Pharmacology, Biochemistry and Behavior 90 (2008) 325–330

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Apomorphine-induced turning behavior in 6-hydroxydopamine lesioned rats is increased by histidine and decreased by histidine decarboxylase, histamine H_1 and H_2 receptor antagonists, and an H_3 receptor agonist

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ARTICLE INFO

Article history:
Received 1 March 2008
Accepted 10 March 2008
Available online 25 March 2008

Keywords:
Parkinson's disease
Histamine
Receptor
Turning behavior
Rat

ABSTRACT

The role of histamine and its receptors in basal ganglia neurocircuitry was assessed in apomorphine-induced turning behavior. Rats with unilateral 6-hydroxydopamine lesions of the substantia nigra pars compacta and medial forebrain bundle were administered histaminergic agents, and apomorphine-induced turning behavior was tested on Days 7 and 14 post-lesion. Compared with saline-treated rats, histidine (500 mg/kg, i.p.), a precursor of histamine, increased turning behavior ($p<0.05$), while α-fluoromethylhistidine (α-FMH, 25 μg, i.c.v.), an irreversible inhibitor of histidine decarboxylase, decreased turning behavior ($p<0.05$) but only on Day 14 post-lesion. Both the histamine H_1 receptor antagonist pyrilamine (10 and 50 μg, i.c.v.) and the H_2 receptor antagonist cimetidine (10 and 50 μg, i.c.v.) significantly decreased turning behavior on Days 7 and 14 post-lesion. The histamine H_3 receptor agonist immepip (10 μg, i.c.v.) decreased turning behavior ($p<0.05$) on Day 14 post-lesion. The present findings indicate the complex interactions of histamine on basal ganglia function.

1. Introduction

Histamine regulates several basic brain functions, including the sleep–wake cycle, energy and endocrine homeostasis, synaptic plasticity, and learning (Haas and Panula, 2003). In addition, histamine is involved in the regulation of movement. Intracerebroventricular (i.c.v.) administration of histamine in rats has been found to produce a biphasic effect on locomotion frequency in an open-field (Chiavegatto et al., 1998). Histamine or its precursor inhibited methamphetamine-induced locomotor hyperactivity (Itoh et al., 1984) and stereotyped behavior in mice (Joshi et al., 1981). Hyperactivity and the development of behavioral sensitization were facilitated in histidine decarboxylase knockout mice and histamine H_1 and H_2 receptor double-knockout mice (Iwabuchi et al., 2004).

Parkinson's disease is a neurodegenerative disorder characterized by aberrant basal ganglia function. The pathophysiology of Parkinson's disease includes a selective loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), leading to profound reductions in striatal dopamine (Forno, 1996). The histaminergic and dopaminergic systems have a close relationship in the basal ganglia (Maisonnette et al., 1998; Onodera et al., 1998). Dopamine D_2 receptor antagonists block methamphetamine-induced elevations in histamine release in the rat striatum (Onodera et al., 1998). Unilateral ibotenic acid lesions in the tuberomamillary nucleus, the major source of neuronal histamine, result in an increase of dopamine and homovanillic acid in the neostriatum in rats (Maisonnette et al., 1998).

Four selective histamine receptors (H_1–H_4) have been described, and autoradiographic studies have demonstrated the presence of H_1, H_2, and H_3 receptors within the basal ganglia (Palacios et al., 1981; Arrang et al., 1987; Bouthenet et al., 1988; Ruat et al., 1990; Honrubia et al., 2000; Ryu et al., 1994a). Increased density of H_3 receptors has been found in the substantia nigra of Parkinson's disease patients (Anichtchik et al., 2001) and in the ipsilateral striatum and substantia nigra in 6-hydroxydopamine (6-OHDA)-lesioned rats (Ryu et al., 1994b; Anichtchik et al., 2000a). H_2 receptor binding was not altered (Martinez-Mir et al., 1993). No study of H_1 receptors has yet been reported in Parkinson's patients. H_3 receptor ligands were recently demonstrated to reduce turning behavior induced by levodopa or apomorphine in 6-OHDA-lesioned rats (Huotari et al., 2000; Garcia-Ramirez et al., 2004). To date, no systemic studies have investigated the roles of histamine and its three receptors (H_1–H_3) in basal ganglia neurocircuitry.

In the present study, we investigated the effects of a histamine precursor, a histamine synthetase inhibitor, a histamine H_3 receptor agonist, a histamine H_3 receptor antagonist, and two H_1 and H_2 receptor antagonists on apomorphine-induced turning behavior in 6-OHDA-lesioned rats to evaluate the effect of histamine and its receptors on basal ganglia synaptic output.

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doi:10.1016/j.pbb.2008.03.010

2. Materials and methods

2.1. Animals

All experiments were carried out in accordance with the ethical guidelines of the Zhejiang University Animal Experimentation Committee and were in compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The animals used in this study were male Sprague–Dawley rats (220–270 g, Grade II, Certificate No. 22-9601018, Experimental Animal Center, Zhejiang University, China) maintained in individual cages with a 12-h light/dark cycle (lights on from 08:00–20:00 h). Water and food were available *ad libitum*. Experiments were performed each day between 10:00 and 17:00 h.

2.2. Drugs

Apomorphine hydrochloridehemihydrate, histidine monohydrochloride, pyrilamine, cimetidine, clobenpropit, immepip (Sigma, St. Louis, MO, USA), and α-fluoromethylhistidine (Merck Sharp & Dohme Research Laboratory, Rahway, NJ, USA) were dissolved in sterile saline. 6-Hydroxydopamine hydrochloride (Sigma, St. Louis, MO, USA) was dissolved in 0.9% saline containing 0.2 mg/ml ascorbic acid.

2.3. Surgery

In a pilot experiment, four rats were unilaterally infused with 6-OHDA (8 μg in 4 μl 0.9% saline containing 0.2 mg/ml ascorbic acid) into the medial forebrain bundle (MFB) (anterior/posterior, +0.2; rostral, 2; dorsal/ventral, 8.0) (Paxinos and Watson, 1997). Apomorphine-induced turning behavior was tested on Days 7, 14, 21, and 28 after 6-OHDA infusion. One week post-lesion, the animals did not show any obvious turning behavior. One month post-lesion, we detected only modest turning behavior (3–4 turns per minute). Therefore, two site lesions were used in our final experiment (i.e., substantia nigra pars compacta [SNpc] and MFB) in accordance with the literature (Day et al., 2006; Kirik et al., 1998; Barneoud et al., 2000). One hundred and eighteen rats were unilaterally infused with 6-OHDA into both the SNpc (anterior/posterior, −4.8; rostral, 1.6; dorsal/ventral, 8.2) and MFB (anterior/posterior, +0.2; rostral, 2; dorsal/ventral, 8.0). Sham-operated rats (n=6) received an identical volume of ascorbic acid vehicle. Subsequently, guide cannulae made of stainless steel tubing with a 700 μm outer diameter were implanted into the lateral ventricle (anterior/posterior, −1.0; rostral, 1.5; dorsal/ventral, 3.8). Detailed protocols of the procedure have been published previously (Liu et al., 2007).

2.4. Drug treatments

On both Days 7 and 14 post-lesion, all histaminergic agents were injected i.c.v. with a 10 μl Hamilton microsyringe connected by polyethylene tubing to a stainless steel needle protruding 1 mm beyond the tip of the guide cannula into the lateral ventricle, except for histidine which was injected intraperitoneally (i.p.). The i.c.v. infusion volume was 5 μl over a period of 5 min at a constant rate (1 μl/1 min). The needle was removed after 3 min. The administration routes and doses were based upon previous studies (Zhang et al., 2003a,b; Chen et al., 1999; Sibilia et al., 1992; Eidi et al., 2003; Puebla and Arilla, 1996; Parolaro et al., 1989; Zarrindast et al., 2002). Methodological differences in drug treatment existed between the present experiment and our previous work (Liu et al., 2007). In the present experiment, histaminergic agents were administered 30 min prior to apomorphine-induced turning behavior on Days 7 and 14 post-lesion. In our previous work, histaminergic agents were administered daily, and the time interval between drug treatment and the assessment of turning behavior was at least 5 h (Liu et al., 2007).

2.5. Testing of turning behavior

The 6-OHDA-induced lesions on Days 7 and 14 have been evaluated with Tyrosine hydroxylase, a rate-limited enzyme for DA-biosynthesis, immunohistochemistry in our previous work (Liu et al., 2007). To ensure the stability of the behavioral parameters, apomorphine-induced turning behavior was tested twice on Days 7 and 14 post-lesion. All experiments were carried out between 12:00 and 17:00 h. Rats were placed in individual hemispherical stainless steel bowls (diameter 32 cm) with a harness secured around their chests. The harness was connected to an automatic four-channel rotameter (Qingdao University, China). Thirty minutes after histaminergic agent treatment (1 h for α-FMH), rats received subcutaneous injection of apomorphine (0.5 mg/kg) according to previous studies (Burton et al., 1991; Agnati et al., 2004; Ohno et al., 1989; Han and Wang, 2007; Pollack and Strauss, 1999; Matsuya et al., 2007). The number of full turns was recorded for each rat during a 1-h test session. To ensure the success of the unilateral lesion, all rats were injected with apomorphine again on Day 21 post-lesion, and only those rats that showed more than seven turns per minute were used for statistical analyses. To determine whether any drug by itself could induce turning behavior in 6-OHDA-lesioned rats (n=6), the histaminergic drugs (without apomorphine) were administered, and animals were observed for 1 h on Day 7 (histidine, 500 mg/kg, i.p.), Day 8 (α-FMH, 25 μg, i.c.v.), Day 9 (pyrilamine, 50 μg, i.c.v.), Day 10 (cimetidine, 50 μg, i.c.v.), Day 11 (immepip, 10 μg, i.c.v.), and Day 12 (clobenpropit, 10 μg, i.c.v.) post-lesion.

2.6. Statistical analysis

All data are expressed as mean±SEM. Statistical significance was assessed by one-way analysis of variance (ANOVA) with the least significant difference test using SPSS software version 13.0. Values of $p<0.05$ were considered statistically significant.

3. Results

3.1. Effects of histidine, α-FMH, pyrilamine, cimetidine, immepip, and clobenpropit alone on behavior in 6-OHDA-lesioned rats

None of the histaminergic agents induced any turning behavior when administered alone in 6-OHDA-lesioned rats.

3.2. Histidine, a precursor of histamine, increased and α-FMH, an inhibitor of histidine decarboxylase, decreased apomorphine-induced turning behavior in 6-OHDA-lesioned rats

In the 6-OHDA-infused group, apomorphine induced contralateral turning behavior. The turning rate increased quickly in the first 20 min after apomorphine injection and reached a peak at 20–30 min and then decreased toward baseline. An increase of contralateral turning was observed as 273.0±26.4 turns in 1 h on Day 7 (n=10) to 440.8±56.7 turns in 1 h on Day 14 (n=10) after 6-OHDA infusion.

On Day 7, histidine (500 mg/kg, i.p.) increased the turning rate slightly during the first 20–50 min after apomorphine injection, while α-FMH (25 μg, i.c.v.) decreased turning behavior during the first 35 min. The cumulative number of turns showed that there was no significant change after histidine and α-FMH injection, although histidine increased (288.3±24.7, n=10) and α-FMH decreased (219.9±32.0, n=10) the number of turns. On Day 14, histidine increased, and α-FMH decreased, the turning rate during the entire turning process (0–60 min). Histidine increased the cumulative number of turns by 38% (608.8±60.9, n=10, $p<0.05$), and α-FMH decreased the number of turns by 37% (278.6±32.4, n=10, $p<0.05$) (Fig. 1A–C).

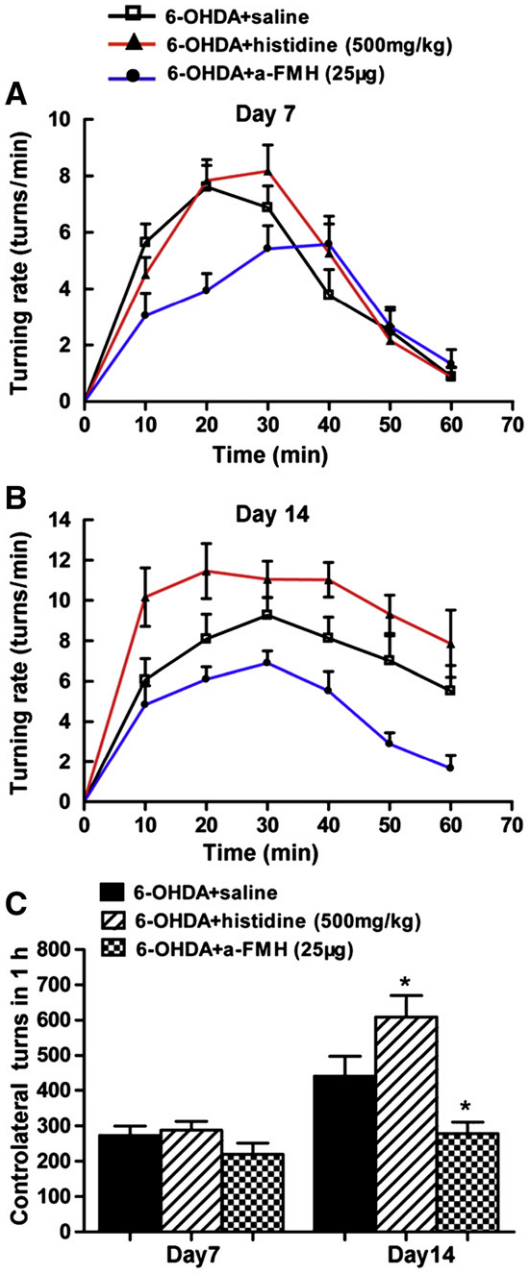

Fig. 1. Effect of histidine or α-FMH on apomorphine-induced turning behavior in 6-OHDA-lesioned rats. Turning behavior challenged by apomorphine was tested 30 min after acute injection of histidine (500 mg/kg, i.p.) or 1 h after injection of α-FMH (25 μg, i.c.v.) on Days 7 and 14 post-lesion, respectively. (A) Time course (7 days post-lesion). (B) Time course (14 days post-lesion). (C) Cumulative number of turns in 1 h. Turning rate and cumulative turns are shown as mean±SEM. $n=10$. *$p<0.05$ compared to 6-OHDA-lesioned group by one-way ANOVA followed by least significant difference test.

3.3. Histamine H_1 receptor antagonist pyrilamine and H_2 receptor antagonist cimetidine decreased apomorphine-induced turning behavior in 6-OHDA-lesioned rats

On Days 7 and 14 post-lesion, both pyrilamine (10, 50 μg, i.c.v.) and cimetidine (10, 50 μg, i.c.v.) induced a significantly lower turning rate than saline treatment during the entire turning process after apomorphine injection (Fig. 2A). The cumulative number of turns in the saline-treated group was 251.4±36.2 on Day 7 and 482.4±32.4 on Day 14, respectively. Compared to saline treatment, pyrilamine (10 μg) decreased the cumulative number of turns in 1 h by 55% on Day 7 (114.1±20.8, $p<0.05$, $n=12$) and by 48% on Day 14 (252.3±43.6, $p<0.05$, $n=12$) post-lesion. Pyrilamine (50 μg) decreased the cumulative number of turns in 1 h by 56% on Day 7 (109.7±22.5, $p<0.05$, $n=12$) and by 54% on Day 14 (224.8±21.3, $p<0.05$, $n=12$) post-lesion (Fig. 2B).

Cimetidine (10, 50 μg, i.c.v.) dose-dependently decreased the cumulative number of turns in 1 h. At the dose of 10 μg, cimetidine decreased the cumulative number of turns in 1 h by 29% on Day 7 (178.8±21.1, $p<0.05$, $n=12$) and by 59% on Day 14 (197.7±15.9, $p<0.05$, $n=10$) post-lesion. At the dose of 50 μg, cimetidine decreased the number of turns in 1 h by 55% on Day 7 (113.8±22.5, $p<0.05$, $n=12$)

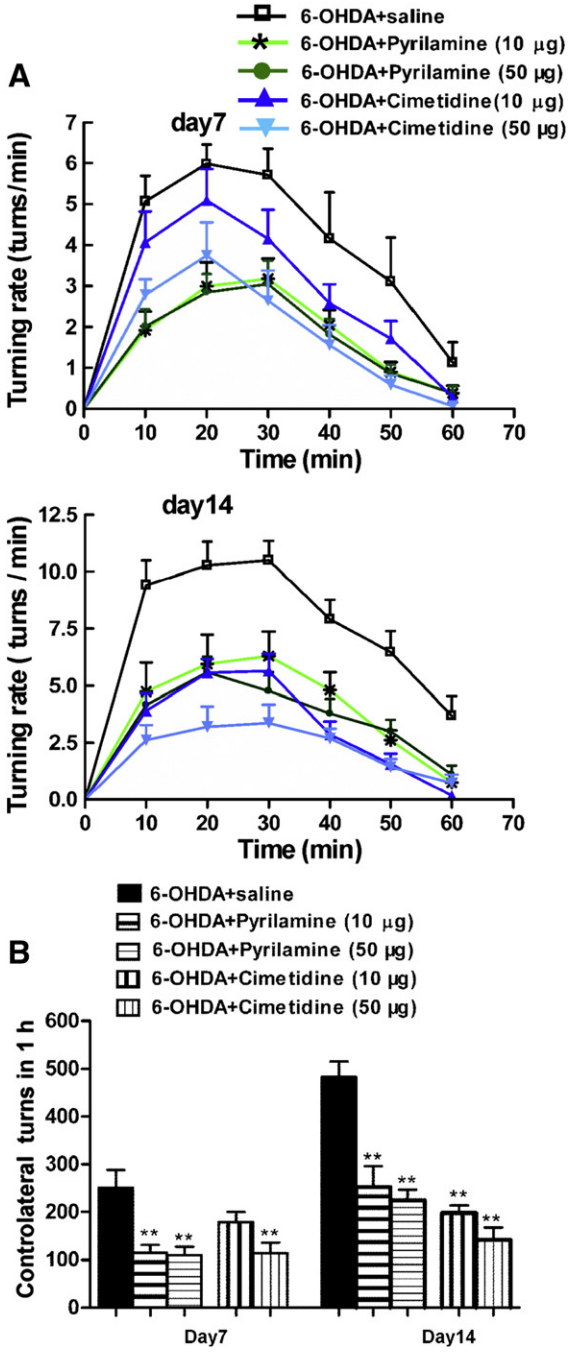

Fig. 2. Effect of pyrilamine or cimetidine on apomorphine-induced turning behavior in 6-OHDA-lesioned rats. Turning behavior challenged by apomorphine (0.5 mg/kg, s.c.) was tested 30 min after injection of pyrilamine (10, 50 μg, i.c.v.) or cimetidine (10, 50 μg, i.c.v.) on Days 7 and 14 post-lesion, respectively. (A) Time course. (B) Cumulative number of turns in 1 h. Turning rate and cumulative turns are shown as mean±SEM. **$p<0.01$ compared to 6-OHDA-lesioned group by one-way ANOVA followed by least significant difference test.

and by 71% on Day 14 (141.3 ± 26.7, $p < 0.05$, $n = 12$), an effect which was more rapid than at the 10 μg dose (Fig. 2B).

3.4. Histamine H_3 receptor agonist immepip decreased, but H_3 receptor antagonist clobenpropit had no effect on, apomorphine-induced turning behavior in 6-OHDA-lesioned rats

On Day 7 post-lesion, the H_3 receptor agonist immepip (10 μg, i.c.v.) did not significantly alter the turning rate compared to the control group, although on Day 14 it significantly decreased the turning rate during the entire turning process. The H_3 receptor antagonist clobenpropit (10 μg, i.c.v.) only had a minimal effect on turning behavior (Fig. 3A, B).

Immepip (10 μg, i.c.v.) decreased the cumulative number of turns in 1 h by 10% on Day 7 (226.8 ± 22.8, $p > 0.05$, $n = 10$) and by 46% on Day 14 (259.3 ± 33.5, $p < 0.05$, $n = 10$) post-lesion. Clobenpropit (10 μg, i.c.v.) decreased the cumulative number of turns only by 4% on Day 7 (242.5 ± 14.9, $p > 0.05$, $n = 10$) and by 14% on Day 14 (414.7 ± 46.0, $p > 0.05$, $n = 10$) post-lesion (Fig. 3C).

4. Discussion

Unilateral lesioning of the nigrostriatal pathway by 6-OHDA is one of the most useful animal models of Parkinson's disease (Deumens et al., 2002). After 6-OHDA infusion, the loss of dopaminergic neurons in the SNpc results in supersensitivity of postsynaptic dopamine receptors in the striatum. When a dopamine agonist (e.g., apomorphine) is administered, rats rotate away from the lesion side (contralaterally). Turning behavior induced by apomorphine originates from an imbalance of basal ganglia synaptic output between the two brain hemispheres. In Parkinson's disease patients and in animal models, the motor disturbance is associated with an imbalance in the activity of "direct" and "indirect" pathways of information innervating the basal ganglia (DeLong, 1990; Bergman et al., 1990; Albin et al., 1995). Turning behavior has been used to study neurotransmitter interactions in the basal ganglia and to screen potential antiparkinsonian compounds (Schwarting and Huston, 1996).

Histidine (500 mg/kg, i.p.) has been reported to markedly increase histamine levels in the cortex, hippocampus, and hypothalamus, and α-FMH (50 μg, i.c.v.) has been shown to decrease histamine in the frontoparietal cortex to 67% of control values 1 h after administration (Puebla and Arilla, 1995). In the present study, exogenous histidine caused enhanced turning behavior, and α-FMH decreased turning behavior, indicating histaminergic involvement in apomorphine-induced contralateral turning behavior.

In addition, we found that administration of the H_3 receptor agonist immepip (10 μg, i.c.v.) decreased turning behavior on Day 14 post-lesion, which is consistent with Huotari et al. (2000) and Garcia-Ramirez et al. (2004). A proposed mechanism for this effect is that H_3 receptors in the substantia nigra pars reticulata (SNpr) may regulate synaptic output from the basal ganglia, most likely by postsynaptically reducing γ-aminobutyric acid (GABA) release from nigrostriatal terminals. The histamine H_3 receptor provides negative feedback as an autoreceptor to restrict histamine synthesis and release (Arrang et al., 1987). Previous studies have reported that peripheral injection of immepip caused a sustained decrease in histamine release in the hypothalamus and cortex (Jansen et al., 1998; Lamberty et al., 2003). Thus, similar to α-FMH, the H_3 receptor agonist immepip (10 μg, i.c.v.) may inhibit turning behavior by presynaptically decreasing brain histamine.

Histamine is a nonspecific endogenous histamine receptor agonist and can excite H_1–H_3 receptors. In the present study, histidine, which increases histamine synthesis, increased turning behavior, and the H_3 receptor agonist immepip decreased the behavior, suggesting that H_1 and H_2 receptors also may be involved in turning behavior. Both the H_1 receptor antagonist pyrilamine and the H_2 receptor antagonist cimetidine significantly decreased turning behavior, indicating that the stimulating effect of histamine on turning behavior might be mediated postsynaptically by both H_1 and H_2 receptors. The excitatory effect of H_1 and H_2 receptors may overlap the inhibitory effect induced by H_3 receptors, which might be a possible reason why the effects of H_1 or H_2 antagonists were more pronounced than that of histidine. Thus, in addition to the H_3 receptor, H_1 and H_2 receptors may participate in the modulation of basal ganglia pathways. The effect of histamine receptors on basal ganglia pathways is supported by some behavior studies. Molinari et al. (1995) found that the H_2 receptor antagonist famotidine improved motor symptoms in Parkinson's disease patients.

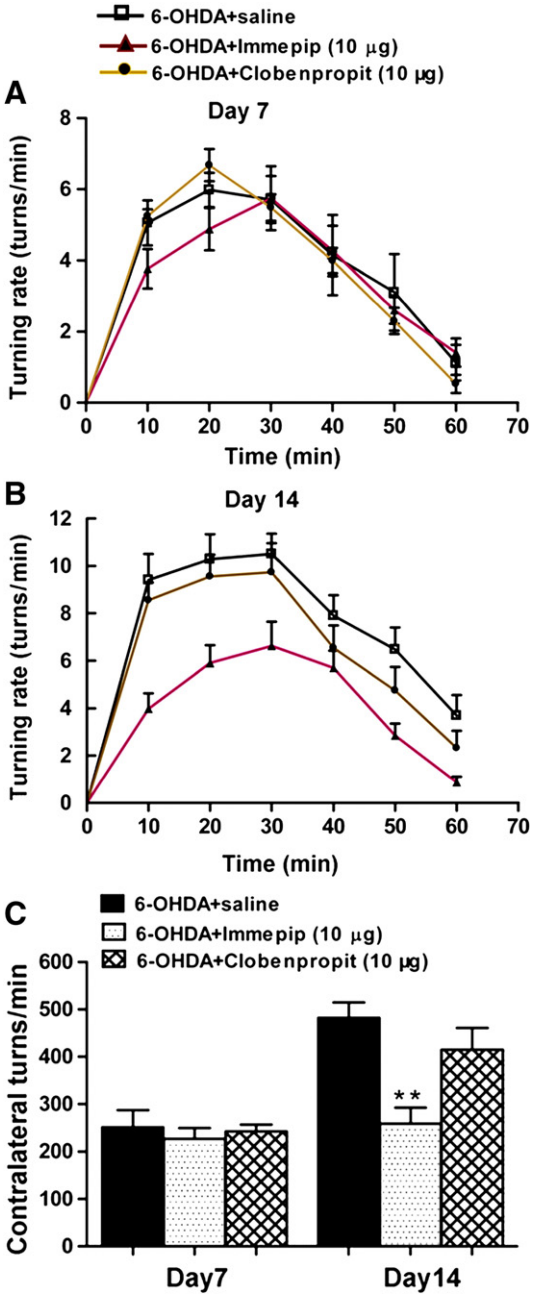

Fig. 3. Effect of immepip or clobenpropit on apomorphine-induced turning behavior in 6-OHDA-lesioned rats. Turning behavior challenged by apomorphine (0.5 mg/kg, s.c.) was tested 30 min after an acute injection of immepip (10 μg, i.c.v.) or clobenpropit (10 μg, i.c.v.) on Days 7 and 14 post-lesion, respectively. (A) Time course (7 days post-lesion). (B) Time course (14 days post-lesion). (C) Cumulative number of turns in 1 h. Turning rate and cumulative turns are shown as mean ± SEM. $n = 10$. $^{**}p < 0.01$ compared to 6-OHDA-lesioned group by one-way ANOVA followed by least significant difference test.

Gomez-Ramirez et al. (2006) found that H_3 receptor agonists reduced L-DOPA-induced chorea, but not dystonia, in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesion nonhuman primate model of Parkinson's disease.

Pyrilamine and cimetidine showed similar effects in the present study. Although H_1 and H_2 receptors have different cellular excitatory pathways, it is possible that H_1 and H_2 receptors are simultaneously involved in behavioral effects induced by histamine. Orexin A-induced antinociception was greater in histamine H_1 or H_2 receptor knockout mice than in wildtype mice in four assays of pain. Furthermore, treatment with a combination of orexin A and D-chlorpheniramine (a histamine H_1 receptor antagonist) or cimetidine (a histamine H_2 receptor antagonist) in C57BL/6 mice resulted in greater antinociception than orexin A administered alone (Mobarakeh et al., 2005). In addition, long-term potentiation in the CA1 area of the hippocampus was significantly reduced in both H_1 and H_2 knockout mice compared to wildtypes (Dai et al., 2007).

In addition to the dopaminergic system, there may be other differences between the intact and lesioned sides. Anichtchik et al. (2000a) found that histaminergic fibers were increased in the substantia nigra on the lesioned side, compared to the unlesioned side, in a rat model of Parkinson's disease. An autoradiographic study showed that H_3 receptors were increased in the striatum and substantia nigra in 6-OHDA-lesioned rats (Ryu et al., 1994b). Although both hemispheres are exposed to drugs affecting the histaminergic system, responses from the lesioned and unlesioned sides may be different, thus affecting turning behavior.

Histamine fibers have a wide distribution in the brain, including in the striatum, globus pallidus, and SNpr, which are key structures of the basal ganglia (Rinne et al., 2002; Airaksinen and Panula, 1988; Panula et al., 1989). Injection of an H_1 receptor antagonist produced a sustained increase in extracellular dopamine in the neostriatum (Dringenberg et al., 1998). Dopamine release on the unlesioned side was markedly greater than on the lesioned side and counteracted the supersensitivity of postsynaptic D_1 or D_2 receptors on the lesioned side, thereby decreasing the turning rate. Moreover, histamine may depolarize cholinergic interneurons in the rat striatum via H_1 receptors (Bell et al., 2000) and excite globus pallidus neurons via H_2 receptors (Chen et al., 2005). Stimulation of H_1 and H_2 receptors located on cholinergic or GABAergic neurons enhances acetylcholine release, and stimulation of H_2 receptors located on dopaminergic neurons exerts an opposite effect (Prast et al., 1999). A direct excitatory or inhibitory role of histamine on SNpr GABA projection neurons via different histamine receptors also has been reported (Zhou et al., 2006). These studies indicate that the histaminergic role in turning behavior may be quite complex.

It should be noted that the effect of some histaminergic agents in the present study was more pronounced on Day 14 than on Day 7 post-lesion. A recent study reported that neuronal reactivity in the basal ganglia network considerably differs between the early and late stages in 6-OHDA-lesioned rats (Breit et al., 2007). We speculate that the more severe the late-stage lesion effects in the basal ganglia are, the stronger the effects of histamine on turning behavior will be.

In conclusion, the present findings indicate that endogenous histamine has complex interactions with basal ganglia neurocircuitry via H_1, H_2, and H_3 receptors. These results may help elucidate the role of histamine in the regulation of motor behavior, both in normal and pathophysiological conditions.

Acknowledgements

This work was supported by the Key Project of Natural Science Foundation in Zhejiang Province (No. Z205321). We thank Prof. Dick F. Swaab and Dr. Ai-Min Bao (Netherlands Institute for Neuroscience, Amsterdam, The Netherlands) for their discussions and modifications of the manuscript.

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