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European Journal of Pharmacology 333 (1997) 123–128

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Effects of corticosterone on 5-HT_{1A} and 5-HT_2 receptor binding and on the receptor-mediated behavioral responses of rats

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Received 22 April 1997; revised 27 June 1997; accepted 1 July 1997

Abstract

The effects of corticosterone after binding to 5-HT_{1A} and 5-HT_2 receptors were studied in rats. Binding of [^{3}H]8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) to 5-HT_{1A} receptors in the hippocampus decreased 24 h after both acute and chronic (14 day) administration of CORT (50 mg/kg, s.c.). Chronic, but not acute, CORT treatment increased [^{3}H]ketanserin binding to 5-HT_2 receptors in the frontal cortex. Receptor-mediated behavioral responses were also examined following acute and chronic CORT treatment. Flat body posture and hypothermia induced by 8-OH-DPAT, a 5-HT_{1A} receptor agonist, were attenuated following chronic, but not acute, CORT administration. (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), a 5-HT_2 receptor agonist, induced wet-dog shakes, but not hyperthermia and this response was increased 24 h after the chronic administration of CORT. These findings indicate that both 5-HT_{1A} and 5-HT_2 receptor functions were changed following chronic exposure to high levels of CORT. Such changes in these receptor systems may play an important role in the etiology of affective disorders. © 1997 Elsevier Science B.V.

Keywords: Corticosterone; 5-HT_{1A} receptor; 5-HT_2 receptor; Body temperature; 5-HT (5-hydroxytryptamine, serotonin) syndrome; Wet-dog shake

1. Introduction

We previously reported that chronic, but not acute, forced swim stress in rats increased frontal cortical 5-HT_2 receptor levels and the severity of the wet-dog shakes that they mediate (Takao et al., 1995). Since chronic forced swim stress did not alter 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations, the up-regulation of 5-HT_2 receptors does not seem to be due to lower presynaptic serotonergic activity following stress. In our previous paper, we could not explain the precise mechanisms of the up-regulation of 5-HT_2 receptors.

Stress has been shown to alter endocrine functions in the hypothalamic–pituitary–adrenal axis. Forced swim stress results in increased serum corticosterone levels in rats (Abel and Hannigan, 1992). One possible mechanism by which chronic forced swim stress up-regulates 5-HT_2 receptors is that increased plasma corticosterone levels after stress may change 5-HT_2 receptor function. In our previous study (Takao et al., 1995), we concluded that 5-HT_2 receptors may be closely related to responses to chronic forced swim stress in rats, which may be a model of some depressive conditions in animals.

The recent discovery of multiple biochemical and functional subtypes of 5-HT receptors has given new impetus to studies investigating the function of 5-HT in affective disorders (Cowen, 1991; Peroutka, 1988). The 5-HT receptor subtypes, particularly 5-HT_{1A} and 5-HT_2 receptors, have been postulated to play an important role in the pathogenesis of depression. Additionally, the 5-HT_2 receptor partial agonists, ipsapirone and gepirone (Heller et al., 1990; Jenkins et al., 1990) and the 5-HT_2 receptor antagonist, ritanserin (Reyntjens et al., 1986), are proposed to have antidepressant activity. These findings suggest that there is a malfunction in serotonergic neural transmission, particularly that mediated by 5-HT_{1A} and 5-HT_2 receptors, in patients with affective disorders.

The action of steroid hormones in the regulation of 5-HT function is of continuing psychoneuroendocrine interest in view of the hypercortisolism typical of affective disorders (Christie et al., 1986) and the marked effect of

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tricyclic antidepressants on hippocampal glucocorticoid receptors (Seckl and Frick, 1992).

This study was designed to investigate the effect of acute and prolonged exposure to elevated levels of corticosterone on the binding capacity of 5-HT_{1A} and 5-HT_2 receptors and on their receptor-mediated behavioral responses in rats.

2. Materials and methods

2.1. Animals

Male Wistar rats, weighing 150–200 g (Charles River Japan, Yokohama), were used. They were housed in groups of 5 under controlled temperature (23 ± 3°C) and lighting conditions (dark period 20.00–8.00 h), with free access to food and water.

2.2. Corticosterone administration

Corticosterone-21 acetate was suspended in 0.5% methylcellulose. The suspension at a dose of 50 mg/kg was injected subcutaneously in rats for 1 day or 14 days. Control animals only received the 0.5% methylcellulose vehicle. 24 h after administration of the last dose of CORT the plasma CORT levels were measured. Then the animals were killed for the receptor binding assay and the behavioral studies were carried out.

2.3. Measurement of plasma CORT

Plasma CORT levels were measured using a commercially available radio-immunoassay (RIA) kit (ICN Biomedicals).

2.4. Receptor binding assay

2.4.1. Preparation of membranes

24 h after administration of the last dose of CORT, the animals were killed by decapitation and their brains were removed. The hippocampus and frontal cortex were dissected out and stored at −80°C. The frozen tissues were thawed and homogenized in 0.32 M sucrose in a Polytron homogenizer (setting 7, 10 s). The homogenate was centrifuged at $1000 \times g$ for 10 min and the supernatant was collected and recentrifuged at $50\,000 \times g$ for 20 min. The resultant pellet was resuspended in 50 mM Tris–HCl buffer (pH 7.4 at 25°C) and incubated at 37°C for 15 min. The tissue suspension was recentrifuged at $50\,000 \times g$ for 20 min. The pellet was resuspended in 50 mM Tris–HCl buffer (about 1 mg/ml protein) and stored at −80°C until assayed.

2.4.2. 5-HT_{1A} receptors

5-HT_{1A} receptors were measured, using [^{3}H]8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), according to the method of Schlegel and Peroutka (1986). Aliquots (200 μl) of the hippocampal tissue suspension were incubated in duplicate at 30°C for 30 min with 100 μl of 50 mM Tris–HCl buffer containing 4 mM $CaCl_2$, 10 μM pargyrine, 0.1% ascorbic acid (pH 7.4 at 25°C) and 1 nM [^{3}H]8-OH-DPAT and 700 μl of buffer. Non-specific binding was defined with 10 μM 5-HT.

2.4.3. 5HT_2 receptors

5-HT_2 receptors were measured, using [^{3}H]ketanserin, according to the method of Leysen et al. (1982). Aliquots (200 μl) of the frontal cortical tissue suspension were incubated in duplicate at 37°C for 15 min with 100 μl of 50 mM Tris–HCl buffer (pH 7.4 at 25°C) containing 0.5 nm [^{3}H]ketanserin and 700 μl of buffer. Non-specific binding was defined with 1 μM methylsergide.

2.5. Measurement of 5-HT_{1A} receptor-mediated behavioral responses

8-OH-DPAT-induced hypothermia and flat body posture were observed in the same animal 24 h after administration of the last dose of CORT. Two animals were put into clear plastic cages ($370 \times 220 \times 195$ mm) at an ambient temperature of 23 ± 1°C for at least 2 h before drug administration. Their body temperatures were measured with a thermistor probe (connected to an electronic thermometer) inserted 2 cm into the rectum. Temperatures were measured immediately before drug administration. The animals were then treated with 8-OH-DPAT (0.3 mg/kg, s.c.) and returned to their cages. Flat body posture observation periods of 1 min were initiated 5 min after the drug injection and this observation was repeated every 5 min over a period of 30 min. Flat body posture was scored, using the ranked intensity scale (0 = absent, 1 = equivocal, 2 = present, 3 = marked) described by Tricklebank et al. (1984). Scores were summed for 6 observation periods. Body temperature was measured again 30 min following drug administration. The hypothermic response to 8-OH-DPAT was calculated from the decrease in body temperature following drug administration.

2.6. Measurement of 5-HT_2 receptor-mediated behavioral responses

(±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced hyperthermia and wet-dog shakes were induced in the same animal 24 h after administration of the last dose of CORT. Adaptation to the environment and measurement of the body temperature were used to gauge 5-HT_{1A} receptor-mediated behavioral responses.

The animals were treated with (±)-DOI (1 mg/kg, s.c.) and returned to their cages. Immediately after injection, the number of wet-dog shakes was recorded over a 30-min period, as reported previously (Bedard and Pycock, 1977). Body temperature was measured again 30 min following (±)-DOI administration. The hyperthermic re-

sponse to (±)-DOI is presented as the decrease in body temperature following drug administration.

2.7. Chemicals

Corticosterone-21-acetate was purchased from Sigma. [^{3}H]8-OH-DPAT (6086.5 GBq/mmol) and [^{3}H]ketanserin (2220.0 GBq/mmol) were purchased from New England Nuclear. 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) and (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) hydrochloride were purchased from Research Biochemicals International.

2.8. Statistics

The receptor binding assay data were analyzed with the Dunnett test. For flat body posture and wet-dog shakes, the data were analyzed with the Wilcoxon test. Temperature change data were analyzed with one-way analysis of variance (ANOVA) followed by Student's *t*-test.

3. Results

3.1. Changes in plasma CORT

Both acute and chronic CORT (50 mg/kg) treatment significantly increased the plasma CORT levels (intact control = 17.9 ± 4.8 μg/dl, acute CORT = 46.4 ± 4.1 μg/dl, chronic CORT = 45.7 ± 3.6 μg/dl).

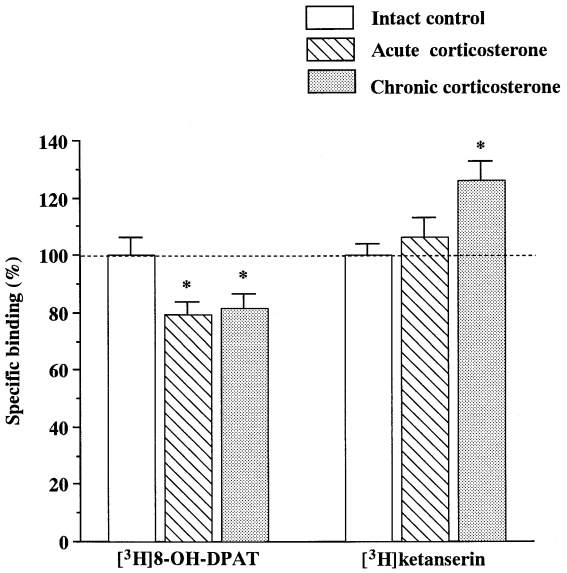

Fig. 1. Effects of acute and chronic treatment with corticosterone on 5-HT$_{1A}$ and 5-HT$_2$ receptors. We used [^{3}H]8-OH-DPAT and [^{3}H]ketanserin to label 5-HT$_{1A}$ and 5-HT$_2$ receptor binding sites, respectively. Values, the means ± S.E. for 8 rats, represent the percentages of specific binding in the control rats ([^{3}H]8-OH-DPAT; 110.9 ± 7.0, [^{3}H]ketanserin; 92.2 ± 3.6 fmol/mg protein). * $P < 0.05$.

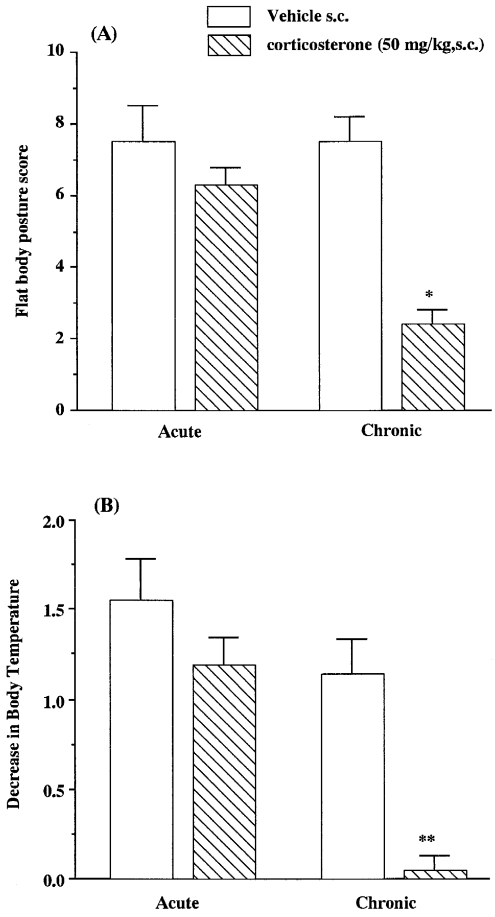

Fig. 2. Effects of acute and chronic corticosterone treatment on flat body posture (A) and the decrease in body temperature (B) induced by 8-OH-DPAT (0.3 mg/kg, s.c.). Values are the means ± S.E. for 7 to 8 rats. * $P < 0.05$; ** $P < 0.01$.

3.2. Changes in 5-HT$_{1A}$ and 5-HT$_2$ receptor binding

Both acute and chronic CORT treatment significantly decreased the binding of [^{3}H]8-OH-DPAT to 5-HT$_{1A}$ receptors in hippocampal membranes (Fig. 1). The binding of [^{3}H]ketanserin to 5-HT$_2$ receptors in the frontal cortex was significantly increased following chronic, but not acute, CORT administration.

3.3. Changes in 5-HT$_{1A}$ and 5-HT$_2$ receptor-mediated behavioral responses

Chronic administration of CORT significantly attenuated the 5-HT$_{1A}$ receptor agonist 8-OH-DPAT-induced flat body posture, while acute CORT treatment tended to, but did not do so significantly (Fig. 2A). 5-HT$_2$ receptor agonist (±)-DOI-induced wet-dog shakes were significantly prolonged following chronic CORT treatment, but acute CORT treatment did not increase this significantly (Fig. 3A).

In animals chronically treated with the solvent vehicle, the administration of 8-OH-DPAT produced a hypothermic

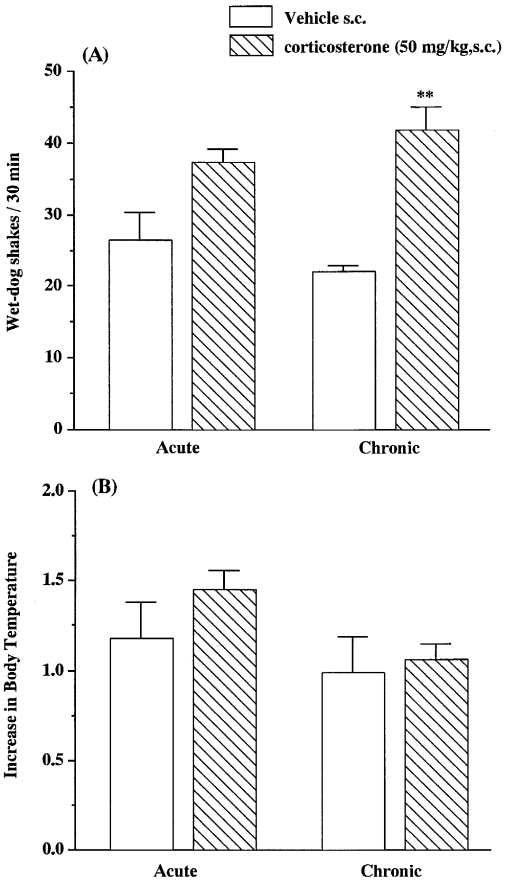

Fig. 3. Effects of acute and chronic treatment with corticosterone on wet-dog shakes (A) and the increase in body temperature (B) induced by (±)-DOI (1 mg/kg, s.c.). Values are means ± S.E. for 8 rats. ** $P < 0.01$.

response ($P < 0.01$ versus vehicle treated animals (0.39 ± 0.09°C)) whereas the administration of (±)-DOI produced hyperthermia ($P < 0.01$ versus vehicle-treated animals (0.34 ± 0.05°C)). Chronic administration of CORT significantly attenuated 8-OH-DPAT-induced hypothermia, while acute CORT treatment tended to, but did not do so significantly (Fig. 2B). (±)-DOI-induced hyperthermia was slightly, but not significantly, prolonged following acute CORT treatment, while behavior was not altered after chronic CORT administration (Fig. 3B).

4. Discussion

In this study, we demonstrated that hypercorticism, which raises circulating corticosterone levels, produced changes in brain serotonergic neural function, affecting the 5-HT_{1A} and 5-HT_2 receptor systems, in rats.

In binding assay studies, hypercortisolism decreased 5-HT_{1A} receptor binding in hippocampal membranes, while it increased 5-HT_2 receptor binding in the frontal cortex. CORT has been shown to alter presynaptic serotonergic neurotransmission, which may affect postsynaptic 5-HT_{1A} and 5-HT_2 receptor function. For example, adrenalectomy, which decreases plasma CORT levels, results in anatomically specific decreases in indices of 5-HT metabolism, while stressful procedures, which raise CORT levels, produce corresponding increases in 5-HT turnover (Curzon et al., 1972; Van Loon et al., 1981). The activity of tryptophan hydroxylase, the rate-limiting 5-HT biosynthetic enzyme, appears to be sensitive to circulating CORT levels (Singh et al., 1990).

Chronic forced swim stress, which has been reported to increase CORT levels (Abel and Hannigan, 1992), did not alter the concentration of 5-HT and 5-hydroxyindole acetic acid (5-HIAA) in the rat frontal cortex, while it increased the number of 5-HT_2 receptors (Takao et al., 1995). A similar response, the up-regulation of 5-HT_2 receptors without any change in presynaptic serotonergic neurotransmission, has been reported after the chronic administration of adrenocorticotropic hormone (ACTH) (Kuroda et al., 1992). A recent autoradiographic study found that chronic exposure to high levels of CORT decreased binding at 5-HT_{1A} receptors in the hippocampus in the rat (Mendelson and McEwen, 1992). Using in situ hybridization techniques, the expression of 5-HT_{1A} receptor mRNA in the hippocampus was found to be increased after adrenalectomy, while it was decreased after chronic CORT treatment, given by means of a subcutaneously implanted CORT pellet (Chalmers et al., 1993; Meijer and Kloet, 1994). These reports suggest that CORT may act by directly regulating 5-HT_{1A} and 5-HT_2 receptors, without modulating presynaptic serotonergic neurotransmission. Further investigation of the mechanisms by which CORT treatment alters 5-HT_{1A} and 5-HT_2 receptor binding in rats has been carried out.

To corroborate the results from these binding studies, central 5-HT_{1A} and 5-HT_2 receptor functions in vivo were evaluated by measuring the receptor-mediated behavioral responses induced by the receptor agonists 8-OH-DPAT and (±)-DOI. The flat body posture induced by 8-OH-DPAT and wet-dog shakes induced by (±)-DOI are accepted to be 5-HT_{1A} and 5-HT_2 receptor-mediated, respectively (Tricklebank et al., 1984; Heaton et al., 1988). 8-OH-DPAT-induced hypothermia and (±)-DOI-induced hyperthermia in the rat are also accepted to reflect 5-HT_{1A} and 5-HT_2 receptor function, respectively (Hjorth, 1985; Pranzatelli, 1990).

In this study, chronic, but not acute, CORT treatment significantly decreased both 8-OH-DPAT-induced flat body posture and hypothermia in rats. Our results are consistent with earlier findings showing the attenuation of the behavioral syndrome in rats treated with CORT (50 mg/kg, s.c. 2 × daily) for 4 or 5 days induced by the non-selective 5-HT agonist, 5-methoxy-*N*,*N*-dimethyltryptamine (Dickinson et al., 1985) or by the 5-HT_{1A} selective agonist, 8-OH-DPAT (Haleem, 1992). Young et al. (1992) also observed the attenuation of the hypothermic response to 8-OH-DPAT after pre-treatment with CORT for 10 days,

but not for 3 days. The reduction of 5-HT_{1A} receptor-mediated behavioral responses following chronic CORT treatment may be explained by the decrease in 5-HT_{1A} receptor binding. However, acute CORT significantly decreased 5-HT_{1A} receptor binding, but did not significantly alter its receptor-mediated behavioral responses. These results suggests that a time lag exists between changes in 5-HT_{1A} receptors and the behavioral responses.

In our study, chronic CORT treatment increased both 5-HT_2 receptor binding and the wet-dog shakes induced by (±)-DOI, while acute CORT treatment tended to, but did not do so significantly. A similar response, the up-regulation of 5-HT_2 receptors, has been reported after the chronic administration of adrenocorticotropic hormone (ACTH) (Kuroda et al., 1992). Experiments following on from our previous study (Takao et al., 1995) showed that (±)-DOI-induced wet-dog shakes increased after acute and chronic treatment, as well as after forced swim stress, while frontal cortical 5-HT_2 receptor levels increased after chronic, but not acute stress.

Although 5-HT_2 receptor binding and receptor-mediated wet-dog shakes increased following chronic CORT treatment, the hyperthermia response which this receptor mediates was unchanged by this treatment. The regulation of temperature is primarily controlled by hypothalamic neurons, while the increase in 5-HT_2 receptor binding and wet-dog shakes were demonstrated in the frontal cortex and spinal cord, respectively (Fone et al., 1991). Autoradiographic studies demonstrated that [^{125}I]DOI binding to 5-HT_2 receptors is generally sparse in the rat hypothalamus (Appel et al., 1990). Thus it is possible that the few 5-HT_2 receptors mediating (±)-DOI-induced hyperthermia are not up-regulated following either acute or chronic CORT treatment. Changes in 5-HT_{1A} and 5-HT_2 receptor binding, both in the spinal cord and hypothalamus, after CORT administration need to be investigated further.

5-HT malfunctions, particularly in 5-HT_{1A} and 5-HT_2 receptors, are often seen in human depression. The density of 5-HT_2 receptor binding sites was found to be increased in the postmortem brains of depressed patients and suicide victims (Arango et al., 1990; Arora and Meltzer, 1989), as well as in the platelets of drug-free depressed patients (Pandey et al., 1990). 5-HT_2 receptor-stimulated calcium mobilization is increased in the platelets of patients with major depression (Kusumi et al., 1991). There have been few studies of 5-HT_{1A} receptor binding sites (Cheetham et al., 1990; Matsubara et al., 1991), although recently the sub-sensitivity of the 5-HT_{1A} receptor-mediated hypothermic response to ipsapirone and buspirone was reported in patients with unipolar depression (Lesch et al., 1990; Cowen et al., 1994). These clinical studies suggest that down-regulation of 5-HT_{1A} receptors and up-regulation of 5-HT_2 receptors are important in the pathogenesis of depression.In summary, down-regulation of 5-HT_{1A} receptors and up-regulation of 5-HT_2 receptors occurred following chronic, but not acute CORT treatment.

Further work is in progress to study how hypercortisolism affects the regulation of these receptors. Such studies may help to elucidate the pathophysiology and pathogenesis of depression.

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