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Cross-talk between an activator of nuclear receptors-mediated transcription and the D_1 dopamine receptor signaling pathway

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Abstract

Nuclear receptors are transcription factors that usually interact, in a ligand-dependent manner, with specific DNA sequences located within promoters of target genes. The nuclear receptors can also be controlled in a ligand-independent manner via the action of membrane receptors and cellular signaling pathways. 5-Tetradecyloxy-2-furancarboxylic acid (TOFA) was shown to stimulate transcription from the MMTV promoter via chimeric receptors that consist of the DNA binding domain of GR and the ligand binding regions of the PPARβ or LXRβ nuclear receptors (GR/PPARβ and GR/LXRβ). TOFA and hydroxycholesterols also modulate transcription from NF-κB- and AP-1-controlled reporter genes and induce neurite differentiation in PC12 cells.

In CV-1 cells that express D_1 dopamine receptors, D_1 dopamine receptor stimulation was found to inhibit TOFA-stimulated transcription from the MMTV promoter that is under the control of chimeric GR/PPARβ and GR/LXRβ receptors. Treatment with the D_1 dopamine receptor antagonist, SCH23390, prevented dopamine-mediated suppression of transcription, and by itself increased transcription controlled by GR/LXRβ. Furthermore, combined treatment of CV-1 cells with TOFA and SCH23390 increased transcription controlled by the GR/LXRβ chimeric receptor synergistically. The significance of this in vitro synergy was demonstrated in vivo, by the observation that SCH23390 (but not haloperidol)-mediated catalepsy in rats was potentiated by TOFA, thus showing that an agent that mimics the in vitro activities of compounds that activate members of the LXR and PPAR receptor families can influence D1 dopamine receptor elicited responses.

1. Introduction

Nuclear receptors are transcription factors that usually interact, in a ligand-dependent manner, with specific DNA sequences located within promoters of target genes (Evans, 1988). The activity of the nuclear receptors can also be controlled in a ligand-independent manner via the action of membrane receptors. For example, stimulation of D_1 dopamine receptors activates transcriptional control that is exerted by COUP-TF, progesterone or estrogen receptors (ER) in the absence of hormone. This is thought to be mediated via increased cellular cAMP levels (Turgeon and Waring, 1994; O'Malley et al., 1995; Power et al., 1991a,b, 1992). Furthermore, activation of the mitogen-activated protein kinase (MAPK) signaling pathway by growth factors, such as EGF or IGF, influences transcriptional control that is mediated by nuclear receptors (NRs; Aronica and Katzenellenbogen, 1993; Kato et al., 1995).

Transcriptional control by NRs is further complicated by the fact that NRs can also influence gene transcription without physically binding to cognate steroid response elements (SREs). Glucocorticoid receptors (GR) and ER were shown to modulate transcription controlled at AP-1, SP1, C/EBP and NF-κB sites by binding to the respective

Abbreviations: GR, glucocorticoid receptor; PPAR, peroxisome proliferation receptor; LXR, liver X receptor; TOFA, 5-tetradecyloxy-2-furancarboxylic acid.

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transcription factors (Stein and Baldwin, 1993; Diamond et al., 1990; Jonat et al., 1990; Perkins et al., 1993; Ray et al., 1994; Stein et al., 1993a,b). Such interactions may explain the effects of GR on the expression of the interleukins, IL-6 and IL-8 (Ray and Prefontaine, 1994; Stein and Baldwin, 1993; Mukaida et al., 1994). Similarly, the androgen receptor (AR) was shown to modulate transcription from the promoter of the low affinity neurotrophin receptor gene without directly interacting with a specific DNA element (Kalio et al., 1994). This type of receptor/transcription factor interaction could be responsible for AR or ER suppression of transcription from the promoter of the IL-6 gene that lacks a typical ER or AR SRE (Bellido et al., 1995). In addition, glucocorticoids were also shown to induce the expression of inhibitory protein-kappa B (I-κB), which inhibits the activity of the nuclear transcription factor NF-κB (Auphan et al., 1995; Scheinin et al., 1985; Scheinman et al., 1995). Thus, the regulation of transcription is the result of multiple signaling pathways each modulating the control elements of a given gene. This was clearly illustrated by the demonstration that D_1 dopamine receptor stimulation mimics the effect of progesterone on lordosis via a progesterone receptor-dependent mechanism (Mani et al., 1994, 1996).

Dopamine receptors are cell membrane receptors that bind the neurotransmitter, dopamine and have a structure characteristic of G protein-coupled receptors, with seven transmembrane domains. Dopamine receptors are localized mainly in the central nervous system, but low levels are also found in kidney, lower esophagus, cardiac arteries and autonomic ganglia (Strange, 1993). Molecular cloning revealed that five genes code the dopamine receptor family. On the basis of effects on adenylyl cyclase, the dopamine receptor family is divided into two functional types: those that activate the enzyme (D_{1A} and $D_5/_{1B}$ receptors), and those that inhibit it (D_2, D_3 and D_4) (Kebabian, 1992, 1993; Niznik and Van Tol, 1992; Seeman and Van Tol, 1993; Sibley et al., 1993). The D_1-like and D_2-like receptor groups can be differentiated using specific agonists and antagonists, such as the D_1 antagonist SCH23390, and the D_2 antagonist haloperidol (Chipkin, 1988; Seeman and Van Tol, 1993; Barnett et al., 1988; Maziere et al., 1992; McQuade et al., 1988). The two receptor classes serve as targets for drugs used in the treatment of Parkinson disease, schizophrenia and other disorders (McHugh and Coffin, 1991; Coffin et al., 1989; Ellenbroek et al., 1989; Hietala et al., 1990).

Recently we identified a compound, 5-tetradecyloxy-2-furancarboxylic acid (TOFA), that stimulates transcription from the MMTV promoter via chimeric receptors that consist of the DNA binding domain of GR and the ligand binding regions of the PPARβ or LXRβ nuclear receptors(Schmidt et al., 1999). This compound also modulates transcription from NF-κB- and AP-1-controlled reporter genes and, like NGF, induces neurite differentiation in PC12 cells. Since activation of the D_1 dopamine receptor stimulates transcription controlled by NRs (Power et al., 1991a,b), we compared the effects of TOFA and dopamine on transcription controlled by nuclear receptors.

In this communication, we show that (1) D_1 dopamine receptor ligands modulate transcription from the MMTV promoter, AP-1 and NF-κB in a cell and promoter context specific manner, (2) TOFA and the D_1 receptor antagonist, SCH23390 act synergistically, in vitro, in transcription controlled by the GR/LXRβ chimeric receptor and (3) TOFA pretreatment potentiates SCH23390-induced catalepsy in the rat. These findings, therefore, demonstrate cross-talk between D_1 dopamine receptors and NRs that are activated by TOFA.

2. Materials and methods

2.1. Materials

Tissue culture reagents were from Gibco/BRL Life Technologies, Grand Island, NY. TOFA was obtained from Merck Chemical Collection, Merck Research Laboratories. All other reagents were from Sigma, St. Louis, MO. TOFA was dissolved in DMSO. Dopamine, SCH23390 and SCH39166 were dissolved in water.

2.2. Plasmids and transfection assays

All DNA constructs used in this work were described previously (Schmidt et al., 1999). Briefly, two chimeric receptors were prepared by fusing the amino terminal portion that includes the DNA binding domain of the rat glucocorticoid receptor (amino acid residues 1 to 505) to either the putative ligand binding domain of the human PPARβ (first cloned as NUC-1 receptor (Schmidt et al., 1992) or the human LXRβfirst cloned as NER receptor (Shinar et al., 1994). In the GR/PPARβ chimera, the GR portion of the receptor was fused to the amino residues 148 to 441 of NUC-1 receptor while GR/LXRβ chimera was generated by fusing the GR region to amino residues 155 to 461 of the NER receptor. Fib-luc plasmid is the pGL2-basic vector that is under the control of the rat minimal gamma fibrinogen basal promoter (−54 to +38) (Frantz et al., 1994). The NF-κB-luc and AP-1-luc are reporter plasmids in which three copies of either AP-1 or NF-κB binding sites were inserted next to the minimal gamma fibrinogen basal promoter described above (Frantz et al., 1994).

2.3. Transfections

CV-1 cells, established simian kidney cells were previously shown to respond to dopamine and COS cells that are CV-1 cells that were transformed by an origin-defective mutant of SV40 which code for wild-type T antigen were used in these experiments (Gluzman, 1981; Power et al., 1991a,b). Transient transfection of COS and CV-1 cells was

performed as described (Schmidt et al., 1992, 1999). Cells were plated into 12 well dishes in phenol red-free DMEM supplemented with 10% charcoal stripped fetal calf serum. The next day, the cells were transfected with DNA, as a calcium phosphate precipitate. About 18 h later, the cells were washed and ligands or the appropriate vehicle controls were added to the medium. Forty-eight hours later cell extracts were prepared and assayed for luciferase enzyme activity using the luciferase assay system (Promega). Each transfection was performed in triplicate and the fluorescence of each sample measured using the AutoClinilumat (Berthold, Bad Wildbad, Germany). Statistical analysis of all the transfection experiments was determined by one way analysis of variance (ANOVA).

2.4. Drug-induced catalepsy

Mature male rats weighing 200–250 g were injected subcutaneously with 0.4 mg/kg TOFA or the vehicle, DMSO. Twenty-four hours later, rats were administered the D_1 or D_2 dopamine antagonists, SCH23390 (0.5 mg/kg) or haloperidol (16 mg/kg) or vehicle control solution, and the duration of catalepsy (immobility) was measured as previously described (Undie and Friedman, 1988). The procedures are in compliance with the National Institutes of Health Guide for care and use of Laboratory Animals (Publication No. 85-23, revised 1985).

3. Results

3.1. Dopamine suppresses transcription controlled by nuclear receptors in CV-1 cells

It was important to determine if CV-1 cells, maintained in our laboratory, express functional dopamine receptors as previously reported (Power et al., 1991a,b). As shown in Fig. 1, treatment of CV-1 cells with micromolar concentrations of dopamine, dose dependently increased cellular cAMP. Treatment with TOFA did not change cAMP levels (Fig. 1). Furthermore, TOFA did not influence dopamine-mediated cAMP accumulations (data not shown). In CV-1 cells that were co-transfected with the MMTV-luciferase reporter gene and with either GR/LXRβ or GR/PPARβ chimeric receptors, dopamine-induced a dose-dependent suppression of luciferase expression (Fig. 2). In concentrations that increased cellular cAMP levels, dopamine elicited a dose-related suppression of transcription that when compared to vehicle controls reached 55% inhibition at 100 μM dopamine. In contrast, exposure of COS cells to similar concentrations of dopamine did not influence the expression of luciferase (Fig. 2). However, a higher dose of dopamine (150 μM) suppressed transcription in COS cells (not shown).

To examine the potential interaction between dopamine and TOFA signaling pathways, we tested the combined

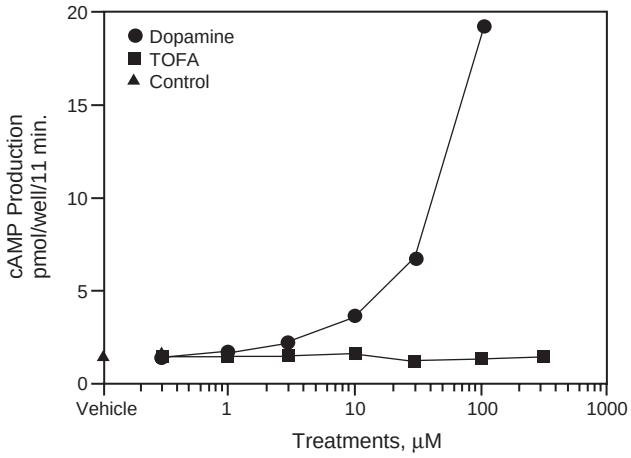

Fig. 1. Dopamine stimulates cellular cAMP levels in CV-1 cells. CV-1 cells were grown to confluency in 6 well plates and switched to serum free medium containing IBMX. The cells were treated with either dopamine, TOFA or DMSO (control) for 11 min and the accumulated levels of cellular cAMP were measured by RIA (Amersham Pharmacia Biotech, Piscataway, NJ).

treatment of dopamine and TOFA on GR/LXRβ-controlled transcription in CV-1 and COS cells. In agreement with previous results (Schmidt et al., 1999), TOFA stimulated transcription mediated by the GR/LXRβ chimeric receptor in both CV-1 and COS cells (Fig. 3). Treatment with 100 μM dopamine, on the other hand, suppressed GR/LXRβ-mediated luciferase expression in CV-1 but not in COS cells (Figs. 2 and 3). Pretreatment of cells with dopamine suppressed TOFA-stimulated luciferase expression by 54% in CV-1 cells (Fig. 3). The results suggest that TOFA and dopamine signaling pathways have opposing effects on transcription in CV-1 cells.

3.2. Effect of dopamine and D_1 receptor antagonist, SCH23390 on transcription from the MMTV promoter

To verify that the suppression of transcription mediated by dopamine was indeed due to activation of D_1 dopamine receptors, we tested whether the selective dopamine receptor antagonist, SCH23390, prevents dopamine-induced suppression of luciferase expression. CV-1 cells co-transfected with GR/LXRβ and MMTV-luciferase plasmids were treated with SCH23390, in the presence or absence of dopamine. As shown in Fig. 4, SCH23390 prevented dopamine-mediated suppression of transcription. However, at 100 μM, SCH23390 stimulated transcription in these cells (Fig. 4). A similar increase of transcription was also observed with another D_1 receptor antagonist, SCH39166 (not shown).

3.3. Dopamine modulates transcription controlled by NF-κB and AP-1 transcription factor binding sites

Previously, we showed that in addition to modulating GR/LXRβ-controlled transcription from the MMTV pro-

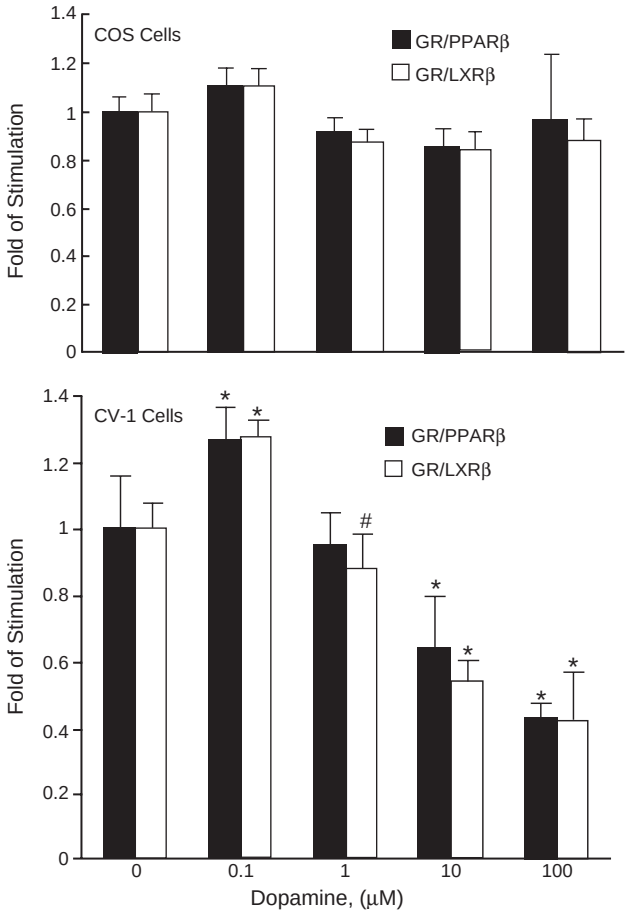

Fig. 2. Suppression of GR/PPARβ- and GR/LXRβ-controlled transcription by dopamine. CV-1 and COS-7 cells were co-transfected with the MMTV driven luciferase reporter gene and with either chimeric GR/PPARβ or GR/LXRβ receptors. The cells were treated by dopamine and luciferase assays were performed as described in methods. *P<0.0001 and $^{\#}p$<0.054 compared to vehicle treatment.

moter, TOFA also stimulated transcription controlled by the AP-1 and NF-κB transcription factor binding sites (Schmidt et al., 1999). Therefore, we compared the effects of treatment of CV-1 cells with dopamine, SCH23390 or TOFA on transcription from reporter genes that are under the control of NF-κB or AP-1 binding sites. Treatment with TOFA, dopamine or SCH23390 did not influence transcription from the minimal gamma fibrinogen promoter (Fig. 5). In these cells, 20 μM TOFA stimulated transcription from the NF-κB reporter gene by more than fourfold but had no effect on the AP-1 reporter gene (Fig. 5). Treatment of CV-1 cells with 150 μM dopamine significantly increased transcription from the AP-1-controlled reporter gene by 50% while 45% inhibition of transcription from the NF-κB reporter gene did not achieve statistical significance (p=0.08, Fig. 5). Treatment of cells with SCH23390 resulted in a small but significant 35% increase in AP-1 site-controlled transcription (Fig. 5) but not in transcription from the NF-κB controlled reporter

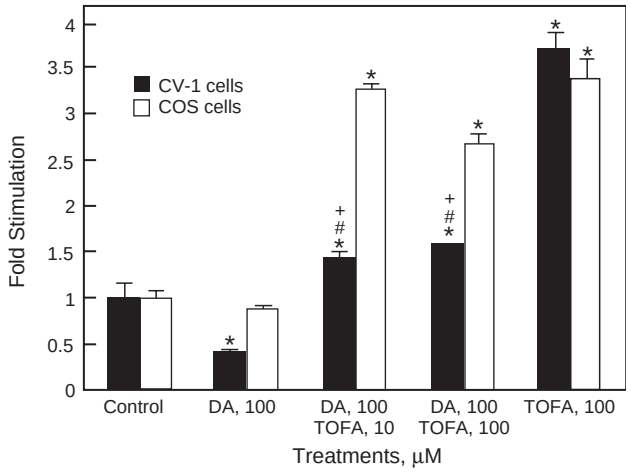

Fig. 3. Opposing effects on GR/LXRβ-controlled transcription by dopamine and TOFA treatments. CV-1 and COS-7 cells were co-transfected with the MMTV driven luciferase reporter gene and with GR/LXRβ chimeric receptors. The cells were treated with dopamine (DA), TOFA or the combination of dopamine and TOFA at the indicated concentrations and luciferase assays were performed as described in methods. *p<0.0001 compared to control; $^{\#}p$<0.0001 compared to 100 μM TOFA; ^{+}p<0.02 compared to treatment with dopamine alone.

gene. The results therefore suggest that TOFA and dopamine influence transcription in a promoter and context-dependent manner.

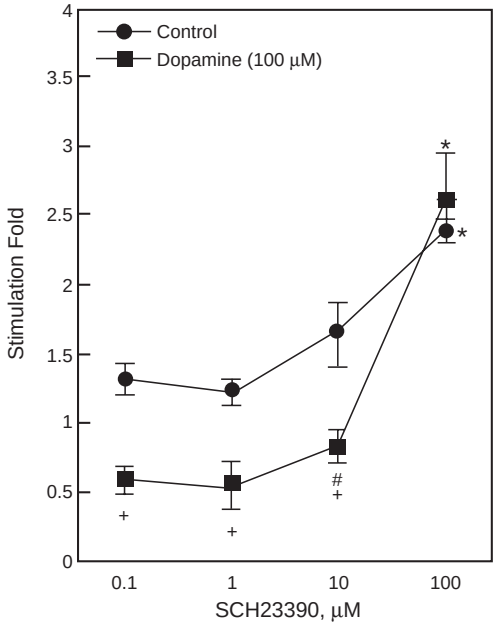

Fig. 4. Effect of D_1 dopamine receptor antagonist on dopamine suppression of GR/LXRβ-controlled transcription. CV-1 cells were co-transfected with the MMTV-luc reporter gene and the GR/LXRβ chimeric receptor. Cells were treated with vehicle or 100 μM dopamine and with the indicated concentrations of the D_1 dopamine receptor antagonist, SCH23390. Luciferase assays were performed as described in methods. *p<0.009 compared to vehicle; ^{+}p0.006 compared to the corresponding SCH23390 treatment without dopamine; $^{\#}p$<0.052 compared to vehicle treatment.

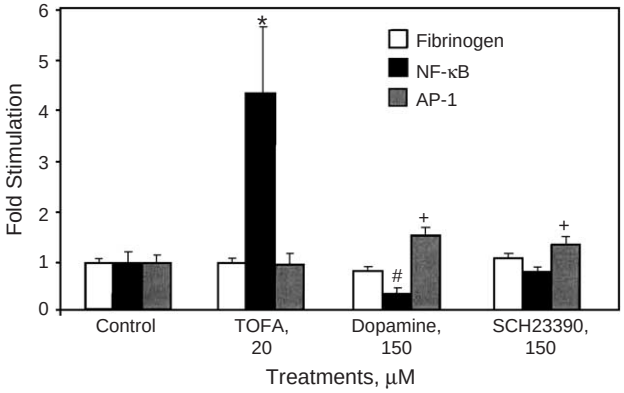

Fig. 5. Effects of dopamine, SCH32290 or TOFA on AP-1- and NF-κB-controlled transcription. CV-1 cells were transfected with the Fibrinogen-luc, NF-κB-luc or the AP-1-luc reporter genes. The transfected cells were treated with vehicle, dopamine, TOFA or SCH23390 and assayed for luciferase activity as described in methods; *$p<0.0001$ compared to control, $^{+}p<0.05$ compared to control; $^{\#}p<0.09$ compared to control.

3.4. D_1 dopamine receptor antagonists and TOFA synergistically increase transcription controlled by the GR/LXRβ receptor

The interaction between TOFA and the dopamine receptor signaling pathway was further studied by examining the influence of TOFA and D_1 dopamine receptor inhibitors on transcription. CV-1 cells were co-transfected with the chimeric GR/LXRβ receptor and MMTV reporter plasmids and treated with low concentrations of TOFA (5 μM) and the D_1 receptor antagonists, SCH23390 (10 μM) or SCH39166 (10 μM). At these doses, these agents had little influence on transcription (Fig. 6). However, combined with TOFA, the dopamine receptor antagonists increased luciferase expression (Fig. 6), suggesting that TOFA and D_1 dopamine receptor inhibition were synergistic in their effects on transcription.

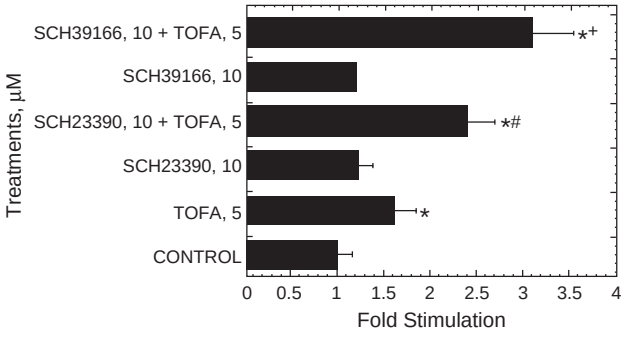

Fig. 6. D_1 dopamine receptor antagonists and TOFA synergistically increase GR/LXRβ-controlled transcription. CV-1 cells were co-transfected with the MMTV-luc reporter gene and GR/LXRβ chimeric receptor. The cells were treated with vehicle, TOFA, SCH23390 or SCH39166 at the indicated concentration. Luciferase assays were performed as described in methods, *$p<0.0014$ different from control; $^{\#}p<0.0001$ different from TOFA or SCH23390 treatment; $^{+}p<0.0001$ different from TOFA or SCH39166 treatment.

Table 1
Effect of TOFA on drug-induced catalepsy

Pretreatment	Treatment	Duration (s)
TOFA	None	0
Control	SCH23390	3.1±1.3
TOFA	SCH23390	75.1±17.3*
Control	Haloperidol	20.3±6.7
TOFA	Haloperidol	28.9

Groups of 9–12 rats were pretreated subcutaneously with 0.4 mg/kg TOFA or vehicle and challenged with vehicle, 0.5 mg/kg SCH23390 or 0.1 mg/kg haloperidol 24 h later. The duration of catalepsy is presented as mean±SEM. *$p<0.01$ compared to control+SCH23390 by the student 't' test.

3.5. TOFA potentiates SCH23390-induced catalepsy in rats

Treatment with D_1 dopamine receptor antagonists induces catalepsy in rodents. Based on the suggested synergism between TOFA and dopamine D_1 antagonist, we examined the potential interaction between TOFA and SCH23390, in vivo, by testing the influence of TOFA on SCH23390-induced catalepsy. Rats pretreated with a subcutaneous injection of 0.4 mg/kg TOFA or with vehicle were injected, 24 h later, with 0.5 mg/kg SCH23390 and the duration of the cataleptic response was measured. TOFA increased the duration of SCH23390-induced catalepsy 25-fold (Table 1). This interaction of TOFA with the D_1 receptor antagonists appears to be specific, since TOFA did not potentiate catalepsy induced by the D_2 dopamine receptor antagonist, haloperidol. Treatment with TOFA alone did not induce catalepsy and did not elicit any other apparent behavioral change in control rats. A similar potentiation of SCH23390-induced catalepsy was also observed following intraventricular injection of TOFA prior to treatment with the D_1 dopamine antagonist (data not shown).

4. Discussion

Using nuclear receptor-controlled transcription assays, we found in CV-1 cells that dopamine suppresses transcription from the MMTV promoter which is controlled by either GR/PPARβ or GR/LXRβ chimeric receptors. This effect is limited to the MMTV promoter, as we did not observe significant inhibition of transcription from the minimal γ-fibrinogen promoter or from the minimal γ-fibrinogen promoter that is under the control of NF-κB or AP-1 binding sites. On the other hand, dopamine treatment weakly stimulated transcription that is under the control of the AP-1 binding site. The actions of dopamine were probably mediated by the D_1 dopamine receptor since D_1 and not D_2 dopamine receptor antagonists prevented the suppression of transcription by dopamine. This is supported by the observation that dopamine elicited an increase in cellular cAMP that was sensitive to the D_1 dopamine receptor antagonist, SCH23390. These observations are also

in agreement with previous reports demonstrating that CV-1 cells express functional D_1 dopamine receptors that can induce transcription controlled by nuclear receptors (Power et al., 1991a,b). In addition to antagonizing the activities of dopamine in CV-1 cells, we also noted that SCH23390 increased transcription controlled by the chimeric receptors, GR/LXRβ and GR/PPARβ, suggesting that SCH23390 may be an inverse agonist in this D_1 dopamine receptor system. However, it is unusual for this dopamine receptor antagonist to exert pharmacological activity beyond its known blocking action at the D_1 dopamine receptor, and in fact this compound was recently described to be a neutral antagonist in a neuronal test system (Cai et al., 1999). It is possible that serum contains low levels of dopamine and the D_1 receptor antagonist blocks its action. Alternatively, the D_1 dopamine receptor antagonist might interact with other, as yet undetermined, components of the signaling cascade that ultimately affect gene transcription.

The in vitro data presented in the present communication suggest possible cross-talk between the actions of SCH23390 and TOFA, and this is reinforced by the in vivo finding of a parallel interaction with regard to drug-induced catalepsy in the rat. The finding that TOFA treatment per se does not elicit catalepsy and that it does not potentiate D_2 dopamine receptor antagonist-mediated catalepsy suggest a selective interaction between the D_1 dopamine receptor system and TOFA signaling. The potentiation of SCH23390-induced catalepsy by TOFA appears to be unique in several aspects. Since TOFA and SCH23390 do not share similarities in molecular structure or pharmacologic action, it is likely that the agents act on distinct targets that converge to influence transcription or catalepsy. Although TOFA is an inhibitor of fatty acid synthesis and may incorporate into cell membrane lipids (Halvorson and McCune, 1984; Arbeeny et al., 1992; Otto et al., 1985; Parker et al., 1977), it is unlikely that, at the concentrations used in the present in vivo experiments, TOFA causes significant inhibition of fatty acid synthesis. It is more likely that TOFA, acting via modulation of gene expression, interacts with D_1 dopamine receptor signaling pathways.

TOFA or other compounds acting via nuclear receptors may be of therapeutic benefit in conditions for which D_1 antagonists, such as SCH23390 were shown to be of potential utility. For example, SCH23390 may be useful in treating cocaine overdose and in the prevention of cocaine addiction (Lomax and Daniel, 1991; Witkin et al., 1991, 1993). The D_1 dopamine receptor antagonists also prevent the development of intraocular pressure in certain hydrodynamic disorders in patients with increased intracranial pressure, and prevent memory loss associated with lesions of central nervous system cholinergic pathways (Boyson and Alexander, 1990; McGurk et al., 1992; Virno et al., 1992). In these conditions, TOFA may be useful in potentiating the actions of dopamine receptor antagonists.

Previously, we demonstrated that TOFA and some hydroxycholesterols transactivated transcription controlled by the steroid receptor LXRβ, mimicked the activity of NGF and promoted in vitro neuronal differentiation of pheochromocytoma (PC12) cells (Schmidt et al., 1999). Furthermore, TOFA is a ligand that activates members of the PPAR and LXR receptor families. It will be of interest to test whether synthetic and receptor selective ligands for these receptors can mimic the actions of TOFA on SCH23390-induced catalepsy and thus provide additional insight into the function of these receptors in the central nervous system.

Acknowledgements

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