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WAY-100635 inhibits 8-OH-DPAT-stimulated oxytocin, ACTH and corticosterone, but not prolactin secretion

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Abstract

Previous studies suggest that the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) increases the secretion of oxytocin, adrenocorticotropic hormone (ACTH), corticosterone and prolactin but not renin. However, the lack of selective 5-HT_{1A} receptor antagonists made it difficult to confirm that 5-HT_{1A} receptors mediate the neuroendocrine responses to 8-OH-DPAT. This study investigated the effects of increasing doses of a selective 5-HT_{1A} receptor antagonist, *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexanecarboxamide (WAY-100635) on neuroendocrine responses induced by the 5-HT_{1A} receptor agonist 8-OH-DPAT in adult male rats. 8-OH-DPAT, 500 μg/kg s.c., increased plasma levels of oxytocin (to 970% above basal levels); ACTH (to 1622% above basal levels), corticosterone (to 458% above basal levels) and prolactin (to 313% above basal levels), but not renin. The lowest dose of WAY-100635 (0.1 mg/kg s.c.) significantly inhibited the 8-OH-DPAT-induced increase in plasma oxytocin but not ACTH or corticosterone levels. At a dose of 1 mg/kg (s.c.), WAY-100635 completely blocked the oxytocin and ACTH responses and maximally inhibited the corticosterone response to 8-OH-DPAT, although corticosterone levels were still above basal. In contrast, the increase in prolactin secretion, induced by 8-OH-DPAT was not inhibited by any dose of WAY-100635. At the highest dose of WAY-100635 (10 mg/kg, s.c.), basal prolactin levels were markedly elevated (1550%) and administration of 8-OH-DPAT significantly elevated plasma renin concentration. Taken together, these data indicate that: (1) 8-OH-DPAT stimulates oxytocin, ACTH, and corticosterone but not prolactin secretion via activation of 5-HT_{1A} receptors and (2) blockade of 5-HT_{1A} receptors may unmask 8-OH-DPAT simulation of renin secretion via non-5-HT_{1A} receptor mechanisms. © 1998 Elsevier Science B.V.

Keywords: 5-HT (5-hydroxytryptamine, serotonin); 5-HT_{1A}, receptor; (Antagonist); Hypothalamus; Receptor reserve; Hormone; Neuroendocrine

1. Introduction

Previous studies indicate that the prototypical 5-HT_{1A} receptor agonist 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino) tetralin increases plasma levels of oxytocin, adrenocorticotropic hormone (ACTH), and corticosterone (Gilbert et al., 1988; Di Sciullo et al., 1990; Pan and Gilbert, 1992; Bagdy and Kalogeras, 1993; Li et al., 1993; Fletcher et al., 1996). Despite the suggestion that 8-OH-DPAT increases oxytocin secretion via stimulation of 5-HT_{1A} receptors, (Bagdy and Kalogeras, 1993; Li et al., 1993) the involvement of 5-HT_{1A} receptors in mediating the oxytocin response to 8-OH-DPAT was not confirmed due to lack of availability of selective 5-HT_{1A} receptor antagonists.

A role for 5-HT_{1A} receptors in the secretion of prolactin also has been suggested. For example, 8-OH-DPAT elevates prolactin levels (Carlsson and Eriksson, 1986; Di Sciullo et al., 1990) but the non-selective 5-HT_{1A} and β-adrenoceptor antagonist pindolol does not inhibit this effect (Aulakh et al., 1988). Also, evidence supporting an involvement of 5-HT_{1A} receptors in renin secretion is ambiguous. High doses of the 5-HT_{1A} agonist ipsapirone increase plasma renin concentration, while 8-OH-DPAT decreases renin concentration (Lorens and Van de Kar, 1987). These data suggest a potential, but unsubstantiated role of 5-HT_{1A} receptors in renin release, since until recently, pharmacological antagonism studies could only be performed using partial 5-HT_{1A} receptor antagonists, such as NAN 190 and WAY-100135 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexanecarboxamide, or non-selective 5-HT_{1A} receptor antagonists such as spiperone (5-$HT_{1A/2A}$ and dopamine D_2 receptor antagonist) and pindolol (5-HT_{1A} and β-adrenoc-

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eptor antagonist). Therefore, the present study utilized the novel, selective high affinity 5-HT_{1A} receptor antagonist WAY-100635 to determine which plasma hormone responses shown to be elevated by 8-OH-DPAT are due to activation of 5-HT_{1A} receptors.

2. Methods

2.1. Animals

Adult male Sprague Dawley rats (225–275 g) were purchased from Harlan (Indianapolis, IN). Animals were housed two per cage in a light (12 h light and dark cycle, lights on at 7 a.m.), humidity and temperature controlled room, for at least 5 days before the experiment. Food and water were available ad libitum. Each experimental group consisted of 8–10 animals. All procedures were conducted in accordance with the National Institute for Health (NIH) Guide for the Care and Use of Laboratory Animals as approved by the Loyola University Institutional Animal Care and Use Committee (IACUC).

2.2. Drugs

8-hydroxy-2-(di-*n*-propylamino) tetralin hydrobromide (8-OH-DPAT) was purchased from Research Biochemical (Natick, MA) and was injected at the dose of 500 μg/kg, s.c. WAY-100635, (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexanecarboxamide was a gift from Wyeth-Ayerst (Princeton, NJ), and was injected at a dose of 0.1, 1 and 10 mg/kg, s.c. All the drugs were dissolved in saline and injected in a volume of 1 ml/kg.

2.3. Neuroendocrine challenge tests

WAY-100635 was administered at doses of 0.1, 1 and 10 mg/kg (s.c.), 1 h before killing. These doses of WAY-100635 were based on previously published studies (Critchley et al., 1994) that demonstrated that a dose of 0.01 mg/kg of WAY-100635 injected intravenously was the minimal effective dose that inhibited the 8-OH-DPAT (0.1 mg/kg i.v.) induced increase in plasma ACTH. Since the antagonist was administered by the s.c. injection route rather than i.v., larger doses were used. Rats were then administered either saline or 8-OH-DPAT (500 μg/kg, s.c.), 15 min before killing. This dose of 8-OH-DPAT was previously shown to produce a maximal neuroendocrine response (Li et al., 1993). The time interval for 8-OH-DPAT was based on data (Di Sciullo et al., 1990), indicating that plasma levels of prolactin reach a peak at 15 min and return to basal level at 30 min. The other hormones elevated by 8-OH-DPAT, remained elevated for at least 30 min (Di Sciullo et al., 1990). The rats were sacrificed by decapitation and trunk blood was collected in centrifuge tubes containing 0.5 ml of a 0.3 mM EDTA solution (pH 7.4). Plasma aliquots were stored at −70°C until hormone levels were determined via radioimmunoassays. Plasma oxytocin, ACTH, corticosterone, prolactin and renin concentrations were examined by radioimmunoassays described in detail elsewhere (Li et al., 1993).

2.4. Statistical analysis

The data were analyzed by a two-way analysis of variance (ANOVA) followed by the Newman–Keuls' multiple range test (Steel and Torrie, 1960), using a computer program (NWA STATPAK Portland, OR). All data are represented as group means and the standard error of the means (S.E.M.).

3. Results

8-OH-DPAT (500 μg/kg, s.c.) significantly increased plasma oxytocin, ACTH, corticosterone, and prolactin but not renin levels. Fig. 1 demonstrates that WAY-100635 dose-dependently blocked the 8-OH-DPAT-induced elevation in plasma oxytocin levels. The lowest dose of WAY-100635 used (i.e., 0.1 mg/kg, s.c.), significantly inhibited the effect of 8-OH-DPAT on plasma oxytocin levels (by 28%; $F(3,57) = 33.82$, $p < 0.01$). The dose of 1 mg/kg of WAY-100635 completely blocked the oxytocin response to 8-OH-DPAT. This was the maximal inhibition and the oxytocin response to 8-OH-DPAT was not further reduced by 10 mg/kg of WAY-100635. None of the doses of WAY-100635 altered basal oxytocin levels.

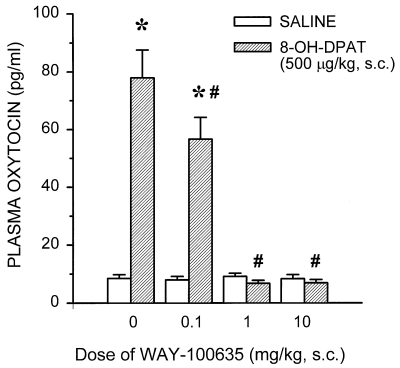

Fig. 1. The effect of increasing doses of WAY-100635 on plasma oxytocin levels in rats challenged with either saline or 8-OH-DPAT (500 μg/kg, s.c.). The blank bars represent rats challenged with saline, while the cross-hatched bars represent rats challenged with 8-OH-DPAT (500 μg/kg, sc). The data represent the mean ± S.E.M. of 8–10 rats per group. Two-Way ANOVA: main effect of WAY-100635, $F(3,57) = 33.0$, $p < 0.01$; main effect of 8-OH-DPAT, $F(1,57) = 84.2$, $p < 0.01$; Interaction between WAY-100635 and 8-OH-DPAT, $F(3,57) = 33.82$, $p < 0.01$. * Significant effect of 8-OH-DPAT, $p < 0.01$; # Significant effect of WAY-100635, $p < 0.01$ (Newman–Keuls' test).

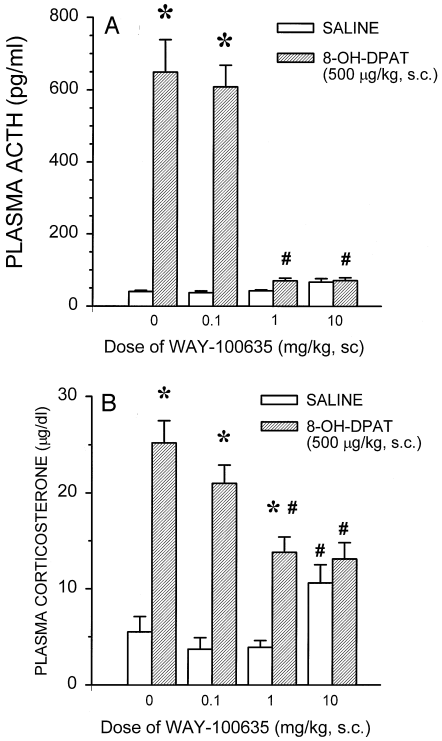

Fig. 2. The effect of increasing doses of WAY-100635 on plasma ACTH (A) and corticosterone (B) levels in rats challenged with either saline or 8-OH-DPAT (500 μg/kg, s.c.). The blank bars represent rats challenged with saline, while the cross-hatched bars represent rats challenged with 8-OH-DPAT (500 μg/kg, sc). The data represent the mean $\pm$ S.E.M. of 8–10 rats per group. The two-Way ANOVA for ACTH: main effect of WAY-100635, $F(3,57) = 36.9$, $p < 0.01$); main effect of 8-OH-DPAT, $F(1,57) = 137.43$, $p < 0.01$; interaction between WAY-100635 and 8-OH-DPAT, $F(3,57) = 41.22$, $p < 0.01$. For corticosterone, the main effect of WAY-100635, $F(2,55) = 51.00$, $p < 0.01$; main effect of 8-OH-DPAT, $F(1,55) = 106.08$, $p < 0.01$; Interaction between WAY-100635 and 8-OH-DPAT, $F(3,55) = 10.47$, $p < 0.01$. * Significant effect of 8-OH-DPAT), $p < 0.01$; # Significant effect of WAY-100635, $p < 0.01$ (Newman–Keuls' test).

In contrast to oxytocin, the lowest dose of WAY-100635 (0.1 mg/kg, s.c.) did not significantly inhibit the ACTH response to 8-OH-DPAT. However, at 1 mg/kg, s.c., WAY-100635 markedly inhibited the 8-OH-DPAT-induced elevation of ACTH by 89.2% (Fig. 2A; $F(3,57) = 41.22$, $p < 0.01$) and the magnitude of ACTH inhibition was comparable at 10 mg/kg of WAY-100635. Basal levels of ACTH were not significantly altered by any dose of WAY-100635. Similar to ACTH, 8-OH-DPAT-stimulated corticosterone secretion was markedly inhibited by 1 mg/kg of WAY-100635 (by 45.24%; $F(3,55) = 10.47$, $p < 0.01$; Fig. 2B), although not to the same extent as the inhibition of the ACTH response. No further inhibition of corticosterone response to 8-OH-DPAT was observed at 10 mg/kg, s.c. of WAY-100635, although basal corticosterone levels were significantly elevated at this dose of WAY-100635.

WAY-100635 did not significantly attenuate the 8-OH-DPAT-induced increase in plasma prolactin concentration

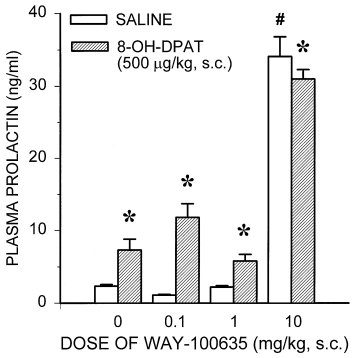

Fig. 3. The effect of increasing doses of WAY-100635 on plasma prolactin levels in rats challenged with either saline or 8-OH-DPAT(500 μg/kg, s.c.). The blank bars represent rats challenged with saline, while the cross-hatched bars represent rats challenged with 8-OH-DPAT (500 μg/kg, sc). The data represent the mean $\pm$ S.E.M. of 8–10 rats per group. Two-Way ANOVA: main effect of WAY-100635, $F(3,52) = 175.8$, $p < 0.01$; main effect of 8-OH-DPAT, $F(1,52) = 15.24$, $p < 0.01$; Interaction between WAY-100635 and 8-OH-DPAT: $F(3,52) = 7.43$, $p < 0.01$. * Significant effect of 8-OH-DPAT, $p < 0.01$; # Significant effect of WAY-100635, $p < 0.01$ (Newman-Keuls' test).

(Fig. 3) at any of the doses tested, but again, the highest dose of WAY-100635 (10 mg/kg, s.c.) dramatically increased basal prolactin levels (1550%; $F(3,52) = 175.8$, $p < 0.01$). Consistent with previous studies, Fig. 4 shows that 8-OH-DPAT does not stimulate renin release when injected alone. However, while WAY-100635 did not elevate basal plasma renin concentration at any of the doses used, at the highest dose of WAY-100635 (10 mg/kg), 8-OH-DPAT significantly elevated plasma renin concentration (285% above basal levels; $F(3,56) = 10.92$, $p < 0.01$).

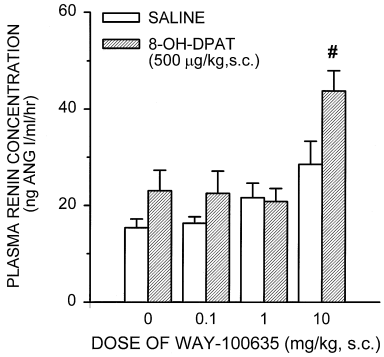

Fig. 4. The effect of increasing doses of WAY-100635 on plasma renin concentration in rats challenged with either saline or 8-OH-DPAT (500 μg/kg, s.c.). The blank bars represent rats challenged with saline, while the cross-hatched bars represent rats challenged with 8-OH-DPAT (500 μg/kg, sc). The data represent the mean $\pm$ S.E.M. of 8–10 rats per group. Two-Way ANOVA: the main effect of WAY-100635, $F(3,56) = 10.93$, $p < 0.01$; main effect of 8-OH-DPAT, $F(1,56) = 7.70$, $p < 0.01$; interaction between WAY-100635 and 8-OH-DPAT, $F(3,56) = 1.92$, NS. # Significant effect of WAY-100635, $p < 0.01$ (Newman–Keuls' test).

4. Discussion

The present study provides evidence that activation of postsynaptic 5-HT_{1A} receptors mediates the effect of 8-OH-DPAT on plasma ACTH, corticosterone and oxytocin, but not prolactin or renin. Previous studies suggested that 8-OH-DPAT increases the secretion of ACTH, corticosterone and oxytocin through activation of postsynaptic 5-HT_{1A} receptors (Gilbert et al., 1988; Fuller and Snoddy, 1990; Bagdy and Kalogeras, 1993; Li et al., 1993). However, definitive evidence for the involvement of 5-HT_{1A} receptors has not been obtained because the only available antagonists were either non-selective for 5-HT_{1A} receptors or had some partial agonist activity.

WAY-100635 is more selective for 5-HT_{1A} receptors than other drugs, as shown in biochemical and electrophysiological studies (Cliffe et al., 1993; Fletcher et al., 1993; Routledge et al., 1993; Escandon et al., 1994; Fornal et al., 1996). In radioligand binding assays, WAY-100635 displayed a high affinity ($pIC_{50} = 8.87$) for 5-HT_{1A} receptors in rat hippocampal membranes (Forster et al., 1995). The affinity of WAY-100635 for 5-HT_{1A} receptors is 100 times higher than its affinity for other receptors (e.g. 5-HT_{1B}, 5-HT_{1D} 5-HT_{2C}, 5-HT_7, dopamine D_1, D_2, D_4) (Forster et al., 1995). WAY-100635 also has appreciable affinity for α_1-adrenoceptors ($pIC_{50} = 6.64$) although this is about 100 times lower than its affinity for 5-HT_{1A} receptors. Therefore, the availability of a selective, high affinity 5-HT_{1A} receptor antagonist provided the means to determine whether low doses of WAY-100635 could antagonize the 8-OH-DPAT-induced stimulation of hormone secretion, indicating the specific involvement of activation of 5-HT_{1A} receptors.

Unlike previously used non-selective 5-HT_{1A} receptor antagonists, lower doses of WAY-100635 did not alter basal levels of oxytocin, ACTH, corticosterone, prolactin or renin. This suggests that at doses up to 1 mg/kg (s.c.), WAY-100635 possesses no agonist activity at 5-HT_{1A} or other monoamine receptors, such as α_1 adrenoceptors. Activation of α_1 receptors stimulates the secretion of ACTH and corticosterone (Takao et al., 1988; Gunion et al., 1992). Our data indicate that WAY-100635 dose-dependently blocked 8-OH-DPAT-induced oxytocin, and inhibited 8-OH-DPAT-induced ACTH and corticosterone secretion. These results suggest that the effect of 8-OH-DPAT on the secretion of oxytocin, ACTH, and corticosterone is mediated via activation of 5-HT_{1A} receptors. When administered in the lowest dose employed in our study, (i.e. 0.1 mg/kg, s.c.), WAY-100635 inhibited only 8-OH-DPAT-induced oxytocin but not ACTH or corticosterone secretion. The higher potency of WAY-100635 in inhibiting oxytocin vs. ACTH and corticosterone responses suggests that there may be a smaller 5-HT_{1A} receptor reserve for 8-OH-DPAT-induced secretion of oxytocin than for ACTH or corticosterone. This can be explained by the fact that neurons in the paraventricular nucleus that mediate the secretion of oxytocin are different from the corticotropin releasing hormone (CRH) neurons that control the secretion of ACTH. 5-HT_{1A} receptors activate magnocellular oxytocin neurons in the hypothalamic paraventricular nucleus to secrete oxytocin from their nerve terminals in the posterior lobe of the pituitary gland into the peripheral circulation (Bagdy and Makara, 1994). In contrast, activation of parvocellular cells in a more medial subregion within the hypothalamic paraventricular nucleus mediates the secretion of ACTH (Bagdy and Makara, 1994; Li et al., 1997a,b). These parvocellular CRH neurons send their projections to the median eminence, from where CRH is then transported via the pituitary portal vessels to the anterior pituitary gland to release ACTH (Taylor and Fishman, 1988). Therefore, 5-HT_{1A} receptors that stimulate oxytocin release may differ from 5-HT_{1A} receptors that stimulate CRH release with regard to the differential receptor/G-protein or G-protein/effector coupling at the levels of both paraventricular nucleus and pituitary gland. Evidence for differential 5-HT_{1A} receptor reserve among the hormone responses to 8-OH-DPAT also is suggested from the difference in magnitude of the attenuation, by WAY-100635, of 8-OH-DPAT stimulated ACTH vs. corticosterone secretion. At the dose of 1 mg/kg, WAY-100635 reduced the ACTH response to almost basal levels while the corticosterone response was reduced to only 45% of control. Our results are in agreement with previous findings (Meller and Bohmaker, 1994) that demonstrate a larger 5-HT_{1A} receptor reserve for corticosterone (80%) than for ACTH (50%) in response to 8-OH-DPAT. Another possibility is that 8-OH-DPAT could trigger peripheral mechanisms at the level of the adrenal gland, in addition to stimulating ACTH secretion, to stimulate the secretion of corticosterone.

Our data also demonstrate that 5-HT_{1A} receptors do not appear to mediate the effect of 8-OH-DPAT on the secretion of prolactin, or at best play only a minor role. Although 8-OH-DPAT stimulates prolactin secretion, WAY-100635 did not significantly inhibit this effect at a dose (1 mg/kg s.c.), that completely blocks the ACTH and oxytocin responses to this 5-HT_{1A} agonist. These data indicate that 5-HT_{1A} receptors may not be involved in 8-OH-DPAT-induced elevation of plasma prolactin. However, at the highest dose of 10 mg/kg, WAY-100635 increased basal prolactin levels. A similar finding was reported by Groenink et al. (1996) who also demonstrated that WAY-100635 could elevate basal prolactin levels. As mentioned previously, WAY-100635 is about 100 times more selective for 5-HT_{1A} receptors than for other indoleamine or catecholamine receptors. Nevertheless, at the high dose there could be a potential role for other receptors in WAY-100635-induced elevation of basal prolactin levels.

Similar to prolactin, the effect of 8-OH-DPAT on renin secretion does not appear to be mediated via 5-HT_{1A} receptors since neither 8-OH-DPAT nor WAY-100635

alone changed basal renin concentration. In addition, the lack of change in basal renin concentration, even after the highest dose of WAY-100635 used in our study argues against an involvement of α_1 adrenoceptors in basal renin release. Although WAY-100635 has a moderate affinity ($pIC_{50} = 6.64$) for this receptor, a potential blockade of α_1 adrenoceptors would induce a surge of renin release because the hypotensive effect of α_1 adrenergic antagonists, such as prazosin, stimulates renin secretion (Cavero and Roach, 1980; Ehmke et al., 1989; Takagi et al., 1992). The inability of 8-OH-DPAT to stimulate renin release was expected since other 5-HT_{1A} agonists did not increase renin release (Van de Kar et al., 1985; Lorens and Van de Kar, 1987; Rittenhouse et al., 1992; Li et al., 1993; Battaglia and Cabrera, 1994; Levy et al., 1995). However, the highest dose (i.e. 10 mg/kg) of WAY-100635 exposed an 8-OH-DPAT stimulation of renin release. It is difficult to deduce from this result whether 8-OH-DPAT affected central or peripheral receptors to cause an increase in renin secretion. Although no evidence exists regarding the potential role of central 5-HT_{1A} receptors in renin release, previous studies (Rittenhouse et al., 1994) suggest a stimulatory role for central 5-HT_2 receptors. If WAY-100635 preferentially blocks 5-HT_{1A} receptors and if these receptors have an inhibitory influence on renin release, this action of WAY-100635 would enable us to observe an effect of 8-OH-DPAT on other 5-HT receptor subtypes or non-serotonergic receptors such as monoamine or peptide receptors. Indeed, 8-OH-DPAT was shown to have partial agonist affinity for both dopamine D_2 ($pK_i = 5.24$) (Smith and Cutts, 1990; Gobert et al., 1995) and dopamine D_1 receptors ($pK_i \leq 5.00$) (Hajós-Korcsok and Sharp, 1996). Since activation of peripheral dopamine D_1 receptors increases renin release (Yamaguchi et al., 1997), WAY-100635 could have exposed an 8-OH-DPAT stimulation of dopamine D_1 receptors which would lead to renin release. However, this is not a very likely possibility because of the very low affinity of 8-OH-DPAT for dopamine D_1 receptors. In addition, 8-OH-DPAT is known to cause a mild hypotension (Dabiré et al., 1990; Kubo et al., 1995), which would also stimulate renin release. Although 8-OH-DPAT does not appear to be stimulatory to renin release through activation of 5-HT_{1A} receptors, it is interesting that chronic drug administration can unmask 8-OH-DPAT-induced renin secretion. For example, chronic treatment of rats with fluoxetine can expose 8-OH-DPAT stimulation of renin release (Li et al., 1993). A similar phenomenon was observed following prenatal exposure to cocaine. In male rat offspring exposed to cocaine in utero, 8-OH-DPAT stimulated renin secretion (Battaglia and Cabrera, 1994). The phenomenon where previous drug treatment reveals a stimulatory effect of 8-OH-DPAT on renin secretion could be only partially explained by 8-OH-DPAT-induced stimulation of monoamine receptors, because the irreversible monoamine receptor inactivator *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) also exposes an increase of renin secretion following challenge injection of 8-OH-DPAT (Van de Kar et al., 1997). Since EEDQ inactivates the majority of monoamine receptors, it is possible that 8-OH-DPAT stimulates renin release through activation of a putative peptidergic receptor that is insensitive to irreversible inactivation with EEDQ.

In conclusion, the present study demonstrates that low doses of WAY-100635 can antagonize the 8-OH-DPAT-induced elevation of plasma oxytocin, ACTH, and corticosterone, indicating that 5-HT_{1A} receptors mediate the secretion of these three hormones. Low doses of WAY-100635 (up to 1 mg/kg s.c.) did not alter basal levels of ACTH, oxytocin and corticosterone, suggesting a lack of agonist activity for this drug at postsynaptic 5-HT_{1A} receptors. In contrast, at the highest dose (10 mg/kg, s.c.), WAY-100635 elevated basal corticosterone and prolactin levels and exposed an 8-OH-DPAT-induced renin release, suggesting that these hormone responses may be influenced via non-5-HT_{1A} receptor mechanisms.

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