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Effects of monoamine reuptake inhibitors on wet-dog shakes mediated by 5-HT_{2A} receptors in ACTH-treated rats

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Abstract

We examined the influence of imipramine, a serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor, desipramine, a NA reuptake inhibitor, bupropion, a dopamine reuptake inhibitor, fluvoxamine, a selective 5-HT reuptake inhibitor, and mazindol, a catecholamine reuptake inhibitor, on a 5-HT_{2A} receptor-mediated behavior, (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced wet-dog shakes, in naive and adrenocorticotropic hormone (ACTH)-treated rats. Chronic administration of imipramine, desipramine and mazindol suppressed the number of wet-dog shakes in naive rats. Chronic ACTH (100 μg/rat, s.c.) treatment increased the number. Chronic administration of imipramine did not decrease the number of wet-dog shakes in ACTH-treated rats. On the other hand, desipramine and mazindol inhibited the increase in wet-dog shakes in ACTH-treated rats. Fluvoxamine and bupropion did not have any effect on the (±)-DOI-induced response in naive and ACTH-treated rats. NA reuptake inhibitors may improve the hyperfunction of 5-HT_{2A} receptors induced by chronic ACTH treatment.

Keywords: Imipramine; DOI; Desipramine; Mazindol; Fluvoxamine; Bupropion; ACTH; 5-HT_{2A} receptor; Wet-dog shake

1. Introduction

It is well documented that antidepressants, monoamine reuptake inhibitors, affect serotonin (5-HT)$_{2A}$ receptors in neurochemical and behavioral studies. It has been reported that the repeated administration of monoamine reuptake inhibitors induced a decrease in the density of 5-HT_{2A} receptors in naive rats (McDonald et al., 1984; Peroutka and Snyder, 1980a,b). Several lines of evidence suggested that there are functional interactions between 5-HT_{2A} receptors and the monoaminergic system.

The hypothalamic–pituitary–adrenal (HPA) axis has been postulated to play an important role in the function of 5-HT_{2A} receptors. We have previously reported that chronic administration of corticosterone and adrenocorticotropic hormone (ACTH) potentiates (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced wet-dog shaking behavior, which is mediated via activation of the 5-HT_{2A} receptor (Takao et al., 1997; Kitamura et al., 2002). Kuroda et al. (1992) have reported that, in rats, chronic ACTH treatment increases the binding of [^{3}H]ketanserin to 5-HT_{2A} receptors in the forebrain neocortex and chronic administration of corticosterone increases the density of this receptor. Namely, activating the HPA axis changed the function of the 5-HT_{2A} receptor. As we used naive rats in previous studies, a model of the hyperfunction of 5-HT_{2A} receptors induced by chronic treatment with ACTH is interesting from the viewpoint of receptor function. We previously reported that the administration of imipramine, a 5-HT and noradrenaline (NA) reuptake inhibitor, for 14 days attenuated a 5-HT_{2A} receptor-mediated behavior, (±)-DOI-induced wet-dog shakes, in naive rats. Chronic ACTH

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treatment increased the wet-dog shake response induced by (±)-DOI. This effect of ACTH, increasing the (±)-DOI-induced wet-dog shakes, was not inhibited by a chronic administration of imipramine (Kitamura et al., 2002). The reason why chronic administration of imipramine did not inhibit the increase in (±)-DOI-induced wet-dog shakes in ACTH-treated rats is unknown. Also, the mechanism by which the hyperfunction of 5-HT_{2A} receptors is inhibited by certain types of monoamine reuptake inhibitors remains to be elucidated. To the best of our knowledge, there is no published data on the effect of selective 5-HT or NA reuptake inhibitors and dopamine (DA) reuptake inhibitors on 5-HT_{2A} receptor-mediated behavior in ACTH-treated rats.

Therefore, we examined the effect on (±)-DOI-induced wet-dog shaking behavior of the NA and 5-HT reuptake inhibitor imipramine, the NA reuptake inhibitor desipramine, the selective 5-HT reuptake inhibitor (SSRI) fluvoxamine, the DA reuptake inhibitor bupropion and the catecholamine reuptake inhibitor mazindol, following chronic administration of ACTH for 14 days in rats. We discuss the involvement of NA, 5-HT and DA in these 5-HT_{2A} receptor-mediated behavioral responses.

2. Materials and methods

2.1. Animals

Male Wistar rats (Charles River, Japan) with initial weights of 180–230 g were utilized. The rats were kept on a constant light–dark cycle (lights on: 07:00–19:00 h), with standard laboratory food and tap water in a climate-controlled environment (23 ± 1 °C with approximately 60% humidity). We abided by the guidelines on animal experimentation of Okayama University Graduate School of Medicine and Dentistry, and all procedures were licensed by the institutional animal experimentation review committee.

2.2. Drugs

The following drugs were used: imipramine hydrochloride (Wako Pure Chemical, Tokyo, Japan), desipramine hydrochloride (Sigma-Aldrich Co., St. Louis, MO), mazindol (Novartis Pharma Co., Basel, Switzerland), fluvoxamine maleate (Solvay Pharmaceutical Co., Brussels, Belgium), bupropion hydrochloride (Sigma-Aldrich Co.), (±)-DOI (Sigma-Aldrich Co.), ketanserin tartrate (Research Biochemicals Inc., Natick, Mass.) and ACTH-(1–24)-zinc (Cortrosyn-Z: Daiichi Pharmaceutical, Tokyo, Japan). (±)-DOI, imipramine, desipramine, bupropion and ketanserin were dissolved in saline. Mazindol and fluvoxamine were suspended in a 0.5% methylcellulose solution. Rats were injected with imipramine, desipramine, mazindol, fluvoxamine, bupropion, ketanserin and (±)-DOI at 2 ml/kg body weight. ACTH (Cortrosyn-Z) was injected subcutaneously once daily (9:00 to 10:00) at a dose of 100 μg/rat (injection volume was 0.2 ml/rat, s.c.) for 14 days. The vehicle was saline injected at 0.2 ml/rat (s.c.). Control rats received an equivalent volume of vehicle for the same duration.

2.3. Experimental procedures

2.3.1. Measurement of (±)-DOI-induced wet-dog shakes and effect of ketanserin

Rats were placed in individual clear polycarbonate home cages (35 × 30 × 17 cm) and treated with (±)-DOI (0.3–3 mg/kg, s.c.). Immediately after injection, the number of wet-dog shakes was recorded over a 30-min period, as described previously (Bedard and Pycock, 1977). Ketanserin (0.03–0.3 mg/kg, i.p.) was administered 15 min before the (±)-DOI (1 mg/kg, s.c.) treatment. The observers were blinded to the drug administrations.

2.3.2. Effects of chronic administration of imipramine, desipramine, mazindol, fluvoxamine and bupropion for 14 days on (±)-DOI-induced wet-dog shakes in naive rats

Rats were administered imipramine (1–10 mg/kg, i.p.), desipramine (1–10 mg/kg, i.p.), mazindol (0.1–1 mg/kg, i.p.), fluvoxamine (10–30 mg/kg, i.p.) and bupropion (10 mg/kg, i.p.) once daily for a period of 14 days. The (±)-DOI (1 mg/kg, s.c.)-induced wet-dog shaking response was recorded 1 day after the final administration of imipramine, desipramine, mazindol, fluvoxamine and bupropion.

2.3.3. Effects of chronic administration of imipramine, desipramine, mazindol, fluvoxamine and bupropion for 14 days on (±)-DOI-induced wet-dog shakes in ACTH-treated rats

ACTH (100 μg/rat, s.c.) was administered in combination with imipramine (1–10 mg/kg, i.p.), desipramine (1–10 mg/kg, i.p.), mazindol (0.1–1 mg/kg, i.p.), fluvoxamine (10–30 mg/kg, i.p.) and bupropion (10 mg/kg, i.p.) once daily for a period of 14 days. The number of (±)-DOI (1 mg/kg, s.c.)-induced wet-dog shakes was recorded 1 day after the final administration of ACTH and imipramine, desipramine, mazindol, fluvoxamine or bupropion.

2.4. Statistics

All values are expressed as means ± S.E.M. All data were analyzed using Student's *t*-test or the one-way analysis of variance (ANOVA). The group means were compared with Dunnett's test for multiple comparisons.

3. Results

3.1. (±)-DOI-induced wet-dog shakes and effect of ketanserin

(±)-DOI (0.3–3 mg/kg, s.c.) produced a dose-dependent increase in wet-dog shakes [$F(3.16) = 17.82$, $P < 0.0001$

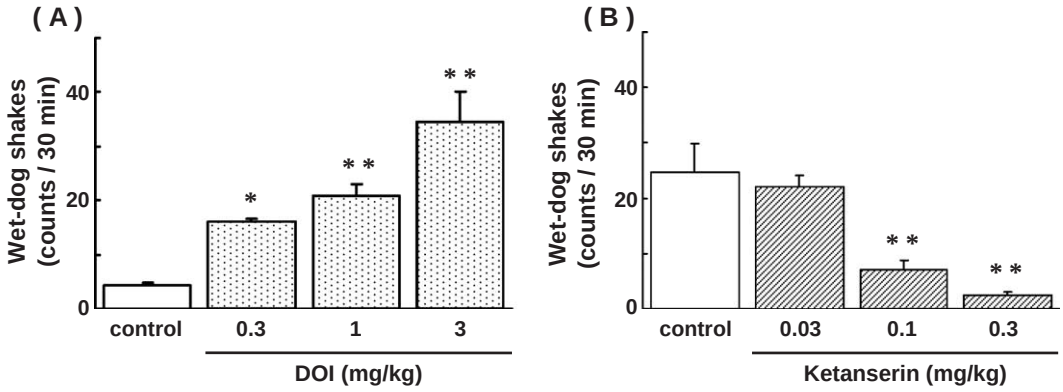

Fig. 1. Measurement of (±)-DOI-induced wet-dog shakes and effect of ketanserin. Rats were administered (±)-DOI (0.3–3 mg/kg, s.c.) and returned to their cages. Immediately after injection, the number of wet-dog shakes was recorded over a 30-min period. All values are expressed as the mean±S.E.M. for five animals per group (A). Ketanserin (0.03–0.3 mg/kg, i.p.) was administered 15 min before (±)-DOI (1 mg/kg, s.c.). All values are expressed as the mean±S.E.M. for six animals per group (B). Data were analyzed by one-way ANOVA, followed by Dunnett's test. $^{**}P<0.01$, significant difference from the control value. $^{*}P<0.05$, significant difference from the control value.

(Fig. 1A)]. Ketanserin (0.03–0.3 mg/kg, i.p.) reduced the number of wet-dog shakes induced by (±)-DOI (1 mg/kg, s.c.) in a dose-dependent manner [$F(3.20)=16.40$, $P<0.001$ (Fig. 1B)].

3.2. Effects of chronic administration of imipramine, desipramine, mazindol, fluvoxamine and bupropion on (±)-DOI-induced wet-dog shakes in rats

Chronic administration of imipramine (1–10 mg/kg, i.p.), desipramine (1–10 mg/kg, i.p.) and mazindol (0.1–1 mg/kg, i.p.) for a period of 14 days significantly decreased the number of (±)-DOI-induced wet-dog shakes [imipramine: $F(3.20)=10.29$, $P<0.01$ (Fig. 2A); desipramine: $F(3.20)=7.75$, $P<0.05$ (Fig. 2B); mazindol: $F(3.20)=3.43$, $P<0.05$ (Fig. 2C)]. Chronic administration of fluvoxamine (10–30 mg/kg, i.p.) and bupropion (10 mg/kg, i.p.) for 14 days had no effect [fluvoxamine (Fig. 2D), bupropion (Table 1)].

3.3. Effects of chronic administration of imipramine, desipramine, mazindol, fluvoxamine and bupropion on (±)-DOI-induced wet-dog shakes in ACTH-treated rats

The number of (±)-DOI-induced wet-dog shakes was increased in ACTH-treated rats compared to saline-treated rats. This increase was not affected by the chronic administration of imipramine (1–10 mg/kg, i.p.) [$F(3.20)=0.03$, $P>0.05$ (Fig. 3A)]. On the other hand, chronic administration of desipramine (1–10 mg/kg, i.p.) and mazindol (0.1–1 mg/kg, i.p.) for a period of 14 days significantly reduced the number of (±)-DOI-induced wet-dog shakes in rats treated with ACTH (100 μg/rat, s.c.) [desipramine: $F(3.20)=3.27$, $P<0.05$ (Fig. 3B); mazindol: $F(3.20)=6.61$, $P<0.01$ (Fig. 3C)]. Chronic administration of fluvoxamine (10–30 mg/kg, i.p.) and bupropion (10 mg/kg, i.p.) for 14 days did not alter the number of wet-dog shakes induced by (±)-DOI when given concurrently with ACTH (100 μg/rat, s.c.) [fluvoxamine (Fig. 3D), bupropion (Table 1)].

4. Discussion

In the present experiment, we confirmed that the administration of imipramine, a NA and 5-HT reuptake inhibitor, for 14 days significantly decreased the number of (±)-DOI-induced wet-dog shakes in naive rats. The chronic administration of imipramine is known to reduce the density of 5-HT_{2A} receptors (Peroutka and Snyder, 1980a,b). We confirmed this phenomenon using behavioral pharmacology in the present study. The chronic administration of desipramine also significantly decreased the (±)-DOI-induced response in naive rats. Although desipramine is a selective NA reuptake inhibitor, it reduces the number of (±)-DOI-induced wet-dog shakes. It is conceivable that NA modifies the function of the 5-HT_{2A} receptor. Eison et al. (1991) reported that the chronic administration of desipramine attenuated the 5-HT_{2A} receptor-mediated quipazine-induced head shaking response in rats. It has been well established that chronic administration of desipramine results in a down-regulation of 5-HT_{2A} receptor activity in rats (Bergstrom and Kellar, 1979; Eison et al., 1991; Peroutka and Snyder, 1980a,b). The mechanism behind this effect of desipramine has been suggested to be the enhancement of noradrenergic transmission from the locus coeruleus nucleus to the dorsal raphe nucleus (Lafaille et al., 1991). This mechanism would result in an increase in raphe cell firing and concomitant increase in the release of 5-HT in cortical regions of the brain. The subsensitivity of the 5-HT_{2A} receptor, characterized by a decrease in 5-HT_{2A} receptor density, may occur after chronic administration of desipramine (Lafaille et al., 1991). The chronic admin-

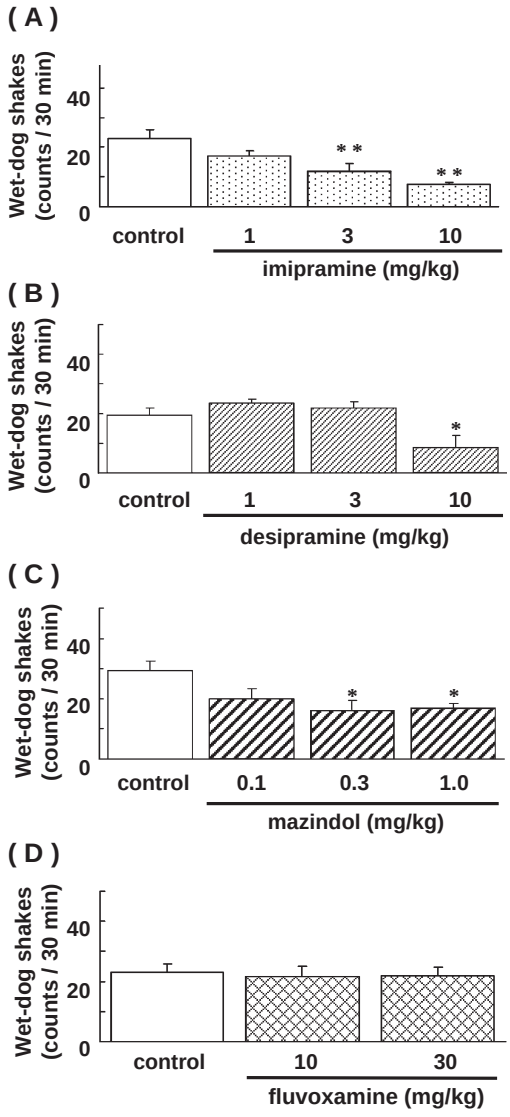

Fig. 2. Effects of chronic administration of imipramine, desipramine, mazindol and fluvoxamine for 14 days on (±)-DOI-induced wet-dog shakes in naive rats. Rats were administered imipramine (1–10 mg/kg, i.p.), desipramine (1–10 mg/kg, i.p.), mazindol (0.1–1 mg/kg, i.p.) and fluvoxamine (10–30 mg/kg, i.p.) once daily for a period of 14 days. Control rats were treated with saline (2 ml/kg, i.p.) once daily for 14 days. The number of (±)-DOI-induced wet-dog shakes was recorded 1 day after the final administration of imipramine, desipramine, mazindol and fluvoxamine. Rats were treated with (±)-DOI (1 mg/kg, s.c.) and returned to their cages. All values are expressed as the mean±S.E.M. for six animals per group. Data were analyzed by one-way ANOVA, followed by Dunnett's test. $^{**}P<0.01$, significant difference from the control value. $^{*}P<0.05$, significant difference from the control value.

istration of mazindol also significantly decreased the number of (±)-DOI-induced wet-dog shakes in naive rats. Mazindol has been suggested to modify the effect of NA and DA on the nervous system (Carruba et al., 1977; Heikkila et al., 1977; Houlihan et al., 1996). Interaction between NA and 5-HT_{2A} receptors would also have occurred in mazindol-injected rats similar to desipramine-injected rats.

Fluvoxamine did not have any effect on the (±)-DOI-induced wet-dog shakes in naive rats. SSRI administered acutely shows a selective inhibition of 5-HT reuptake. If SSRI is administered chronically, it is conceivable that a sub-sensitivity of 5-HT_{2A} receptors characterized by a decrease in 5-HT_{2A} receptor density occurs. However, it was reported that chronic administration of fluvoxamine does not cause any down-regulation of 5-HT_{2A} receptor activity in rats (Ishikane et al., 1994). This may be the reason why (±)-DOI-induced wet-dog shakes were not affected in the chronic fluvoxamine-administered rats. The present study is consistent with results in earlier reports. Maj et al. (1982) reported that fluvoxamine had no effect on 5-hydroxytryptophan-induced head twitch behavior in mice. Pawlowski and Melzacka (1986) showed that fluvoxamine did not affect quipazine-induced head twitching. Furthermore, several studies have shown that chronic administration of SSRIs (paroxetine and fluoxetine) enhanced rather than down-regulated 5-HT_{2A} receptor activity as measured in the cortex or hypothalamus. (Cadogan et al., 1993; Li et al., 1993; Tilakaratne et al., 1995). Accordingly, it is possible to require the noradrenaline reuptake inhibition on the decreasing effects of (±)-DOI-induced wet-dog shakes. It is difficult to explain why fluvoxamine did not affect (±)-DOI-induced wet-dog shakes in our study. Differences in the number of injections, the route of injection, the animal species (rat or guinea pigs) or the evaluable data could be reflected in the experimental results. Further studies are in progress to clarify the effect on 5-HT_{2A} receptor activity of SSRIs.

The DA reuptake inhibitor bupropion, and likewise fluvoxamine, did not affect the (±)-DOI-induced wet-dog shakes. Ferris and Beaman (1983) reported that chronic bupropion treatment did not affect the binding of [^{3}H]spiroperidol to 5-HT_{2A} receptors in the rat frontal cortex. Ascher et al. (1995) found that bupropion did not alter the firing rates of serotonergic neurons in the dorsal

Table 1
The effects of chronic administration of bupropion on (±)-DOI-induced wet-dog shakes in naive and ACTH-treated rats

Drug	Response/30 min
Control	25.0±4.0
Bupropion 10 mg	24.3±8.0
ACTH	47.7±3.2
ACTH+bupropion 10 mg	42.6±4.6

The rats were administered bupropion (10 mg/kg, i.p.) once daily for 14 days. Control rats were treated with saline (2 ml/kg, i.p.) once daily for 14 days. ACTH (100 μg/rat, s.c.) was administered in combination with bupropion (10 mg/kg, i.p.) once daily for a period of 14 days. We measured the number of (±)-DOI-induced wet-dog shakes 1 day after the final treatment with ACTH or bupropion. Rats were treated with (±)-DOI (1 mg/kg, s.c.) and returned to their cages. All values are expressed as the mean±S.E.M. for seven animals per group. Data were analyzed with Student's *t*-test.

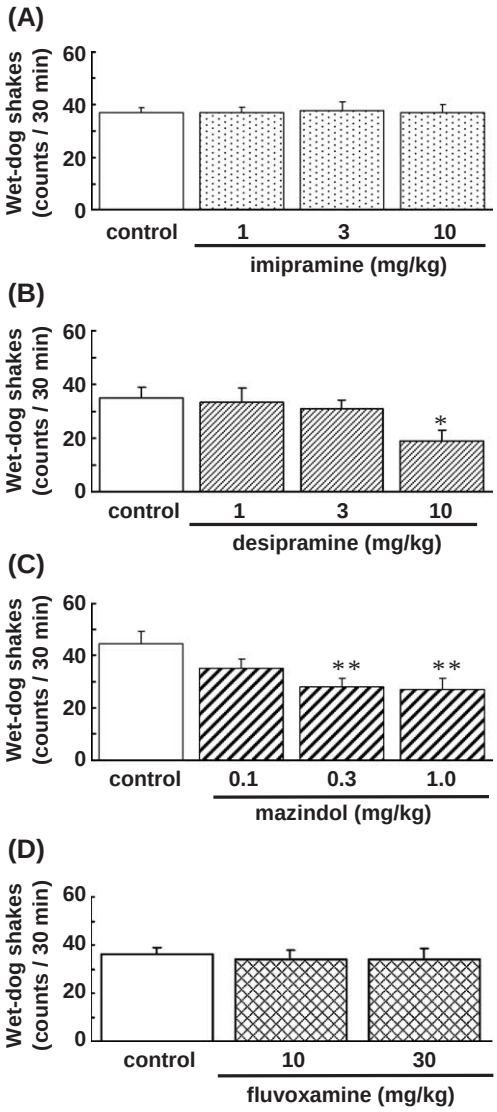

Fig. 3. Effects of chronic administration of imipramine, desipramine, mazindol and fluvoxamine for 14 days on (±)-DOI-induced wet-dog shakes in ACTH-treated rats. ACTH (100 μg/rat, s.c.) was administered in combination with imipramine (1–10 mg/kg, i.p.), desipramine (1–10 mg/kg, i.p.), mazindol (0.1–1 mg/kg, i.p.) and fluvoxamine (10–30 mg/kg, i.p.) once daily for a period of 14 days. Control rats were treated with saline (2 ml/kg, i.p.) once daily for 14 days. The number of (±)-DOI-induced wet-dog shakes was recorded 1 day after the final administration of ACTH and imipramine, desipramine, mazindol and fluvoxamine. Rats were treated with (±)-DOI (1 mg/kg, s.c.) and returned to their cages. All values are expressed as the mean ± S.E.M. for six animals per group. Data were analyzed by one-way ANOVA, followed by Dunnett's test. $^{**}P<0.01$, significant difference from the control value. $^{*}P<0.05$, significant difference from the control value.

raphe. These reports strongly suggest that DA reuptake inhibitors do not influence the functions of 5-HT_{2A} receptors.

We have already reported that chronic ACTH treatment increased the number of (±)-DOI-induced wet-dog shakes in rats (Kitamura et al., 2002). In a neurochemical study, chronic administration of ACTH increased the binding of [^{3}H]ketanserin to 5-HT_{2A} receptors in the frontal cortex, namely this treatment increased the density of 5-HT_{2A} receptors in the forebrain neocortex (Kuroda et al., 1992), suggesting that the 5-HT_{2A} receptor is closely related to the physiological response activating the HPA axis in rats. As mentioned, the administration of imipramine for 14 days significantly suppressed the (±)-DOI-induced wet-dog shakes in naive rats (Kitamura et al., 2002). However, no such effect was recognized in chronic ACTH-treated rats (Kitamura et al., 2002). It seems reasonable to conclude that the effect of imipramine on (±)-DOI-induced wet-dog shakes in ACTH-treated rats occurs mainly via direct 5-HT neurotransmission, namely 5-HT reuptake inhibition. In a preliminary study, we examined the effect of imipramine on extracellular 5-HT concentrations in the rat medial prefrontal cortex after chronic ACTH treatment using the method of in vivo microdialysis. The increase in 5-HT levels induced by imipramine was blocked by chronic ACTH treatment. Namely, the 5-HT reuptake function of imipramine may be attenuated in ACTH-treated rats.

The chronic administration of desipramine significantly suppressed the functions of 5-HT_{2A} receptors mainly via the noradrenergic system in naive rats. However, the effect of the chronic treatment with ACTH was inhibited by the chronic administration of desipramine, completely different from that of imipramine. Desipramine mainly inhibits NA reuptake not 5-HT reuptake. The effect of desipramine was mainly indirect, as mentioned above. It is conceivable that the up-regulation of 5-HT_{2A} receptor activity induced by the chronic administration of ACTH was direct. Namely, these findings suggest that the down-regulation of 5-HT_{2A} receptor activity induced by antidepressants in naive and ACTH-treated rats may be required for the facilitation of NA neurotransmission. In addition, mazindol also had an effect on the number of (±)-DOI-induced wet-dog shakes in ACTH-treated rats. These findings suggest that noradrenaline reuptake inhibitors can normalize the hyperfunction of 5-HT_{2A} receptors induced by chronic ACTH treatment in rats.

In conclusion, the study presented demonstrated for the first time that desipramine and mazindol suppressed the hyperfunction of 5-HT_{2A} receptors in ACTH-treated rats. Namely, the results show that ACTH inhibits the suppression of (±)-DOI-induced wet-dog shakes caused by reuptake inhibitors of NA but not 5-HT or DA.

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