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Effects of selective σ receptor ligands on glucocorticoid receptor-mediated gene transcription in LMCAT cells

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Abstract:
It has been shown previously that σ receptor agonists reveal potential antidepressant activity in experimental models. Moreover, some data indicate σ receptor contribution to stress-induced responses (e.g., conditioned fear stress in mice), though the mechanism by which σ ligands can exert their effects, remains unclear. Recent studies have indicated that antidepressant drugs (ADs) inhibit glucocorticoid receptor (GR) function *in vitro*. The aim of the present study was to find out whether σ receptor ligands are able to directly affect GR action. To this end, we evaluated the effect of σ receptor agonists and antagonists on GR function in mouse fibroblast cells (L929) stably transfected with mouse mammary tumor virus-chloramphenicol acetyltransferase (MMTV-CAT) plasmid (LMCAT cells). For this study, we chose SA 4503, PRE 084, DTG (selective σ_1 or $\sigma_{1/2}$ receptor agonists) and BD 1047, SM 21, rimcazole (σ receptor antagonists). Fluvoxamine, the selective serotonin reuptake inhibitor with $\sigma_{1/2}$ receptor affinity, was used for comparison. It was found that SM 21 (at 1, 3, 10 and 30 μM), BD 1047 (3, 10 and 30 μM) rimcazole (10 μM), and fluvoxamine (at 3, 10 and 30 μM) significantly inhibited corticosterone-induced gene transcription, while DTG, SA 4503 and PRE 084 remained ineffective. Thus, the σ receptor agonists that predominantly showed antidepressant-like activity in behavioral models, were without effect in this *in vitro* model. These results suggest that antidepressant-like activity of σ receptor agonists is independent of corticosterone-induced gene transcription. Therefore, the attenuation of GR function induced by σ receptor antagonists remains ambiguous and requires further study.

Key words:
selective σ ligands, glucocorticoid-mediated gene transcription, fibroblast cells

Introduction

The ability of antidepressant drugs (ADs) to interact with σ receptors in the nanomolar range appears to be relevant to the mechanism of antidepressant action [5, 41]. The σ receptors are classified into two subtypes, σ_1 and σ_2 receptors: the first was cloned from rodent and human tissues while the second has not yet been fully characterized [36, 40]. The σ_1 sites are particularly abundant in the hippocampal formation and other limbic areas (involved in cognition and emotion), while the highest densities of σ_2 receptors were revealed mostly in regions related to motor functions (cerebellum, red nucleus, superior colliculus, various cranial nerve nuclei, substantia nigra and striatum). Although the precise mechanism underlying the functional response of these receptors is still uncertain, it

is accepted that σ receptors can modulate glutamatergic, dopaminergic and serotonergic neurotransmitter systems [4, 8, 12, 13, 27].

Preclinical studies have shown that targeting σ receptors alone is sufficient (but not requisite) to produce antidepressant-like actions. As shown previously, σ receptor agonists (e.g., igmesine, SA 4503, (+)-pentazocine, and recently UMB 23 and UMB 82) produce anti-immobility effects in animal models of depression such as the forced-swimming or tail-suspension tests [5, 41, 48]. Moreover, the high-affinity σ receptor agonist igmesine is promising as AD therapy for humans (phase II clinical trials) [47]. It is believed that σ receptors represent an initial target (similarly to monoamine transporters) in a cascade of events that ultimately results in an antidepressant action.

In patients suffering from major depression, hyperactivity of the hypothalamic-pituitary-adrenocortical (HPA) axis is often observed, and has been implicated in the pathophysiology of this disease [2, 21, 31]. Hitherto obtained data indicate that hyperactivity of the HPA axis in major depression can be induced by impairment of the feedback inhibition mechanism [17, 33]. The synthetic glucocorticoid, dexamethasone, is less potent in lowering blood cortisol levels in depressed patients, as compared to healthy subjects [16, 19, 45]. Clinically effective AD therapy can correct dysfunction of the HPA axis [16, 18]. In contrast, some recent clinical studies reveal that the inhibitors of cortisol synthesis (metyrapone, ketoconazole, aminoglutetimide) also show antidepressant effects [17, 30].

In HPA-hyperactive transgenic mice (with reduced glucocorticoid receptor (GR) expression mainly in neuronal tissue), behavioral changes resembling those observed in depressed patients, such as impairments in food consumption, sleep, learning and memory, are observed [28, 35, 37].

As was demonstrated previously, ADs increase the expression of GR in the CNS, enhance GR-mediated feedback inhibition and thereby decrease cortisol/corticosterone levels. ADs also inhibit some corticosterone-evoked effects, as well as GR-mediated transcription of some genes [6]. GRs are ligand-dependent transcription factors, which bind to a specific DNA sequence (glucocorticoid responsive element – GRE) and regulate expression of many target genes involved in neurotransmission, metabolism, neurodegenerative processes and immune system activity.

The aim of the present study was to determine whether σ receptor ligands are able to directly affect GR-mediated gene transcription. To this end we evaluated the effects of SA 4503 and PRE 084 (the selective σ_1 receptor agonists), di-*o*-tolylguanidine (DTG, $\sigma_{1/2}$ receptor agonist), and BD 1047, SM 21 and rimcazole (the σ receptor antagonists), on the corticosterone-induced chloramphenicol acetyltransferase (CAT) activity in mouse fibroblast cells stably transfected with mouse mammary tumor virus (MMTV)-CAT plasmid. Fluvoxamine, the selective serotonin reuptake inhibitor with high affinity for $\sigma_{1/2}$ receptors, was used for comparison.

Materials and Methods

Cell culture

Effects of these drugs on GR-mediated gene expression were determined in mouse fibroblast cells (L929), stably transfected with mouse mammary tumor virus-chloramphenicol acetyltransferase (MMTV-CAT) reporter plasmid (LMCAT cells). The LMCAT cell line was generously provided by Dr. E.R. Sanchez (Department of Pharmacology, Medical College of Ohio, Toledo, OH, USA). The cells were grown in DMEM (Gibco-BRL, USA) with a 10% heat-inactivated fetal bovine serum (Gibco-BRL, USA) and 0.02% Geneticin (Gibco-BRL, USA) at 37°C, in a 5% CO_2/95% air atmosphere.

Drug treatments

The LMCAT cells (final confluency 80%) were treated for five days with vehicle, N-[2-(3,4-dichlorophenyl)-ethyl]-*N*-methyl-2-(dimethylamino)ethylamine (BD 1047, Tocris Cookson Ltd., UK), 1,3-Di-*o*-tolylguanidine (DTG, Research Biochemicals Int., USA), fluvoxamine maleate (Tocris Cookson Ltd., UK), 2-(4-morpholinoethyl)-1-phenylcyclohexane-1-carboxylate hydrochloride (PRE 084, Tocris Cookson Ltd., UK), rimcazole dihydrochloride (Research Biochemicals Int., USA), 1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)-piperazine dihydrochloride (SA 4503, Santen Pharmaceutical Co. Ltd., Japan), (±)-tropanyl-2-(4-chlorophenoxy)butanoate maleate (SM 21, Tocris Cookson Ltd, UK). The drugs were dissolved in water, except for DTG which was dissolved in a small amount of ethanol, followed by dilution in the medium (the final

concentration of ethanol was < 0.5%). The control cultures were supplemented with the same amount of an appropriate vehicle. All drugs were added at final concentrations of 1, 3, 10 and 30 μM. The medium and drugs were changed once over the course of a 5-day culture. Gene transcription was stimulated by adding 1 μM corticosterone for 2 h before harvesting cells.

Chloramphenicol acetyltransferase (CAT) activity assay

CAT activity was determined as described previously [3, 34]. Cell lysates were prepared by a freeze/thaw procedure. To determine CAT activity, aliquots of lysate (after heating at 60°C for 10 min) were incubated in 0.25 M Tris-HCl buffer (pH = 7.8) with 0.25 μCi D-threo-[dichloroacetyl-1-^{14}C]-chloramphenicol and 0.2 mM n-butyryl coenzyme A at 37°C for 1 h. The butyrylated forms of chloramphenicol (in direct proportion to CAT gene expression) were extracted twice with xylene, washed with 0.25 M Tris-HCl buffer; radioactivity was measured in a β-counter (Beckmann LS 335 liquid scintillation counter). The results are presented as dpm of a butyrylated fraction of chloramphenicol per 10 μg of protein per 1 h of incubation. The protein concentration in cell lysates was determined by the Lowry method [22].

Statistical analysis

The data are presented as the mean ± SEM of four to five independent experiments (in duplicate wells). The significance of differences between the means was evaluated by Duncan's test following one-way analysis of variance.

Results

Addition of corticosterone at a concentration of 1 μM for 2 h increased CAT activity about 35-fold. As was described previously, the effect of corticosterone was completely blocked by addition of 10 μM RU 38486, a specific antagonist of the type II GR, confirming involvement of the GR in this response [7].

None of the drugs examined affected the low baseline levels of non-stimulated CAT activity (data not shown). The lowest concentration of DTG (1 μM) slightly, but significantly, increased corticosterone-induced reporter gene transcription [F (4, 31) = 2.797;

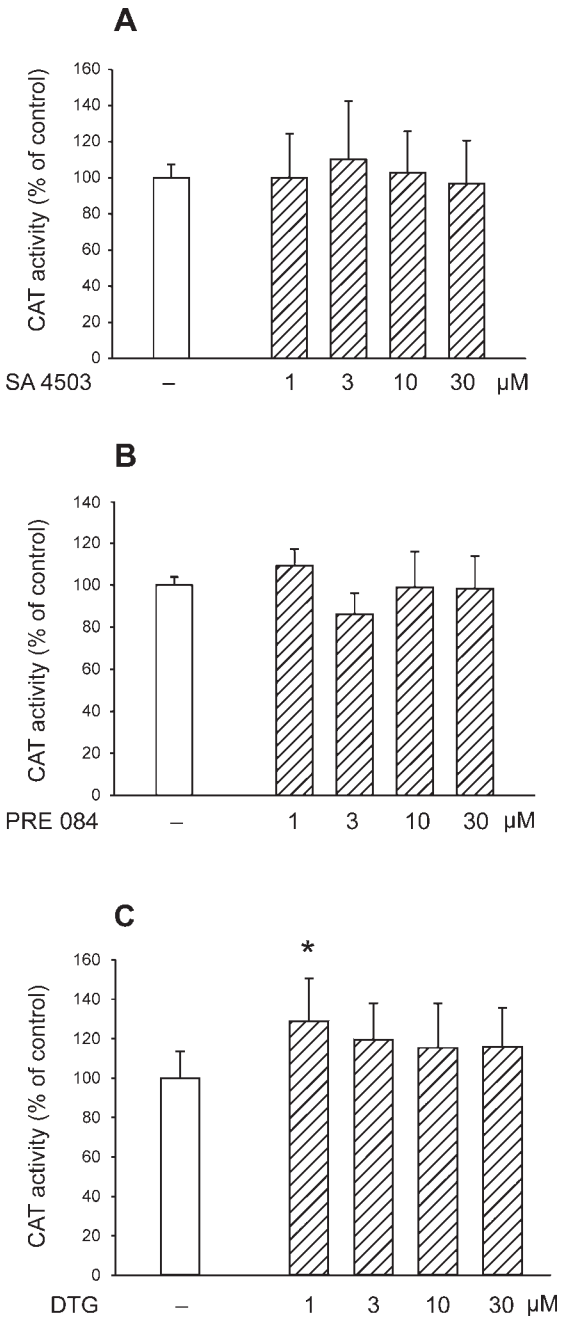

Fig. 1. The effect of σ receptor agonists, SA 4503 **(A)**, PRE 084 **(B)** and DTG **(C)** on corticosterone (1 μM, 2 h)-induced CAT activity in LMCAT cells. SA 4503, PRE 084 and DTG were used at concentrations of 1, 3, 10 and 30 μM for 5 days. Corticosterone (1 μM) was added 2 h before harvesting the cells for assays of CAT enzyme activity. The data are presented as the means ± SEM (% of control). The significance of differences between the means was evaluated by Duncan's test following a one-way analysis of variance (* $p < 0.05$ *vs.* respective control)

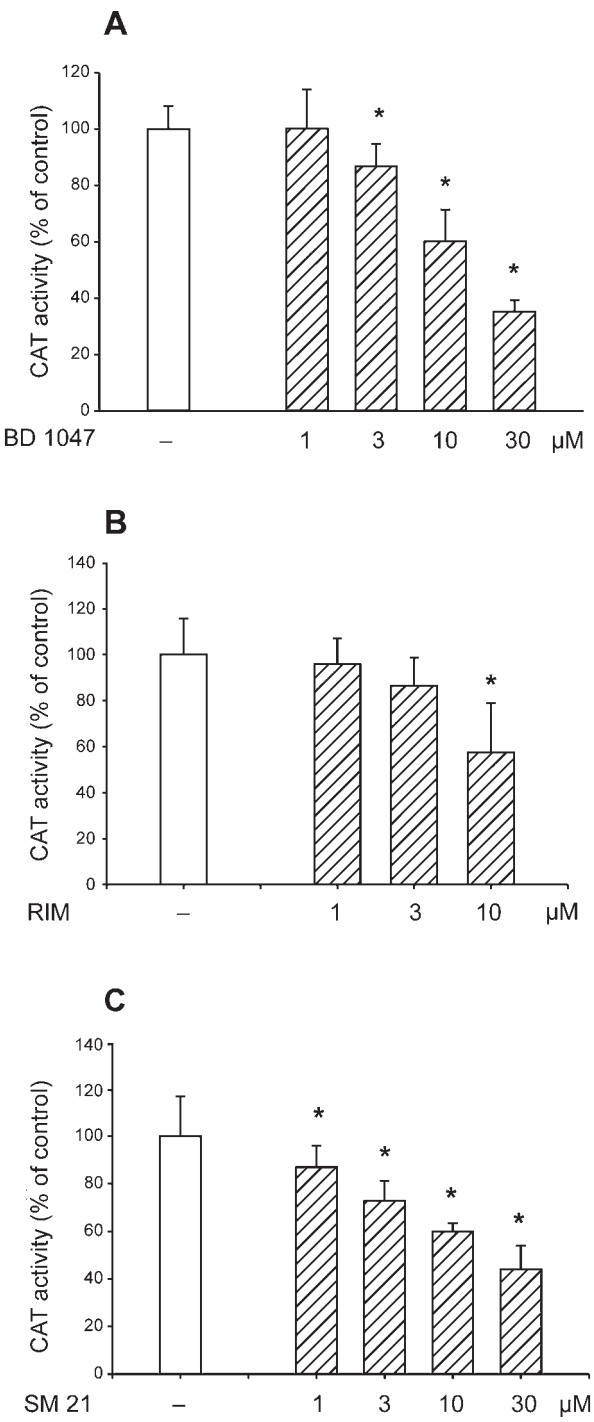

Fig. 2. The effect of σ receptor antagonists: BD 1047 **(A)**, rimcazole **(B)**, SM 21 (C) on corticosterone (1 μM)-induced CAT activity in LMCAT cells. BD 1047, rimcazole and SM 21 were used at concentrations of 1, 3, 10 and 30 μM for 5 days. Corticosterone (1 μM) was added 2 h before harvesting the cells for assays of CAT enzyme activity. The data are presented as the mean ± SEM (% of control). The significance of differences between the means was evaluated by Duncan's test following a one-way analysis of variance (* $p < 0.05$ *vs.* respective control)

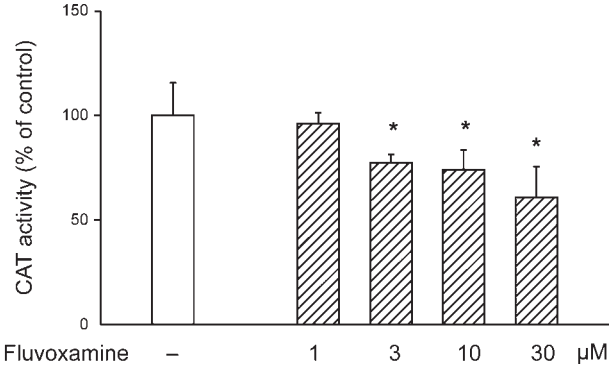

Fig. 3. The effect of fluvoxamine on corticosterone (1 μM)-induced CAT activity in LMCAT cells. Fluvoxamine was used at concentrations of 1, 3, 10 and 30 μM for 5 days. Corticosterone (1 μM) was added 2 h before harvesting the cells for assays of CAT enzyme activity. The data are presented as the mean ± SEM (% of control). The significance of differences between the means was evaluated by Duncan's test following a one-way analysis of variance (* $p < 0.05$ *vs.* respective control)

$p < 0.05$] (Fig. 1C). Treatment of cells with σ receptor agonists – SA 4503 [F (4, 30) = 0.357], PRE 084 [F (4, 17) = 2.352] and higher doses of DTG (3, 10 and 30 μM) failed to affect corticosterone-induced CAT activity (Fig. 1A–C). BD 1047 (3, 10 and 30 but not 1 μM) (Fig. 2A) and rimcazole at 10 μM (Fig. 2B) inhibited corticosterone-induced gene transcription [$F(4, 25) = 5\ 9.916$; $p < 0.001$ and $F(3, 25) = 10.748$; $p < 0.001$, respectively]. The lower concentrations of rimcazole were ineffective but higher doses induced neurotoxic effects. SM 21 (1–30 μM) decreased corticosterone-induced CAT activity in a concentration-dependent manner [$F(4, 31) = 25.12$; $p < 0.001$) (Fig. 2C). Fluvoxamine, used for comparison, significantly inhibited corticosterone-induced gene transcription at concentrations of 3, 10 and 30 μM (its lowest concentration was inactive) [$F(4, 27) = 14.457$; $p < 0.001$] (Fig. 3).

Discussion

According to Su and Hayashi [43], σ_1 receptors are endoplasmic reticular proteins that, when stimulated by ligands, can translocate and thereby increase $[Ca^{2+}]_i$ by enhancing IP_3 receptor signaling at the endoplasmic reticulum, *via* removal of ankyrin (an in-

hibitory cytoskeletal adaptor protein) from the IP_3 receptor. It has been hypothesized that σ receptors represent an initial target in a cascade of events that ultimately results in an antidepressant effect. Although the mechanisms underlying the ability of σ receptor ligands (agonists) to produce antidepressant-like actions have yet to be fully elucidated, results suggest that σ receptor agonists stimulate a variety of neural adaptations in the central nervous system that are relevant to antidepressant action. For example, it has been shown recently that σ_1 receptors up-regulate the release of brain-derived neurotrophic factor (BDNF) [20]. The role of BDNF/TrkB signaling is proposed as one of the possible mechanisms underlying the therapeutic effect of ADs [e.g., 20]. Repeated treatments with some ADs that are σ_1 receptor agonists (e.g., fluvoxamine, used for comparison in this study) significantly potentiate the BDNF-triggered glutamate release in cultured cortical neurons through σ_1 receptor-mediated action (by enhancing the PLC-γ/IP_3/Ca^{2+} signaling pathway) [49]. Su and co-workers report that some ADs showing affinity to σ_1 receptors (e.g., fluvoxamine) enhanced nerve growth factor (NGF)-induced neurite sprouting in PC12 cells [44]. The potentiation of BDNF-triggered glutamate release by fluvoxamine and SA 4503 (a σ_1 receptor agonist) was blocked by NE-100 (the σ_1 receptor antagonist), suggesting a role for σ_1 receptors in blocking the enhancement of NGF-induced neurite outgrowth. Likewise, these results indicated that interaction with IP_3 receptors, PLC-γ, PI3K, P38MAPK, JNK, and Ras/Raf/MAPK signaling pathways are involved in the mechanisms of action for the abovementioned σ_1 receptor ligands [32]. Indeed, it is accepted that the physiological consequences of σ_1 receptor activation are intracellular regulation of Ca^{2+} mobilization and activation of PLC and protein kinase C (PKC) pathways [14, 29].

Since glucocorticoids at high concentration (stress) evoke changes characteristic of depression in experimental conditions, inhibition of GR function may be connected with the therapeutic action of ADs. It was shown that ADs (including imipramine, desipramine, amitriptyline, fluoxetine, mianserin and tianeptine) inhibited corticosterone-induced gene transcription in a concentration- and time-dependent manner. Moreover, imipramine decreases binding of the corticosterone-receptor complex to DNA [7]. This inhibitory effect of imipramine depends partly on the PLC/PKC pathway. Subsequent studies confirmed this assumption by showing that imipramine inhibited PKC activity in LMCAT cells [1]. In conclusion, studies on the mechanism of antidepressant action on GR function revealed that PKC plays a key role in this phenomenon.

The results obtained in this paper indicate that σ_1 receptor agonists SA 4503 and PRE 084 failed to affect corticosterone-induced gene transcription. DTG (σ_1/σ_2 receptor agonist) slightly increased the effect of corticosterone on GR-mediated gene transcription at the lowest concentration investigated. Two out of three σ agonists, DTG and SA 4503, exerted antidepressant-like activity in behavioral models (e.g., forced swim test or tail suspension test in rats and mice). PRE 084 fails to affect the duration of immobility in normal mice, but reduces the period of immobility in adrenalectomized/castrated (AdX/CX) mice. The augmented effect of PRE 084 in AdX/CX mice was fully blocked by BD 1047 [46]. The antidepressant-like activity of fluvoxamine was shown in mice subjected to the forced-swim test [e.g., 48]. Surprisingly, none of the σ_1 receptor agonists under study decrease the CAT activity induced by a high (stress) concentration (1 μM) of corticosterone. In contrast, inhibitory activity (concentration-dependently) was found for BD 1047, rimcazole and SM 21, and fluvoxamine. As was mentioned above, BD 1047 is accepted as σ_1-, while SM 21 is a σ_2-receptor antagonist [11, 23, 24, 42]. Rimcazole has been recognized as an σ_1 antagonist but its affinity to σ receptors is rather low [10, 39]. Interestingly, rimcazole was the first selective σ ligand to be subjected to clinical trial as a potential antipsychotic drug. It was found to improve negative symptoms but exacerbate acute positive symptoms; however, subsequent clinical studies were stopped [15]. In the present study, the neurotoxic effect of rimcazole was observed at its higher concentrations. It is worth mentioning that the newly synthesized σ ligands, e.g., BD 1047, show much higher affinity for σ_1 *vs*. σ_2 receptors, in comparison to previously studied σ ligands which were not selective for σ_1/σ_2 sites.

There is no apparent correlation between the affinity of ligands for σ_1 receptors and their inhibitory effect on corticosterone-induced CAT activity. For example, SA 4503, with affinity to the σ_1 receptor comparable to that of fluvoxamine (IC_{50} = 17.4 nM and 13 nM, respectively) [26, 38], was ineffective in our study. Rimcazole, having relatively low affinity to σ_1 receptor (IC_{50} = 520 nM), [39] induced the decrease

(at one concentration) of corticosterone-induced GR-mediated gene transcription. In addition, SA4503 is defined as an σ_1 receptor agonist, while rimcazole is defined as an antagonist. SM 21, described as an σ_2- receptor preferring antagonist (Ki for σ_1 receptor = 1050 nM, for σ_2 = 145 nM) [25], inhibited corticosterone-induced CAT activity in LMCAT cells in a concentration-dependent manner.

σ Receptor ligands capable of affecting GR-induced gene transcription can act on different processes related to GR action, e.g., the binding of hormones with receptors, dissociations of the steroid-receptor complex from other cytosol proteins, translocation of the hormone-GR complex from the cytoplasm to the nucleus, phosphorylation of GR, binding to DNA, and modulation of the transcription complex. Notably, the action of σ ligands on GR-mediated gene transcription was studied in a fibroblast cell line, so it is unknown if similar mechanisms characterize the process in neurons. Nonetheless, it seems questionable that "antidepressant-like" activity of σ ligands, observed in behavioral studies, could be directly connected with GR function. The decrease in glucocorticoid-mediated gene transcription produced by σ receptor antagonists may be related to their direct inhibition of PKC activity, while DTG may activate that enzyme.

Further studies are required to elucidate whether the inhibition of corticosterone-induced CAT activity is a common feature of σ receptor antagonists or rather is related to pharmacology unique to each compound, thus independent of σ_1 receptor antagonistic activity.

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