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Reciprocal Interactions between Human T-Lymphotropic Virus Type 1 and Prostaglandins: Implications for Viral Transmission

MASAKO MORIUCHI,[1] HIROYASU INOUE,[2] AND HIROYUKI MORIUCHI[1,3]*

Division of Medical Virology, Department of Molecular Microbiology and Immunology, Nagasaki University Graduate School of Medical Sciences,[1] and Department of Pediatrics, Nagasaki University School of Medicine,[3] Nagasaki, and Department of Pharmacology, National Cardiovascular Center Research Institute, Osaka,[2] Japan

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Human T-lymphotropic virus type 1 (HTLV-1), the etiologic agent of adult T-cell leukemia/lymphoma, is transmitted through breast milk and seminal fluid, which are rich in prostaglandins (PGs). We demonstrate that PGE_2 upregulates the HTLV-1 long terminal repeat promoter through the protein kinase A pathway, induces replication of HTLV-1 in peripheral blood mononuclear cells (PBMC) derived from asymptomatic carriers, and enhances transmission of HTLV-1 to cord blood mononuclear cells (CBMC). Furthermore, HTLV-1 Tax transactivates a promoter for cyclooxygenase 2, a PG synthetase, and induces PGE_2 expression in PBMC or CBMC. Thus, HTLV-1 interacts with and benefits from PGs, constituents of its own vehicle for transmission.

Human T-lymphotropic virus type 1 (HTLV-1) is the etiologic agent of adult T-cell leukemia/lymphoma and is transmitted horizontally or vertically through blood, seminal fluid, or breast milk (reviewed in references 13 and 37).

Prostaglandins (PGs) are synthesized and secreted by most human tissues and cell types; however, they are especially abundant in seminal fluid and breast milk (2, 7, 9, 10). PGs, particularly those of the E series, are widely regarded as pleiotropic immunomodulatory molecules, and regulation of their expression appears to be critical for a number of immune responses (reviewed in references 26 and 29). There are two isoforms of cyclooxygenase (COX) that catalyze the formation of PGs from arachidonic acid. While *COX-1* is a housekeeping gene that is expressed constitutively, *COX-2* is an immediate-early response gene that is highly inducible by mitogenic and inflammatory stimuli and is considered essential for the induction of the aforementioned immune responses (reviewed in reference 32).

In this study we demonstrate that (i) PGE_2 upregulates the HTLV-1 long terminal repeat (LTR) promoter through the protein kinase A (PKA) pathway, induces viral replication in peripheral blood mononuclear cells (PBMC) derived from asymptomatic HTLV-1 carriers, and enhances transmission of HTLV-1 to cord blood mononuclear cells (CBMC) and that (ii) HTLV-1 Tax transactivates a *COX-2* promoter and induces PGE_2 production in PBMC. These data suggest that HTLV-1 interacts with and benefits from PGs that are abundant in seminal fluid and breast milk, vehicles for virus transmission.

MATERIALS AND METHODS

Reagents. PGE_2, H7, HA-1004, mitomycin C (MMC), 3′-azido-3′-deoxythymidine (AZT), phorbol 12-myristate 13-acetate (PMA), and ionomycin were purchased from Sigma (St. Louis, Mo.). MMC treatment of cells was performed as described previously (1).

Infectious HTLV-1 stock which was rendered devoid of cell culture supernatants by directly pelleting virions was obtained from Advanced Biotechnologies, Inc. (Columbia, Md.). Glutathione *S*-transferase (GST) and GST-Tax protein were propagated as described previously (23).

Plasmids and transient-expression assays. pU3R-luc, a generous gift of K.-T. Jeang (National Institute of Allergy and Infectious Diseases [NIAID], Bethesda, Md.), carries the luciferase gene under the control of the HTLV-1 LTR. Plasmids pMT-2T (parent plasmid), pMT-Tax (encoding HTLV-1 Tax), pMT-p65 (encoding a NF-κB p65 subunit), and pMT-IκB (encoding I-κBα) were kindly provided by U. Siebenlist (NIAID) (23). The human *COX-2* promoter-luciferase reporter plasmids phPES(−1432/+59), phPES(−327/+59), phPES(−220/+59), phPES(−124/+59), phPES(−52/+59), phPES-KBM (with a mutation at the NF-κB site), phPES-ILM (with a mutation at the NF-IL6 site), phPES-CRM (with a mutation at the cyclic AMP-responsive element [CRE]), phPES-KBM/ILM (with mutations at both the NF-κB and NF-IL6 sites), phPES-KBM/CRM (with mutations at both the NF-κB site and the CRE), phPES-ILM/CRM (with mutations at both the NF-IL6 site and the CRE), and phPES-KBM/ILM/CRM (with mutations at all three elements) were described previously (14, 15).

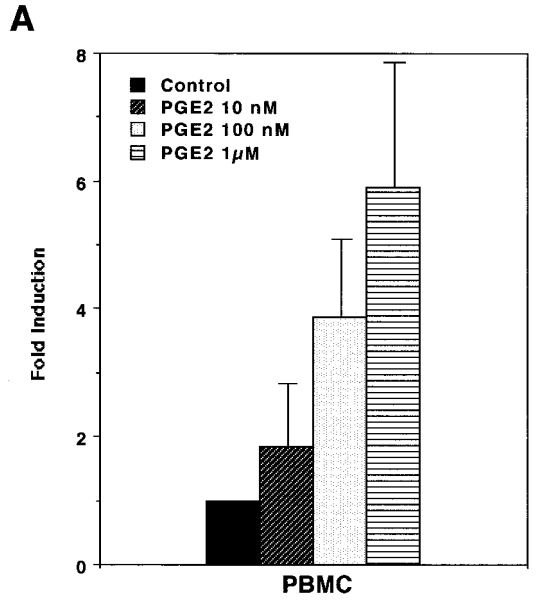
Transfection of the human Jurkat T leukemia cell line or PBMC and luciferase assays for transient-expression assays were performed as described previously (22). Briefly, 20 million Jurkat cells or 40 million PBMC were transfected by electroporation at 300 or 320 V, respectively, and 975 μF with a Gene Pulser II (Bio-Rad, Hercules, Calif.). After electroporation, cells were cultured in RPMI 1640 supplemented with 10% fetal bovine serum (FBS) at 37°C for 40 h. Luciferase activity was determined by using a luciferase assay kit (Promega, Madison, Wis.) with a TD-20e luminometer (Turner).

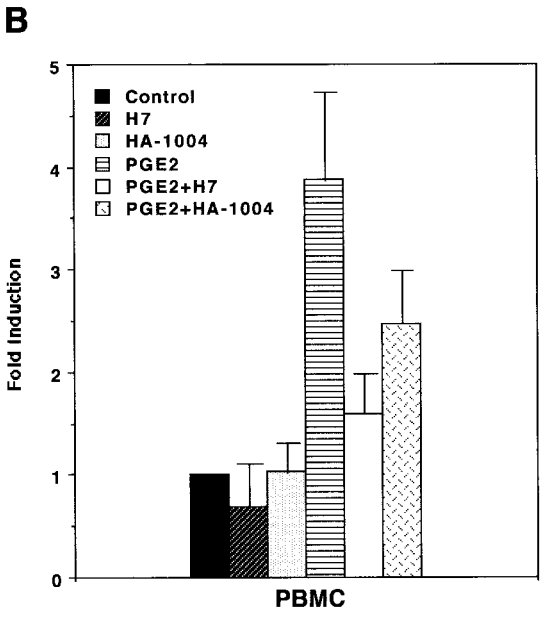
Measurement of PGE_2. The concentration of PGE_2 in the cell culture supernatants was determined in triplicate by enzyme-linked immunosorbent assays (ELISA) according to the manufacturer's instructions (R&D Systems, Minneapolis, Minn.). Where indicated, cells were infected with cell-free HTLV-1 stock (1 μg of protein per 3×10^6 cells) or were treated with GST or GST-Tax at a concentration of 100 ng/ml before cell-free supernatants were collected for PGE_2 measurement.

HTLV-1 infection. For HTLV-1 infection studies, PBMC were obtained from buffy coats of asymptomatic HTLV-1 carriers (Nagasaki Red-Cross Center, Nagasaki, Japan) as described previously (21). The cells were incubated in 24-well culture dishes at a concentration of 3×10^6 per ml in RPMI 1640 supplemented with 10% FBS in the presence or absence of PGE_2 (100 nM).

For HTLV-1 transmission studies, cord blood samples were provided by the Pre- and Post-Natal Care Unit, Nagasaki University School of Medicine Hospital, with consent by donors, and CBMC were cocultured with MMC-treated PBMC obtained from HTLV-1 carriers in the presence or absence of PGE_2 immediately after isolation. Cell-free culture supernatants were collected on day

* Corresponding author. Mailing address: Department of Pediatrics, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. Phone: 81-95-849-7297. Fax: 81-95-849-7301. E-mail: hiromori@net.nagasaki-u.ac.jp.





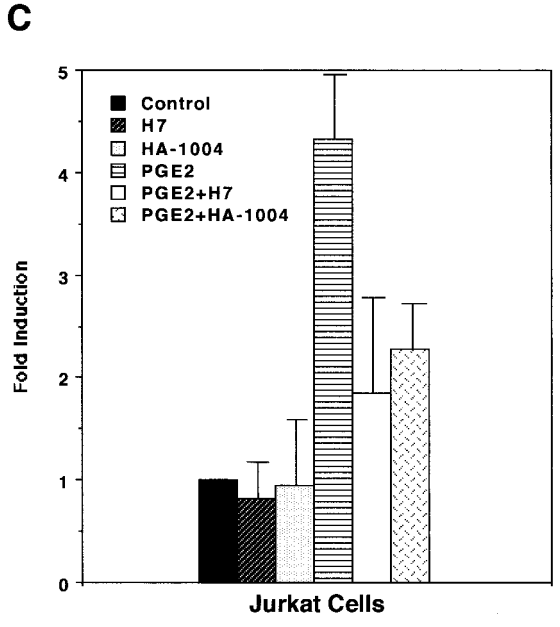


FIG. 1. PGE_2 upregulates HTLV-1 LTR activity. (A) PGE_2 upregulates HTLV-1 LTR activity in a dose-dependent manner. A total of 40 million PBMC were transfected with 10 μg of pU3R-luc and were left unstimulated or were stimulated with the indicated amount of PGE_2, and luciferase activity of the transfected cell lysates was assayed 2 days posttransfection. Fold induction is the luciferase activity relative to that obtained without PGE_2 treatment. Results are means ± standard errors of the means from three independent experiments. (B and C) PKA activity is involved in PGE_2 induction of expression from the HTLV-1 LTR. A total of 40 million PBMC (B) or 20 million Jurkat cells (C) were transfected with 10 μg of pU3R-luc, and luciferase activity of the transfected cell lysates was assayed 2 days posttransfection. Where indicated, cells were treated with PGE_2 (100 nM) in the presence or absence of H7 (1 μM) or HA-1004 (1 μM) for 8 h before harvest. Fold induction is the luciferase activity relative to that obtained in the absence of the reagents. Results are means ± standard errors of the means from six independent experiments.

7 for measurement of HTLV-1 p19 antigen by ELISA (Cellular Products Inc., Buffalo, N.Y.).

RESULTS AND DISCUSSION

PGE_2 upregulates HTLV-1 LTR activity. In order to assess whether PGE_2 could influence expression of HTLV-1, we first performed transient-expression assays. HTLV-1 LTR activity was upregulated by stimulation with PGE_2 in a dose-dependent manner (Fig. 1A). Since PGE_2 levels in seminal fluid and breast milk whey were reported to be 1 to ~70 μM (2, 7, 27) and ~30 nM (10), respectively, and since an overproduction of PGE_2 (up to 100 μM) is seen in a number of medical situations (e.g., allergy, hyper-immunoglobulin E syndrome, Hodgkin's lymphoma, trauma, sepsis, and transplantation) (29), the PGE_2-mediated effect appears to be physiologically relevant. PGE_2 induction of HTLV-1 LTR activity was markedly abolished by H7 (a selective serine/threonine kinase inhibitor that can inhibit PKA, PKC, and PKG) and HA-1004 (a PKA and PKG inhibitor) (Fig. 1B and C). Since PGE_2 has been shown to elevate the level of intracellular cyclic AMP, which activates PKA (27), it is reasonable to assume that PKA activity is required for transcriptional activity of HTLV-1.

PGE_2 induces HTLV-1 replication. In order to determine whether PGE_2 could actually induce replication of HTLV-1, we incubated PBMC obtained from asymptomatic HTLV-1 carriers in the presence or absence of PGE_2. Stimulation with PGE_2 enhanced HTLV-1 infection four- to fivefold as determined by HTLV-1 p19 antigen (Ag) levels (Table 1). Treatment with AZT (2 μM) resulted in a markedly decreased expression of p19 Ag (Table 1). Since AZT has no antiretroviral effect on PBMC already infected with HTLV-1 (18), profound suppression of p19 expression by AZT would indicate that induction of HTLV-1 expression in the presence of PGE_2 required the expansion of HTLV-1 infection. Addition of PGE_2 to the cell culture medium did not appear to influence

TABLE 1. PGE_2 induces HTLV-1 replication[a]

Carrier no.	p19 Ag level (pg/ml) with treatment			
	None	AZT	PGE_2	PGE_2 and AZT
1	64 ± 5	45 ± 4	222 ± 23	108 ± 4
2	56 ± 1	50 ± 5	303 ± 45	98 ± 18
3	80 ± 8	89 ± 6	326 ± 31	142 ± 9

[a] A total of 3×10^6 unfractionated PBMC derived from asymptomatic HTLV-1 carriers were propagated in RPMI 1640 supplemented with 10% FBS at 37°C for 7 days. The cells were either left untreated or treated with PGE_2 (100 nM), AZT (2 μM), or both. Levels of p19 Ag in cell-free culture supernatants were determined by ELISA. Results are means ± standard errors of the means of duplicate wells.

cell viability as determined by trypan blue exclusion (data not shown). Thus, PGE_2, a constituent of seminal fluid and breast milk, appears to induce replication of HTLV-1.

We next investigated whether PGE_2 could accelerate transmission of HTLV-1 to CBMC. Uninfected CBMC were cocultured with MMC-treated carriers' PBMC at a ratio of 10:1 in the presence or absence of PGE_2. It has been shown that MMC-treated cells can no longer support new cycles of retroviral infection (1). As shown in Table 2, the p19 level in the coculture supernatants was increased by treatment with PGE_2. PGE_2 treatment increased p19 Ag levels in cultures of MMC-treated carriers' PBMC; however, they were much lower than those in coculture of these cells with CBMC. These results suggest that expansion to susceptible CBMC is required for the induction of HTLV-1 replication. It has been reported that enterally administered milk leukocytes can invade suckling neonates and become distributed in their lymphoid tissues (16, 36). Therefore, although the exact mechanisms and the target cells in the mucosa of milk-borne infection remain unknown, these results imply that PGE_2 may accelerate viral transmission from maternal lymphocytes in breast milk to neonatal lymphocytes.

HTLV-1 Tax transactivates the *COX-2* promoter. As shown above, induction of PGE_2 production is likely to favor HTLV-1 infection and transmission; therefore, we next wanted to investigate whether HTLV-1 infection could influence expression of

TABLE 2. Expansion by PGE_2 of HTLV-1 infection to CBMC[a]

Culture or coculture	p19 Ag level (pg/ml) with treatment	
	None	PGE_2
CBMC alone	<25	<25
Carrier #4 PBMC alone	33 ± 5	46 ± 6
CBMC plus carrier's PBMC	68 ± 3	186 ± 14
CBMC alone	<25	<25
Carrier #5 PBMC alone	42 ± 4	54 ± 9
CBMC plus carrier's PBMC	89 ± 10	287 ± 23

[a] A total of 3×10^6 unfractionated CBMC derived from uninfected individuals were cocultured with 3×10^5 HTLV-1 carriers' PBMC or cultured individually. Carriers' PBMC had been pretreated with MMC (0.25 mg/ml) for 30 min to render the cells incapable of proliferating and supporting a new round of the viral replicative cycle. The cocultures were maintained at 37°C for 7 days in the presence or absence of PGE_2 (100 nM). Levels of p19 Ag in culture supernatants were determined by ELISA. Similar results were obtained for two other donors (data not shown). Results are means ± standard errors of the means of duplicate wells.

TABLE 3. HTLV-1 induces PGE_2 production[a]

Donor	PGE_2 level (pg/ml) in infection		
	Mock	HTLV-1	Inactivated HTLV-1
A	42 ± 5	165 ± 18	ND
B	<39	66 ± 20	ND
C	50 ± 9	182 ± 35	ND
D	<39	80 ± 18	<39
E	58 ± 8	210 ± 38	78 ± 15

[a] A total of 3×10^6 PBMC obtained from uninfected volunteers were mock infected or infected with cell-free HTLV-1 stock (0.1 μg of protein). In experiments with PBMC derived from donors D and E, HTLV-1 stock was heat inactivated (56°C, 60 min). PGE_2 levels in the culture supernatants were determined by ELISA on day 7 postinfection. Results are means ± standard errors of the means of triplicate wells. ND, not determined.

PGE_2. The HTLV-1 Tax transactivator has been shown to upregulate expression of a number of viral and cellular genes, which usually contributes to viral replication or transformation (reviewed in references 6, 31, and 35). We therefore tested whether Tax could upregulate promoter activity of *COX-2*, a PG synthetase. As shown in Fig. 2A, coexpression of Tax alone upregulated the *COX-2* promoter-luciferase reporter activity in the Jurkat human T-cell line. Tax alone was a relatively weak transactivator for the *COX-2* promoter in PBMC (Fig. 2B); however, stimulation with PMA plus ionomycin in addition to Tax synergistically upregulated the *COX-2* promoter activity in PBMC (Fig. 2B). Such synergy has been observed for other Tax-mediated effects (11, 23). We have also demonstrated that *COX-2* promoter activity was upregulated in PBMC treated with purified Tax protein (GST-Tax) (Fig. 2C).

In order to confirm that HTLV-1 infection or Tax protein induces PGE_2 production, PBMC were infected with HTLV-1 or exposed to purified Tax protein, and PGE_2 levels in the cell culture supernatants were determined by ELISA. HTLV-1-infected cells secrete soluble activity that exerts a number of biological activities on neighboring cells in a paracrine manner, and Tax protein released from infected cells is attributed, at least in part, to the soluble activity (4, 17, 19, 23). Experiment results listed in Tables 3 and 4 clearly demonstrate that HTLV-1 infection or Tax protein could induce PGE_2 production.

Both NF-κB and NF-IL6 sites are required in Tax activation of the *COX-2* promoter. HTLV-1 Tax protein is not able to directly bind to DNA; instead, it interacts with certain cellular transcription factors to exert its transregulatory functions (reviewed in references 6, 31, and 35). The *COX-2* promoter sequence contains several *cis*-acting elements (reviewed in ref-

TABLE 4. Tax protein induces PGE_2 production[a]

Donor	PGE_2 level (pg/ml) in the presence of:	
	GST	GST-Tax
D	80 ± 19	252 ± 48
E	92 ± 20	304 ± 33
F	20 ± 7	121 ± 23

[a] A total of 3×10^6 PBMC obtained from uninfected volunteers were incubated in the presence of either GST or GST-Tax (100 ng/ml) for 2 days. PGE_2 levels in the culture supernatants were determined by ELISA. Results are means ± standard errors of the means of triplicate wells.

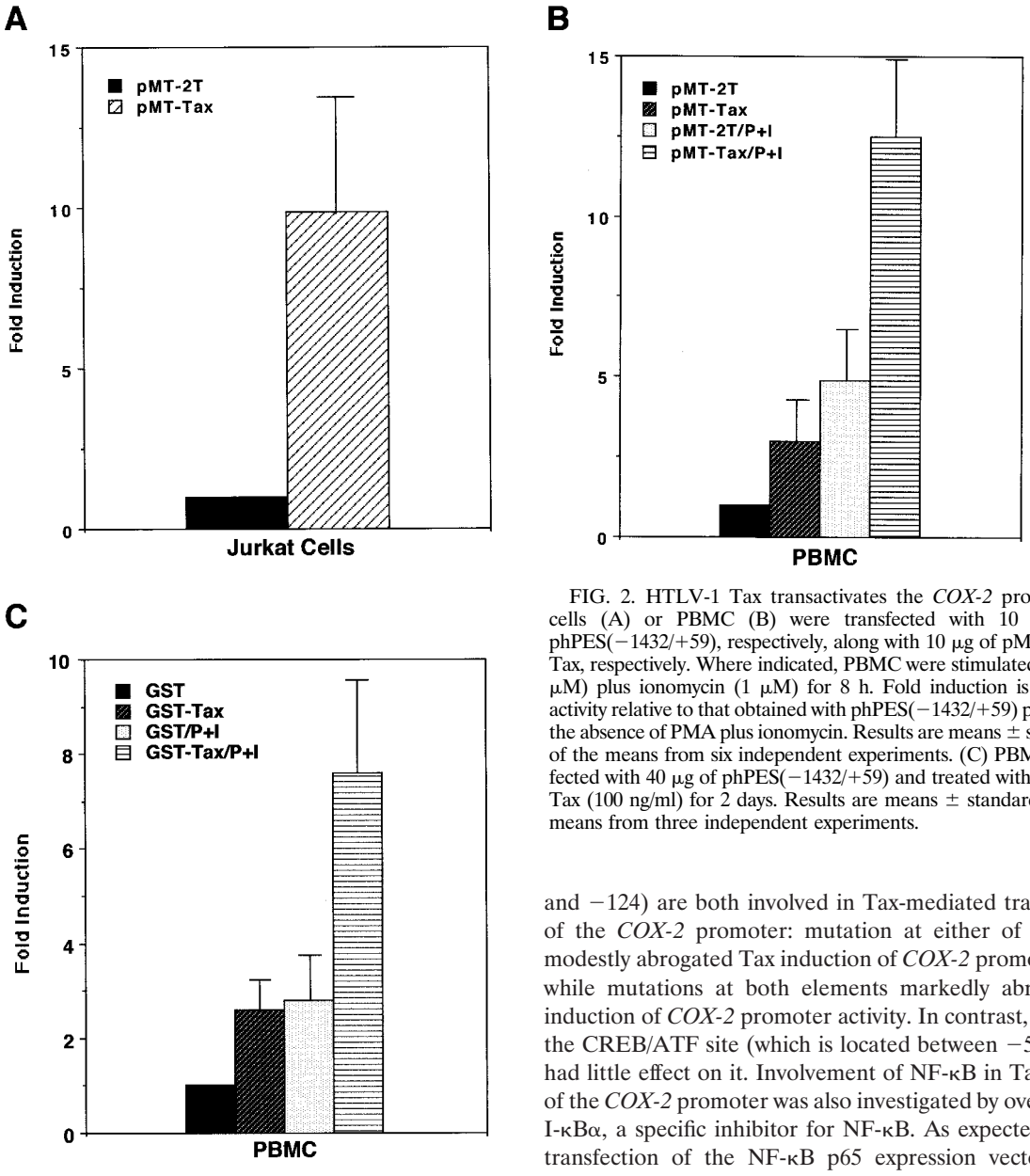


FIG. 2. HTLV-1 Tax transactivates the *COX-2* promoter. Jurkat cells (A) or PBMC (B) were transfected with 10 or 40 μg of phPES(−1432/+59), respectively, along with 10 μg of pMT-2T or pMT-Tax, respectively. Where indicated, PBMC were stimulated with PMA (1 μM) plus ionomycin (1 μM) for 8 h. Fold induction is the luciferase activity relative to that obtained with phPES(−1432/+59) plus pMT-2T in the absence of PMA plus ionomycin. Results are means ± standard errors of the means from six independent experiments. (C) PBMC were transfected with 40 μg of phPES(−1432/+59) and treated with GST or GST-Tax (100 ng/ml) for 2 days. Results are means ± standard errors of the means from three independent experiments.

erence 38), some of which have been shown to be involved in Tax-mediated transactivation in other promoter contexts. In order to determine the *cis*-acting elements involved in Tax-mediated transactivation of the *COX-2* promoter, we tested a number of *COX-2* promoter constructs in transient-expression assays. As shown in Fig. 3A, 5′ truncation of the promoter sequence down to position −327 modestly reduced responsiveness to Tax activation, while truncation down to −220 markedly reduced responsiveness. To further delineate the Tax-responsive region in the promoter sequence spanning −327 to +59 relative to the transcription start site, site-directed mutations were introduced individually or in combination. As shown in Fig. 3B, elements for NF-κB (which is located between −223 and −214) and for NF-IL6 (which is located between −132 and −124) are both involved in Tax-mediated transactivation of the *COX-2* promoter: mutation at either of them alone modestly abrogated Tax induction of *COX-2* promoter activity, while mutations at both elements markedly abrogated Tax induction of *COX-2* promoter activity. In contrast, mutation at the CREB/ATF site (which is located between −59 and −53) had little effect on it. Involvement of NF-κB in Tax activation of the *COX-2* promoter was also investigated by overexpressing I-κBα, a specific inhibitor for NF-κB. As expected, while cotransfection of the NF-κB p65 expression vector with the *COX-2* promoter upregulated the promoter activity, I-κBα counteracted p65-mediated activation (Fig. 3C). Similarly, overexpression of I-κBα markedly abrogated Tax-mediated activation of the *COX-2* promoter (Fig. 3C), suggesting that the NF-κB pathway is critical for its effect. Another NF-κB site is located between −1432 and −327 (H. Inoue and T. Tanabe, unpublished data) and may explain the partial responsiveness of the region to Tax (Fig. 3A).

In the present study we have demonstrated that HTLV-1, which is transmitted vertically or horizontally through breast milk or seminal fluid, respectively, and PGs, which are abundant in these body fluids, benefit from each other. These results confirm a recent study demonstrating that PKA activity is required for HTLV-1 LTR activity (34) and further extend the understanding of reciprocal interactions between HTLV-1 and PGs. PGE_2 enhances HTLV-1 replication by upregulating the HTLV-1 LTR promoter, and HTLV-1 Tax transactivates a

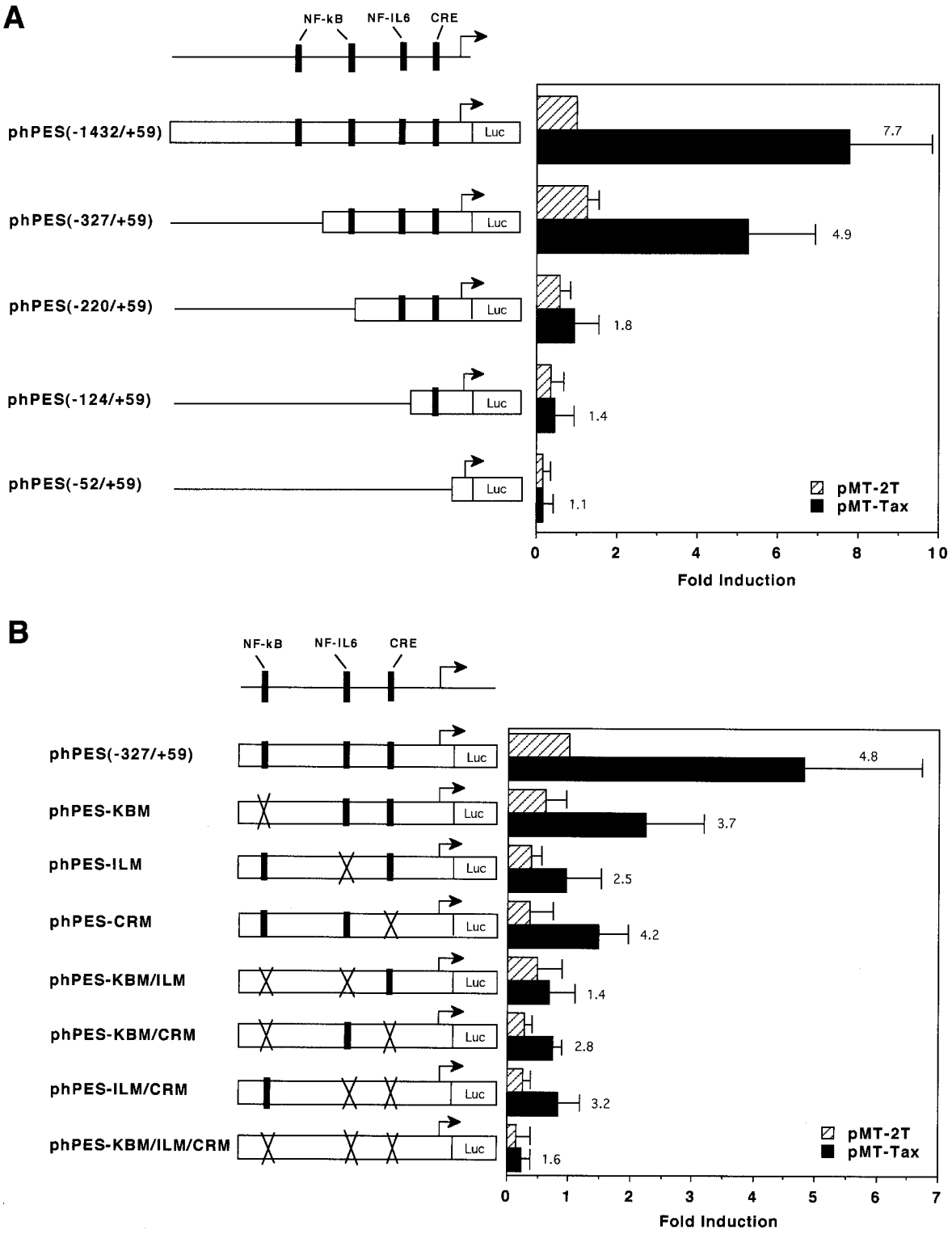


FIG. 3. Both the NF-κB and NF-IL6 sites are involved in Tax activation of the *COX-2* promoter. (A) Jurkat cells were transfected with 10 μg of the luciferase reporter plasmid along with 10 μg of pMT-2T or pMT-Tax. Results are means ± standard errors of the means from four independent experiments. Fold induction by Tax of the respective luciferase reporter is shown to the right of the bars. (B) Jurkat cells were transfected with 10 μg of the luciferase reporter plasmid along with 10 μg of pMT-2T or pMT-Tax. Results are means ± standard errors of the means from six independent experiments. Fold induction by Tax of the respective luciferase reporter is shown to the right of the bars. (C) Jurkat cells were transfected with 10 μg of phPES(−1432/+59) and 10 μg of pMT-2T, pMT-p65, or pMT-Tax along with pMT-2T or pMT-IκB. Results are means ± standard errors of the means from four independent experiments.

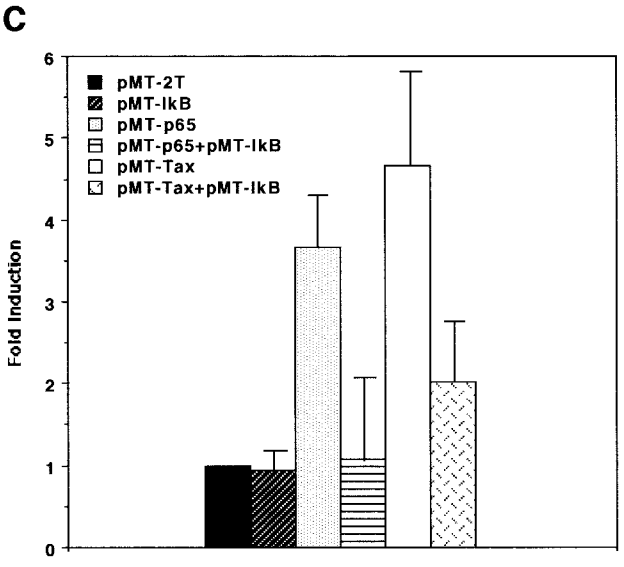


FIG. 3—*Continued.*

promoter for *COX-2*, a PG synthetase, leading to production of PGE_2. Therefore, it is likely that such mutual aid helps accelerate viral transmission through seminal fluid or breast milk. This hypothesis will require experimental evidence.

PGs and other eicosanoids have been shown to play a key role in the regulation of both humoral and cell-mediated immunity, generally tipping the balance in favor of Th2- and Th3-type responses by modulating cytokine and immunoglobulin production as well as T-cell proliferation and activation (reviewed in references 24 and 26). It therefore is not surprising if PGs influence the pathogenesis of infection with a number of pathogens. In fact, recent studies suggested that PGE_2 can modify infection with human immunodeficiency virus type 1, another human retrovirus that is also transmitted through breast milk or seminal fluid (5, 33). Thus, constituents such as PGs in these body fluids may variably influence viral transmission. We are currently investigating PGE_2 levels in asymptomatic HTLV-1 carriers as well as effects of other constituents in these body fluids on HTLV-1 infection. Preliminary results have indicated that several other constituents also benefit HTLV-1 infection (M. Moriuchi and H. Moriuchi, unpublished data).

Although HTLV-1 has oncogenic potential, the mode of oncogenesis by HTLV-1 is poorly understood. It has been shown that HTLV-1-encoded Tax protein is necessary and sufficient for cell immortalization (reviewed in references 20 and 35). Several studies showed that Tax-transgenic mice develop several types of malignancy, including leukemia, mesenchymal tumors, and neurofibromas (3, 8, 12, 25). Tax is able to interact with a number of cellular factors involved in transcription and/or cell cycling and is considered to induce cell transformation through such interactions (reviewed in references 20 and 35). Since PGs have also been associated with carcinogenesis (reviewed in reference 30), Tax activation of *COX-2* through cellular transcription factors (i.e., NF-κB/Rel family proteins) may contribute to HTLV-1-induced oncogenicity. In fact, a recent study has demonstrated that a number of HTLV-1-transformed cell lines do, but most HTLV-1-uninfected cell lines do not, express *COX-2* mRNA (N. Mori [Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan], personal communication), implying a critical role in HTLV-1-induced oncogenicity.

In summary, our studies have identified PGs as another target for HTLV-1 Tax, and reciprocal interactions between HTLV-1 and PGs may have implications for its transmission and oncogenesis.

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