ELSEVIER

European Journal of Pharmacology 309 (1996) 281–286

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Adrenaline release by the 5-HT_{1A} receptor agonist 8-OH-DPAT is partly responsible for pituitary activation

S. Mechiel Korte [a,b,*], Bauke Buwalda [a], E. Ronald De Kloet [b], Béla Bohus [a]

[a] *Department of Animal Physiology and Center for Behavioral and Cognitive Neurosciences, University of Groningen, PO Box 14, 9750 AA Haren, Netherlands*

[b] *Division of Medical Pharmacology, Leiden / Amsterdam Center for Drug Research, Sylvius Laboratories, University of Leiden, PO Box 9503, 2300 RA Leiden, Netherlands*

Received 29 January 1996; revised 29 April 1996; accepted 7 May 1996

Abstract

In male Wistar rats the effect of adrenalectomy on pituitary activation by the 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), was studied. Rats were injected intravenously with 8-OH-DPAT (0.10 mg/kg) in their home cages. Blood samples were withdrawn from freely moving cannulated rats for determination of plasma adrenaline and plasma adrenocorticotropin hormone (ACTH). Adrenalectomized rats showed almost no measurable amounts of plasma adrenaline, but these animals had elevated baseline plasma ACTH levels as compared to sham-operated rats. 8-OH-DPAT treatment led to a large plasma adrenaline response in the sham-operated animals, which was abolished after adrenalectomy. The plasma ACTH response to 8-OH-DPAT was significantly diminished in the adrenalectomized rats as compared to sham animals. This blunted ACTH response in adrenalectomized rats, however, was still considerable in magnitude. The present data thus indicate that the plasma ACTH response to 8-OH-DPAT is due to at least two different mechanisms. First, via 5-HT_{1A} receptor-mediated adrenaline release, which may consequently stimulate the pituitary. Second, a direct action of 8-OH-DPAT on hypothalamic 5-HT_{1A} receptors is assumed, independent of peripheral adrenaline release.

Keywords: 5-HT_{1A} receptor; 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin); Adrenaline; Pituitary; ACTH (adrenocorticotrophin)

1. Introduction

Numerous studies have shown that specific ligands with high affinities for discrete 5-HT receptor subtypes, i.e. 5-HT_{1A}, 5-$HT_{2A/2C}$ and 5-HT_3, are able to facilitate the hypothalamic-pituitary-adrenocortical axis-mediated corticosterone release (Bagdy and Makara, 1994; Rittenhouse et al., 1994; Saphier and Welch, 1994; Welch and Saphier, 1994). Administration of the selective 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) intravenously (Chaouloff et al., 1990b; Korte et al., 1995), intraperitoneally (Lorens and Van de Kar, 1987), subcutaneously (Fuller and Snoddy, 1990; Koenig et al., 1987), intracerebroventricularly (Welch and Saphier, 1994) and intrahypothalamically (Haleem et al., 1989; Korte et al., 1991; Welch et al., 1993) increased plasma adrenocorticotropic hormone (ACTH) and subsequently plasma corticosterone concentrations. We found that plasma adrenaline levels, but not noradrenaline levels, were also elevated, suggesting an additional specific adrenomedullary activation (Korte et al., 1991). In addition, ganglionic blocking drugs (e.g. hexamethonium and chlorisondamine) attenuated the 8-OH-DPAT-induced plasma corticosterone response (Chaouloff et al., 1990b; Saphier and Welch, 1994), suggesting that the adrenaline-releasing properties of 8-OH-DPAT may have contributed to the pituitary-adrenocortical activation. Previously, it has been shown that adrenaline administration increases the ACTH release, also suggesting a stimulatory role for adrenaline in pituitary-adrenocortical activity (Rivier and Vale, 1983, 1985; Tilders et al., 1985).

The present study was designed to investigate the possible contribution of the adrenaline-releasing properties of 8-OH-DPAT in the stimulation of the pituitary. Therefore, the effect of 8-OH-DPAT, in the presence or absence of the source of plasma adrenaline by means of adrenalec-

* Corresponding author. Division of Medical Pharmacology, Sylvius Laboratories, University of Leiden, PO Box 9503, 2300 RA Leiden, The Netherlands.

PII S0014-2999(96)00356-1

tomy, on plasma ACTH release was monitored in permanently cannulated freely moving rats.

2. Materials and methods

2.1. Animals

Male Wistar rats ($n = 26$), weighing 290–340 g at the beginning of the experiments, were used. Immediately after surgery the rats were separated and housed individually in Plexiglas cages (25 × 25 × 30 cm; l × w × h) on a 12-h light-dark regimen (light on between 08:00 and 20:00 h). Room temperature was controlled (21 ± 2°C). All animals had free access to standard rat chow and both tap water and saline. The experiments were carried out between 10:00 and 14:00 h.

2.2. Surgery

A silicon heart catheter (0.95 mm o.d. and 0.5 mm i.d.) was inserted through the right jugular vein of the animal, under halothane anaesthesia. This catheter was used for frequent blood sampling in undisturbed, freely moving rats. The subjects were allowed 1 week for post-surgery recovery. The recovered animals were than adrenalectomized between 15:00 and 16:00 h via a dorsal approach under halothane anaesthesia. Only adrenalectomized rats that had a preference for saline were used. The experiments were carried out the next day.

2.3. Drug treatment

The 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), was dissolved in saline. Injections were given intravenously (i.v.) in a dose of 0.10 mg/kg and in a volume of 1.0 ml/kg. The choice of this dose was based upon earlier experiments (Korte et al., 1995).

2.4. Procedure and blood sampling

To study whether 5-HT_{1A} receptor-mediated plasma adrenaline release contributes to pituitary activation, adrenalectomized rats and sham control rats were treated with 8-OH-DPAT or with vehicle in their home cages. The challenge study was performed under resting conditions in the Wistar rats' home cages. 1 h before the start of the experiment the animals were connected to a polyethylene blood sampling tube (0.4 m length, 1.45 mm o.d. and 0.75 mm i.d.). Blood samples of 0.60 ml were withdrawn for determination of plasma adrenaline and plasma ACTH levels. After each blood sample was taken a similar quantity of heparinized donor blood was returned to avoid diminution of the blood volume with related changes in hemodynamics. Donor blood was obtained from unstressed rats with permanent heart catheters. Blood samples were taken twice before drug treatment (i.e. −10 and −1 min) and at $t = 0$ min the animals were injected with 8-OH-DPAT (i.v.). Further blood samples were taken at 5, 10, 15, 20, 25 and 30 min. The rats were treated only once.

2.5. Chemical determinations

Blood samples were immediately transferred to chilled (0°C) centrifuge tubes containing 0.01% EDTA as antioxidant and 2.5 μl aprotinin (125 000 KUI/ml) as anticoagulant. Blood was centrifuged at 4°C for 10 min at 2600 × *g*, and 100 μl of the supernatant was stored at −20°C for ACTH and at −70°C for the adrenaline measurements. Plasma ACTH was determined using a two-site immunometric assay (Allegro HS ACTH, Nichols) with an intra-assay variability of 3.2% and an inter-assay variability of 7.8%. Determination of plasma adrenaline was performed by high-performance liquid chromatography in combination with electrochemical detection. This system included a LKB 2150 pump (LKB instruments, Bromma, Sweden), a Rheodyne injection valve with a 100-μl loop, a 25-cm analytical column (nucleosil C18; Macherey-Nagel, Gimex Ned), held at 40°C by a column stove (LKB), a 5100-A electrochemical detector with a 5020 guard cell and a 5011 high-sensitivity detector cell (ESA), and a BD 41 two-channel flat bed recorder (Kipp). The guard cell potential in front of the injection valve was +450 mV, the potentials of the working electrodes of the detector cell were −50 and +350 mV, respectively. The mobile phase contained 0.034 M citric acid, 0.043 M Na_2HPO_4, 0.07% heptanesulfonic acid-sodium salt, 0.02% EDTA and 3% methanol 97% H_2O (pH 4.1). Absolute detection level for plasma adrenaline was 0.010 ng/ml.

2.6. Statistics

Statistical analysis of neuroendocrine data was carried out with the aid of a two-way analysis of variance (ANOVA) with between (adrenalectomy vs. sham; 8-OH-DPAT vs. vehicle) and repeated (time point) subject factors. In case of significant effects, the ANOVAs were followed by Tukey's multiple range tests. A P level of < 0.05 was considered as significant.

3. Results

3.1. The effects of adrenalectomy on baseline plasma ACTH and adrenaline levels

Fig. 1A,B shows that 18–22 h after sham surgery or adrenalectomy the baseline plasma adrenaline levels were very low (close to limit of detection), but baseline plasma ACTH levels in vehicle-treated adrenalectomized rats were significantly elevated as compared to vehicle-treated

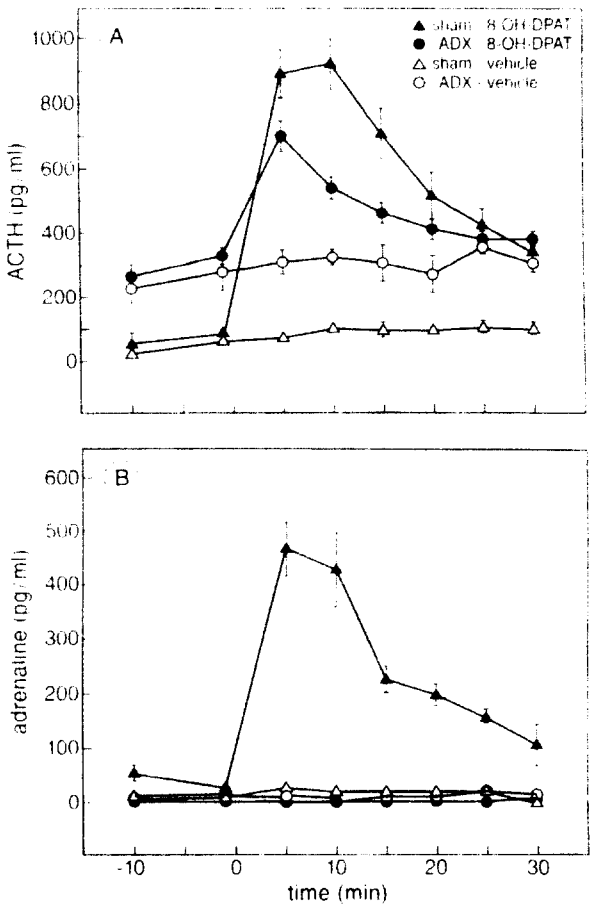

Fig. 1. (A,B) Concentrations (±S.E.M.) of plasma adrenaline and plasma ACTH in adrenalectomized rats (ADX) and sham-operated rats after vehicle or 5-HT_{1A} receptor agonist 8-OH-DPAT treatment (0.10 mg/kg i.v.) under resting conditions.

sham-operated animals during all periods (at least $P < 0.05$).

3.2. The effects of 8-OH-DPAT treatment and adrenalectomy on plasma adrenaline levels

Fig. 1B shows the effects of drug treatment (8-OH-DPAT vs. vehicle) and the effects of surgery (adrenalectomy vs. sham) on plasma adrenaline levels. The ANOVAs revealed a significant effect of drug treatment, $F(1,22) = 92.02$; $P < 0.001$, a significant effect of adrenalectomy, $F(1,22) = 66.27$; $P < 0.001$ and a significant drug treatment × surgery × period effect, $F(7,154) = 22.47$; $P < 0.001$.

In sham-operated rats treatment with 8-OH-DPAT (0.10 mg/kg i.v.) resulted in a significant increase in plasma adrenaline levels as compared to vehicle-treated sham rats from $t = 5$ until $t = 30$ min (at least $P < 0.05$), whereas adrenalectomy abolished the 8-OH-DPAT-induced plasma adrenaline responses during all periods.

3.3. The effects of 8-OH-DPAT treatment and adrenalectomy on plasma ACTH levels

Fig. 1A shows the effects of drug treatment (8-OH-DPAT vs. vehicle) and surgery (adrenalectomy vs. sham) on plasma ACTH levels. The ANOVAs revealed a significant effect of drug treatment, $F(1,22) = 60.77$; $P < 0.001$, a significant effect of adrenalectomy, $F(1,22) = 5.05$; $P = 0.035$ and a significant drug treatment × surgery × period effect, $F(7,154) = 15.44$; $P < 0.001$.

In sham-operated animals treatment with 8-OH-DPAT (0.10 mg/kg i.v.) resulted in a significant increase in plasma ACTH concentrations as compared to vehicle-treated sham controls from $t = 5$ until $t = 30$ min (at least $P < 0.05$).

In adrenalectomized rats 8-OH-DPAT treatment resulted in a significant considerable increase in plasma ACTH response as compared to vehicle-treated adrenalectomized rats from $t = 5$ until $t = 20$ min (at least $P < 0.05$).

In adrenalectomized rats the plasma ACTH response after 8-OH-DPAT challenge was blunted as compared to the one in sham animals at $t = 5$, 10 and 15 min (at least $P < 0.05$).

4. Discussion

4.1. Pituitary activation by different mechanisms

The present study shows that rats, after adrenalectomy, have elevated baseline plasma ACTH levels and have a blunted ACTH response to the 5-HT_{1A} receptor agonist, 8-OH-DPAT. Keller-Wood and Dallman (1984) also have shown that in the absence of the glucocorticoid negative feedback signal, the activity of the hypothalamic-pituitary-adrenocortical axis is increased. It is assumed that the blunted plasma ACTH response in adrenalectomized animals is due to the absence of adrenaline, although 8-OH-DPAT still produced a considerable ACTH response in adrenalectomized rats. Therefore, it is hypothesized that at least two different mechanisms are responsible for the activation of the pituitary by 8-OH-DPAT. First, via an adrenaline-dependent mechanism. Second, via a more direct route, independent of peripheral adrenaline release.

4.2. Adrenaline-dependent mechanism: autonomic pathway

The present study shows that i.v. administered 8-OH-DPAT produced a large increase in plasma adrenaline concentrations, which was accompanied by an increase in plasma ACTH levels in intact animals. The plasma ACTH response was reduced by adrenalectomy, suggesting that adrenaline plays an additional role in the stimulation of the

pituitary. This hypothesis is reinforced by findings of Saphier and Welch (1994), who have shown that the plasma corticosterone response after central administration of high doses of 8-OH-DPAT was attenuated by peripheral 6-hydroxydopamine-sympathectomy, by adrenomedullectomy and by splanchnicectomy. Several studies have reported a parallel activation of the sympatho-adrenomedullary system and the hypothalamic-pituitary-adrenocortical axis after peripheral and hypothalamic administration of high doses of 5-HT_{1A} receptor agonists in conscious rats (e.g. Bagdy et al., 1989; Haleem et al., 1989; Korte et al., 1991; Welch et al., 1993). Both plasma adrenaline as well as plasma ACTH/corticosterone responses were blocked by the 5-HT_{1A} receptor antagonist, (±)-, (−)-pindolol (Chaouloff et al., 1990a; Pan and Gilbert, 1992). The present study and the above-mentioned studies strongly suggest that the 5-HT_{1A} receptor-induced adrenaline release may contribute to the ACTH release, and consequently corticosterone secretion. A possible autonomic pathway involved in the adrenaline-dependent stimulation of the pituitary-adrenocortical axis is postulated. Serotonin via 5-HT_{1A} receptors, located on neurons in the hypothalamus, may ultimately activate the adrenomedullary system (Korte et al., 1991; Liposits et al., 1987). The hypothalamus directly projects to autonomic areas in the brain stem and in the spinal cord (Swanson et al., 1987). These areas are directly connected with the preganglionic sympathetic neurons in the intermediolateral column in the spinal cord and play an important role in the regulation of sympathoadrenal outflow (Sawchenko and Swanson, 1985). In addition, pentobarbital has been demonstrated to block ganglionic neurotransmission (Ho and Harris, 1981) and, consequently, attenuates the plasma adrenaline release (Chaouloff et al., 1990b), the initial vasoconstriction (Bouhelal and Mir, 1990) and the plasma corticosterone response (Welch et al., 1993) to both central and peripheral 8-OH-DPAT. The 5-HT_{1A} receptors involved in 8-OH-DPAT-induced adrenaline release are not necessarily exclusively located in the hypothalamus, because 5-HT_{1A} receptors in brain stem, spinal cord or adrenal medulla also may stimulate adrenaline release (Chaouloff et al., 1990a,b; Strack et al., 1989). Previously, it was reported that adrenaline release into the peripheral circulation of rats can directly stimulate pituitary ACTH release and, consequently, corticosterone release (Rivier and Vale, 1983, 1985; Tilders et al., 1985).

4.3. Indirect reflexive effects

There is a large body of evidence that the 5-HT_{1A} receptor agonists produce cardiovascular responses. High doses 8-OH-DPAT transiently produce vasoconstriction followed by a sustained fall in blood pressure and fall in heart rate (e.g. Bouhelal and Mir, 1990). Saphier and co-workers (Saphier and Welch, 1994; Saphier and Zhang, 1993) suggested that the pituitary-adrenocortical activation is reflexive and secondary to the hypotensive response. The assumption is that the profound hypotension due to 8-OH-DPAT given into the hypothalamic paraventricular nucleus may cause a baroreceptor-mediated activation of ascending noradrenergic pathways, leading to a secondary hypothalamic-pituitary-adrenocortical response (Saphier and Feldman, 1991; Saphier and Welch, 1994). It cannot be excluded that also 5-HT_{1A} receptors on serotonergic cell groups in the brain medulla are involved because microinjection of 8-OH-DPAT into the raphe pallidus raphe magnus also produces profound hypotension (Dreteler, 1991; Valenta and Singer, 1990).

4.4. Adrenaline-independent mechanism: neuroendocrine pathway

The present study shows that 8-OH-DPAT, also in the absence of adrenaline in adrenalectomized animals, produced a considerable plasma ACTH response. An adrenaline-independent mechanism in the activation of the pituitary is suggested. Previously, we and also other laboratories have reported that plasma corticosteroid levels are elevated after central administration of 5-HT_{1A} receptor agonists (Haleem et al., 1989; Korte et al., 1991; Welch et al., 1993). Gilbert et al. (1988) were the first to suggest that central postsynaptic 5-HT_{1A} receptors are involved in hypothalamic-pituitary-adrenocortical axis activation. Pretreatment with the serotonin-synthesis-inhibitor, para-chlorophenylalanine, in rats resulted in near total depletion of brain serotonin content but had no effect on the plasma ACTH rise induced by 8-OH-DPAT. Several studies suggest that 5-HT_{1A} receptors located in the hypothalamus are involved in the activation of the hypothalamic-pituitary-adrenocortical axis. For instance, 8-OH-DPAT, administered into the hypothalamus, elevates plasma corticosterone levels in rats (Haleem et al., 1989; Korte et al., 1991; Welch et al., 1993). In addition, lesions of the hypothalamic paraventricular nucleus prevented 5-HT_{1A} receptor-induced corticosterone release (Bagdy and Makara, 1994), whereas prior administration of a 5-HT_{1A} receptor antagonist, (±)-pindolol, into the hypothalamic paraventicular nucleus attenuated the ACTH release in response to systemically administered 8-OH-DPAT (Pan and Gilbert, 1992). Recently, in our laboratory, it was shown that the 5-HT_{1A} receptor antagonist (+)-WAY100135 (*N*-tert-butyl-3-4(2-methoxyphenyl)piperazin-1-yl-2-phenylpropanamide dihydrochloride) administered into the hypothalamic paraventricular nucleus reduced the plasma corticosterone response during exercise, however, no effect on catecholamine outflow was found (Steffens et al., unpublished observations). This finding did not come by surprise, because in earlier reports we described that a low dose of 8-OH-DPAT (0.05 mg/kg i.v.) increased plasma corticosterone concentrations without changes in plasma adrenaline levels (Korte et al., 1995). The 5-HT_{1A} receptors, mediating the plasma ACTH and

consequent corticosterone response, appear to be located most likely on the corticotropin-releasing hormone (CRH)-synthesizing neurons. However, an indirect activation of these CRH neurons cannot be excluded because the highest density of 5-HT_{1A} receptors are located just above the hypothalamic paraventricular nucleus (Pompeiano et al., 1992). Injection of 8-OH-DPAT into the hypothalamic paraventricular nucleus induces CRH and ACTH release (Pan and Gilbert, 1992). In vitro studies showed that 8-OH-DPAT increased CRH secretion from single explanted hypothalami (Calogero et al., 1989) as well as ACTH release from cultured anterior pituitary preparations (Calogero et al., 1993), suggesting the involvement of 5-HT_{1A} receptors located in both hypothalamus and anterior pituitary. Furthermore, anti-CRH serum partly decreased ACTH and corticosterone responses to 8-OH-DPAT (Calogero et al., 1990). Altogether, these studies strongly suggest that 8-OH-DPAT acts via 5-HT_{1A} receptors on hypothalamic CRH-producing neuronal cell bodies and thereby stimulates CRH secretion into the hypophysial portal system, which in turn induces the anterior pituitary gland to release ACTH into the bloodstream in rat and man.

4.5. Concluding remarks

In humans and rats challenge studies with specific 5-HT receptor ligands are used to study changes in brain 5-HT receptor function. Under the correct conditions this approach is offering a window to the brain. Decreased hypothalamic-pituitary-adrenocortical axis activity after 5-HT_{1A} receptor challenge has been described in humans with unipolar depression and panic disorder (Lesch et al., 1990; Lesch, 1991). A similar result was found in rats 1 day after social defeat (Korte et al., 1995). However, 5-HT_{1A} receptor challenge with a high dose of 8-OH-DPAT, which also elevated plasma adrenaline levels, did not produce such a difference in hypothalamic-pituitary-adrenocortical axis activity (Korte et al., 1990, 1992, 1995). The present study shows that plasma adrenaline plays an additional role in the stimulation of the pituitary. Therefore, knowledge about plasma adrenaline concentrations is required to avoid problems of misinterpretation of hypothalamic-pituitary-adrenocortical axis activity and brain 5-HT_{1A} receptor function

Acknowledgements

This study was supported in part by The Netherlands Organization for Scientific Research (NWO Grant 900-551-057).

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