–Luc, which contains the HREwt, or with a construct containing the HRE mutation used in B. Luciferase activity was determined in cells treated in the presence and absence of 1 μM RA for 48 h.

to −76 showed an extremely low luciferase activity, indicating that NF-κB sites are essential for basal activation of the HIV LTR in SH-SY5Y cells. However, as shown in the inset, stimulation by RA was similar in magnitude to that found for the construct −104HIV-Luc. The importance of the NF-κB elements was also examined with a plasmid (−453ΔNFκB–HIV–Luc) in which the κB sites had been mutated. This mutation caused a dramatic decrease of luciferase activity, though both basal and RA-dependent stimulation were similar to that found for the construct −76HIV–Luc. Therefore, the induction of HIV transcription by RA appears to be NF-κB-independent. Furthermore, SH-SY5Y cells do not contain significant amounts of constitutive p50/p65 NF-κB heterodimers in the nucleus and RA does not promote NF-κB activation in SH-SY5Y cells (data not shown). Deletion of the LTR to −28 bp, which eliminates the three Sp1 sites, essentially abolished promoter activity and under these conditions the effect of RA was undetectable.

To analyze the functional role of the HRE in the response to RA, both hemisites of this element were mutated in the −453HIV LTR construct (Fig. 2). Fig. 2A shows that this mutation abolishes the binding of nuclear proteins from SH-SY5Y cells, and also the binding of recombinant RAR–RXR heterodimers. Fig. 2B shows that mutation of the HRE did not affect basal activity of the LTR and had little inhibitory effect on RA-mediated induction: RA caused a six-fold increase of HIV–Luc activity, whereas the mutated construct showed a four-fold increase. Therefore, although the previously identified HRE participates in the response to RA, additional elements are required for full HIV LTR stimulation by the retinoid.

Since sequences contained between −104 and +89 were able to confer responsiveness to RA, additional binding sites for retinoid receptors should be located downstream of the char-

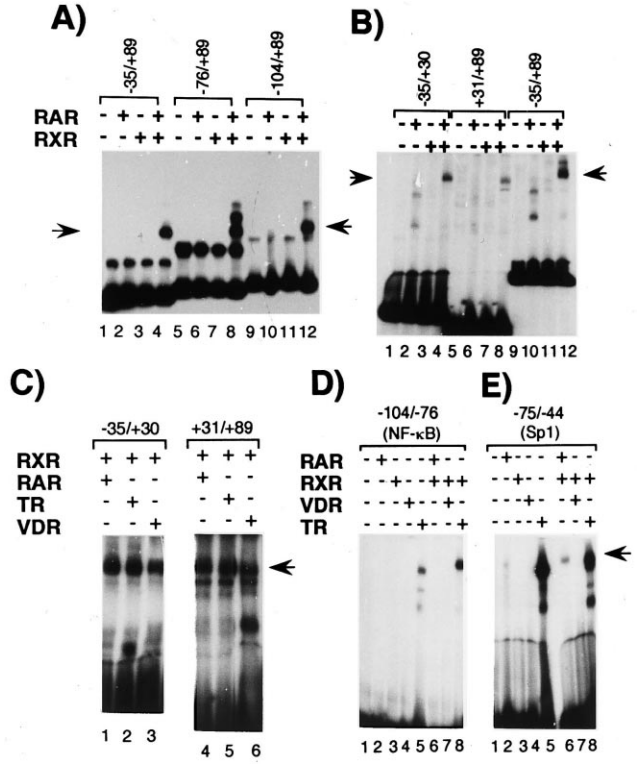

Fig. 3. Binding of nuclear receptors to core HIV promoter sequences. A and B: Mobility shift assays were performed with recombinant RAR and/or RXR (75 ng) and the labeled fragments of the LTR indicated at the top of the panels. C: Binding of recombinant RAR, TR and VDR, alone or in combination with RXR, to the labeled HIV LTR fragments −35/+30 and +31/+89. D and E: Oligonucleotides encompassing sequences −104/−76 and −75/−44 which contain the NF-κB and Sp1 sites of the LTR, respectively, were used for gel retardation assays with RAR, TR or VDR in the presence and absence of RXR. The first lane for each fragment or oligonucleotide shows the mobility of the unretarded probe, and the arrows indicate the retarded complexes formed with the receptor heterodimers.

acterized HRE. To determine the presence of these putative sites, different labeled HIV LTR fragments were subjected to gel retardation assays with recombinant RAR and/or RXR. Fig. 3A shows that the fragment −104/+89 bound RAR–RXR heterodimers (lane 12). This fragment contains the NF-κB sites which have been described to bind receptor heterodimers [24]. However, as shown in Fig. 3D, although strong binding of thyroid hormone receptor heterodimers (TR–RXR) to the κB sites was observed (lane 3), we were not able to detect binding of RAR–RXR to these sequences (lane 2). The vitamin D3 receptor (VDR) was not able to bind to these sites either (lane 3). The promoter fragment −76/+89, however, bound RAR–RXR heterodimers (Fig. 3A, lane 8), confirming that the κB sites were not required for RA receptor binding. This fragment still contains the Sp1 sites and an overlapping element [24,25] which binds TR and TR–RXR heterodimers (Fig. 3E, lanes 5 and 8). RAR and RAR–RXR also bind these sites (Fig. 3E, lanes 2 and 6), although very weakly as compared with TR. Other binding elements for retinoid receptors located closer to the transcription initiation site are present in the LTR, as demonstrated by the finding that sequences contained between nucleotides −35 and +89 bound strongly RAR–RXR heterodimers (Fig. 3A, lane 4). To further analyze binding of RAR–RXR to the proximal promoter, this sequence was split into two new fragments, one containing nucleotides −35 to +30, and the other nucleotides +31 to +80. Fig. 3B compares the binding of retinoid receptors to the three sequences. It was observed that RAR–RXR heterodimers were able to bind to the two fragments, although binding to sequences −35/+30 was stronger than that observed with +31/+89. Fig. 3C shows that both sequences bound also TR–RXR and VDR–RXR heterodimers. Binding to the different fragments was specific as it was competed in the presence of an excess of the corresponding unlabeled sequence, as well as by an excess of nucleotides containing consensus HREs for the different receptors (not illustrated). Taken together, these results demonstrate that the proximal HIV promoter contains at least three different binding sites for retinoid receptors which can contribute to stimulation by RA in SH-SY5Y cells.

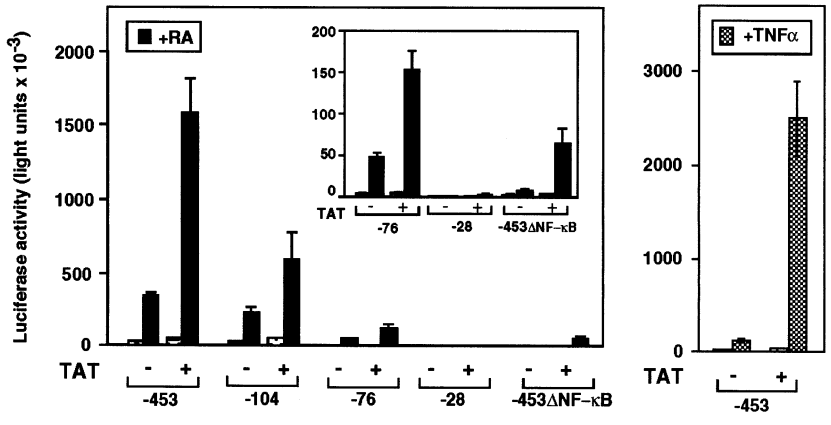

Fig. 4. Synergism of Tat with RA. In the left panel the indicated constructs of the HIV LTR were transfected into SH-SY5Y cells either alone or in combination with 100 ng of an expression vector encoding the viral activator Tat. Luciferase activity was determined in untreated cells and in cells incubated with 1 μM RA for 48 h (black bars). The inset represents a magnification of the luciferase activity obtained in cells transfected with the last three plasmids. Luciferase values were determined in parallel in cells transfected with −453HIV–Luc and incubated in the presence and absence of 10 ng/ml TNFα (right panel).

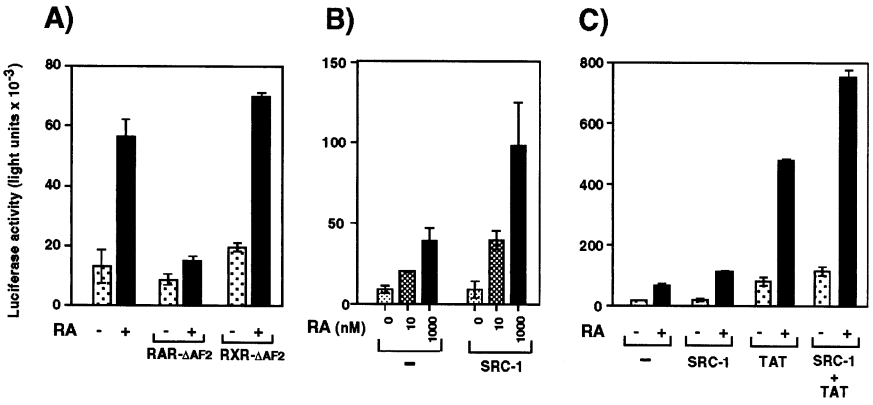

Fig. 5. Influence of nuclear receptor coactivators on the HIV response to RA. A: SH-SY5Y cells were transfected with −453HIV-Luc alone or in combination with 2 μg of expression vectors for truncated versions of RAR and RXR lacking the AF-2 domain. Luciferase activity was determined 48 h later in untreated cells and in cells treated with 1 μM RA. B: Cells were cotransfected with the reporter construct and 2 μg of an expression vector for the coactivator SRC-1. Luciferase activity was determined in cells treated for 48 h with the concentrations of RA indicated. C: −453HIV–Luc was cotransfected with 2 μg of SRC-1 and/or 200 ng of Tat vectors, and luciferase activity determined after 48 h in cells treated in the presence and absence of 1 μM RA.

The viral protein Tat is critical for activation of HIV transcription [23]. To determine whether a functional interaction between Tat and RA occurs, the constructs indicated in Fig. 1 were cotransfected into SH-SY5Y cells with an expression vector encoding Tat. The viral protein alone had little effect on −453HIV–Luc activity but, as shown in Fig. 4A, enhanced significantly the response to RA. With respect to the basal uninduced levels, the activity of the the HIV LTR increased by more than 100-fold in the presence of Tat and the retinoid. This stimulation had a similar magnitude as that produced by TNFα in cells expressing Tat (Fig. 4B). Deletion of the regulatory region and the NF-κB sites reduced luciferase activity, but a clear cooperation of RA with Tat was still detected (Fig. 4A). In contrast, −28HIV–Luc, in which the Sp-1 sites had been deleted, was inactive even in the presence of Tat.

Ligand-dependent transactivation by nuclear receptors depends on the presence of an autonomous activation function domain (AF-2), which is located in the C-terminal region and is required for binding of coactivators [8,9]. In order to analyze the role of this domain in the activation of HIV transcription by RA, SH-SY5Y cells were cotransfected with −453HIV–Luc and expression vectors for deletion mutants of RAR and RXR which lacked the core AF-2 domain. As shown in Fig. 5A, the RAR mutant behaved as an inhibitor of activation mediated by the endogenous receptors and blocked the response to RA. In contrast, the truncated RXR did not significantly affect the response to the retinoid. The effect of transfection with expression vectors encoding the coactivator SRC-1 on the response to two concentrations of RA (10 nM and 1 μM) is illustrated in Fig. 5B. RA increased LTR activity in a dose-dependent manner and SRC-1 significantly enhanced this response. The possibility that SRC-1 could cooperate with Tat to activate the LTR was also explored. Fig. 5C shows that both Tat and SRC-1 independently increased RA-dependent activation and that this stimulation was maximal in SH-SY5Y cells expressing both Tat and SRC-1.

4. Discussion

Studies in transgenic mice have revealed that the promoter of neurotropic HIV-1 strains directs viral gene expression in neurons throughout the nervous system [3]. These results imply that neurons possess a specific transcription machinery capable of HIV-1 activation. Since RA is well known to act as an inducer of neuronal function, we have analyzed the regulation of HIV gene transcription by RA in human neuronal cells. Our results indicate that the retinoid is a potent activator of the HIV LTR in these cells. In fact, stimulation by RA was as strong as that caused by TNFα, a prototypic HIV activator [26]. It has been suggested that the therapeutic use of retinoid antagonists could provide a means of repressing viral replication by inhibiting retinoid-dependent transcription [13,14]. Our data indicate that this approach could indeed be useful to inhibit HIV gene expression in neuronal cells. However, it is unclear whether this pharmacological strategy should be effective, since depending on the cell type both suppressive and inductive effects of RA on HIV expression and virus production have been documented [27,28].

The HRE located in the HIV LTR regulatory region [11] was expected to be responsible for RA-dependent stimulation. However, our data reveal that this HRE does not play a major role in RA-mediated stimulation in SH-SY5Y cells. When this sequence was deleted other downstream-located sequences were able to mediate significant stimulation by the retinoid. Among these elements the κB sites were candidates to be involved in regulation by RA. However, our data show that stimulation of HIV gene transcription by RA appears to be NF-κB-independent, although the κB sites are responsible for most basal LTR activity in SH-SY5Y cells. SH-SY5Y cell nuclei do not contain constitutively active p50/p50 homodimers or p50/p65 heterodimers and therefore other still unidentified nuclear factors which bind to the κB sites must be responsible for basal HIV gene expression in these cells. We have reported similar results in another neuronal cell model, PC12 cells, in which several proteins, different from p50 and p65, bind to the κB sites and activate transcription from the LTR [12]. The transcription factor Sp1 also plays an important role in HIV gene expression in different cell types, and there was the possibility that association of retinoid receptors with the Sp1 sites could be responsible for RA-dependent induction in SH-SY5Y cells. However, although in agreement

with previous observations [24,25] we find that these motifs are strong binding sites for TRs, they are only weak binding sites for RA receptors. In contrast, our studies document the existence of previously unrecognized nuclear receptor binding sites in the HIV core promoter located both upstream and downstream of the TATA box. Like other HREs, homodimers associate only weakly to these motifs, which bind preferentially RAR–RXR heterodimers. In contrast with the LTR κB or Sp1 motifs which are rather selective for TR–RXR, these proximal elements can bind RAR–RXR, TR–RXR and VDR–RXR heterodimers with a similar potency and are, therefore, potential targets for regulation by diverse nuclear receptors. The existence of various binding sites both in the modulatory and in the proximal promoter regions stresses the importance of nuclear receptor signalling pathways in HIV transcription. This multiplicity likely ensures transcriptional regulation of different virus variants by the receptors even after mutation of one particular receptor binding site.

Our results also show that a carboxy-terminal truncated RAR exerts a dominant negative activity blocking stimulation by RA. This shows that RAR AF-2 domain, involved in coactivator recruitment, is essential for retinoid-dependent transactivation of the LTR. In contrast, an equivalent RXR mutant did not affect this response. This finding is compatible with the idea that RXR acts as a heterodimeric partner with RAR, but not as a RXR–RXR homodimer, to stimulate HIV gene expression in SH-SY5Y cells. RXR would thus be required for high affinity binding to the HREs, but the AF-2 domain of RXR would be dispensable for the ligand-dependent transcriptional activity of the RAR–RXR heterodimer. The important functional role of coactivators in the regulation of HIV gene expression by RAR is demonstrated by the increase in RA-dependent transactivation observed in the presence of SRC-1, a coactivator which binds the receptor AF-2 domain in a ligand-dependent manner [10]. These results demonstrate a novel role of this protein in HIV gene expression. Other coactivators appear to play a role in HIV gene transcription. Thus, CBP/p300 which acts as a coactivator for NF-κB, Tat and diverse nuclear receptors, also has been shown to enhance HIV LTR activity in non-neuronal cells [29,30].

We found that RA synergizes with the viral protein Tat to activate HIV gene transcription in neuronal cells. The mechanism underlying this cooperation is still unclear. A physical association of Tat with TR has been documented [31], and it is not unlikely that RAR could also interact with the viral protein. Binding of Tat and the receptors to their close binding sites, as well as coactivator recruitment, could facilitate targeting of the transcriptional machinery to the promoter and the synergistic activation.

Our findings show the participation of receptors, transcription factors and coactivators in the stimulation of HIV gene expression by RA in neuronal cells. Synergism between these factors and Tat demonstrates that both host and viral proteins cooperate to induce RA-mediated transcription of HIV in these cells. Because the LTR represents the main regulatory region that determines expression of genes necessary for viral replication, our results suggest that retinoid receptors may play a role during the infectious process in brain cells and in the progress of neurological damage in AIDS patients.

Acknowledgements: This work was supported by Grant PB97-0135 from the DGES. J.A.R. and J.M.N. have been financed by the Comunidad de Madrid. We thank D. Barettino, R. Evans and M. Parker for plasmids used in this study.

References

[1] Dubois-Dalcq, M., Altmeyer, R. and Chiron, M. (1995) Curr. Opin. Neurobiol. 5, 647–655.
[2] Wiley, C.A., Schrier, R.D., Nelson, J.A., Lampert, P.W. and Oldstone, M.B.A. (1986) Proc. Natl. Acad. Sci. USA 8, 7089–7093.
[3] Corboy, J.R., Buzy, J.M., Zink, M.C. and Clements, J.E. (1992) Science 258, 1804–1808.
[4] Rattner, A., Korner, M., Walker, M.D. and Citri, J. (1993) EMBO J. 12, 4261–4267.
[5] Kaltschmidt, C., Kaltschmidt, B., Neumann, H., Wekerle, H. and Baeuerle, P.A. (1994) Mol. Cell. Biol. 14, 3981–3992.
[6] Kurtz, J., Buzy, J.M., Lindstrom, L. and Clements, J.E. (1996) J. Virol. 70, 7686–7694.
[7] Mangelsdorf, D.J., Thummel, C., Beato, M., Herrlich, P., Schütz, G., Umesono, K., Blumberg, B., Kastner, P., Mark, M., Chambon, P. and Evans, R.M. (1995) Cell 83, 835–839.
[8] Torchia, J., Glass, C.K. and Rosenfeld, M.G. (1998) Curr. Opin. Cell Biol. 10, 373–383.
[9] McKenna, N.J., Lanz, R.B. and O'Malley, B.W. (1999) Endocr. Rev. 20, 321–344.
[10] Oñate, S.A., Tsai, S.Y., Tsai, M.J. and O'Malley, B.W. (1995) Science 270, 1354–1357.
[11] Ladias, J.A. (1994) J. Biol. Chem. 269, 5944–5951.
[12] Recio, J.A. and Aranda, A. (1997) J. Biol. Chem. 272, 26807–26810.
[13] Lee, M.-O., Hobbs, P.D., Zhang, X.-k., Dawson, M.I. and Pfahl, M. (1994) Proc. Natl. Acad. Sci. USA 91, 5632–5636.
[14] Lee, M.-O., Dawon, M.I., Picard, N., Hobb, P.D. and Pfahl, M. (1996) J. Biol. Chem. 271, 11897–11903.
[15] Maciaszek, J.W., Talmage, D.A. and Viglianti, G.A. (1994) J. Virol. 68, 6598–6604.
[16] Towers, G., Harris, J., Lang, G., Collins, M.K.L. and Latchman, D.S. (1995) AIDS 9, 129–136.
[17] Sawaya, B.E., Rohr, O., Aunis, D. and Schaeffer, E. (1996) J. Biol. Chem. 271, 22895–22900.
[18] Devary, Y., Rosette, C., DiDonato, J.A. and Karin, M. (1993) Science 261, 1442–1445.
[19] Sanguedolce, M., Leblanc, B.P., Betz, J.L. and Stunnenberg, H.G. (1997) EMBO J. 16, 2861–2867.
[20] Henttu, P.M.A., Kalkhoven, E. and Parker, M.G. (1997) Mol. Cell. Biol. 17, 1832–1839.
[21] Palomino, T., Sánchez-Pacheco, A., Peña, P. and Aranda, A. (1998) FASEB J. 12, 1201–1209.
[22] Jiménez-Lara, A.M. and Aranda, A. (1999) J. Biol. Chem. 274, 13503–13510.
[23] Jones, K. and Peterlin, B. (1994) Annu. Rev. Biochem. 63, 717–743.
[24] Desai-Yajnik, V. and Samuels, H.H. (1993) Mol. Cell. Biol. 13, 5057–5069.
[25] Rahman, A., Esmaili, A. and Saatcioglu, F. (1995) J. Biol. Chem. 270, 31059–31064.
[26] Duh, E.J., Maury, W.J., Folks, T.M., Fauce, A.S. and Rabson, A.B. (1989) Proc. Natl. Acad. Sci. USA 86, 5974–5978.
[27] Poli, G., Kinter, A.L., Justement, J.S., Bressler, P., Kherl, J.H. and Fauci, A.S. (1992) Proc. Natl. Acad. Sci. USA 89, 2689–2693.
[28] Turpin, J.A., Vargo, M. and Meltzer, M.S. (1992) J. Immunol. 148, 2539–2546.
[29] Perkins, N.D., Felzein, L.K., Betts, J.C., Leung, K., Beach, D.H. and Nabel, G.J. (1997) Science 275, 523–527.
[30] Hottiger, M.O. and Nabel, G.J. (1998) J. Virol. 72, 8252–8256.
[31] Desai-Yajnik, V., Hadzic, E., Modlinger, P., Malhotra, S., Gechlik, G. and Samuels, H.H. (1995) J. Virol. 68, 5103–5112.