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(−)-1-(Benzofuran-2-yl)-2-propylaminopentane enhances locomotor activity in rats due to its ability to induce dopamine release

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Abstract

"Catecholaminergic and serotoninergic activity enhancer" effects are newly found mechanisms of action of a class of compound that enhance impulse propagation-mediated release of catecholamines and serotonin in the brain. In the present study, (−)-1-(benzofuran-2-yl)-2-propylaminopentane hydrochloride [(−)-BPAP HCl], a compound with selective and potent "catecholaminergic and serotoninergic activity enhancer" effects, was tested for its efficacy to potentiate locomotor activity in normal rats and to attenuate hypolocomotion in reserpine-treated rats. (−)-BPAP HCl potentiated locomotor activity in non-habituated rats during a 2-h observation period dose-dependently (0.3–10 mg/kg). (−)-BPAP HCl (1–3 mg/kg) was also effective to reverse reserpine-induced hypolocomotion. The effects of (−)-BPAP HCl in normal and reserpine-treated rats were attenuated by the dopamine D1 receptor antagonist, *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH 23390), suggesting that the effects of (−)-BPAP HCl were mediated by activation of the dopaminergic system. In addition, the administration of (−)-BPAP HCl increased ipsilateral turning in unilaterally 6-hydroxydopamine-lesioned rats, implying presynaptic activation of nigrostriatal dopaminergic terminals by (−)-BPAP HCl. Furthermore, although antiparkinsonian agents, such as apomorphine and amantadine, failed to improve reserpine-induced ptosis, (−)-BPAP HCl significantly improved ptosis. These findings suggested that a "catecholaminergic and serotoninergic activity enhancer" compound, (−)-BPAP, stimulates motor function in rats and improves motor deficits in animal models of Parkinson's disease due to its ability to induce dopamine release.

Keywords: Parkinson's disease; [(−)-BPAP HCl] (−)-1-(benzofuran-2-yl)-2-propylaminopentane hydrochloride; Catecholaminergic and serotoninergic activity enhancer; Reserpine; 6-Hydroxydopamine; (−)-Deprenyl

1. Introduction

The endogenous brain amines, such as β-phenylethylamine and tryptamine, have been found to enhance the electrical stimulation-induced release of [^{3}H]dopamine, [^{3}H]noradrenaline and [^{3}H]serotonin from the isolated rat brainstem (Knoll et al., 1996c). This was the first direct evidence of a novel regulatory mechanism underlying the impulse propagation-mediated release of catecholamines and serotonin in the central nervous system. Thus, Knoll et al. (1996a,b,c, 1999) designated this newly found mechanism as the "catecholaminergic and serotoninergic activity enhancer" mechanism.

(−)-1-(Phenyl-2-yl)-2-propylaminopentane [(−)-PPAP] is a pharmacological reference compound with the "catecholaminergic activity enhancer" effect (Knoll et al., 1996a). Replacement of the benzene ring in (−)-PPAP by a benzofuran ring yielded a compound, (−)-1-(benzofuran-2-yl)-2-propylaminopentane [(−)-BPAP], with a more potent "catecholaminergic activity enhancer" effect and still greater "serotoninergic activity enhancer" effect than (−)-PPAP (Knoll et al., 1999). (−)-BPAP enhanced the electrical stimulation-induced release of dopamine, noradrenaline and serotonin from the rat brainstem (Knoll et al., 1999). In addition, (−)-BPAP fully antagonized tetrabenazine-induced inhibition of learning performance in an active avoidance task (Knoll et al., 1999).

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The dopamine deficiency theory for Parkinson's disease led to a major breakthrough in the treatment of this disease (Ehringer and Hornykiewicz, 1960; Barbeau, 1962; Bernheimer et al., 1963). Based on this theory, replacement treatments were introduced clinically, and indirect and direct dopamine agonists have been shown to be useful in the treatment of Parkinson's disease (Schwab et al., 1951, 1969; Birkmayer and Hornykiewicz, 1961; Calne et al., 1974; Gopinathan et al., 1981). Interestingly, although (−)-deprenyl as a monoamine oxidase-B inhibitor is used as the adjunct of L-DOPA in the treatment of Parkinson's disease (Birkmayer et al., 1977), (−)-deprenyl has also been shown to possess a "catecholaminergic activity enhancer" effect (Knoll et al., 1996a). Accordingly, the "catecholaminergic activity enhancer" effect of (−)-deprenyl may be involved in the beneficial pharmacological effect of this drug in the treatment of Parkinson's disease (Knoll and Miklya, 1995; Knoll et al., 1996a; Knoll, 1998). This led us to examine whether a potent "catecholaminergic activity enhancer" compound such as (−)-BPAP could serve as a new therapeutic agent for the treatment of Parkinson's disease.

The aim of the present study was to clarify the effects of (−)-BPAP on performance, in behavioral tests involving catecholaminergic transmission and a model of Parkinson's disease. First, the effects of (−)-BPAP on spontaneous locomotor activity were tested in normal as well as in reserpine-treated rats. Reserpine interferes with the storage of monoamines in intracellular granules, which results in the depletion of monoamines in nerve terminals (Carlsson, 1975). Reserpine-treated animals show transient hypolocomotion and muscular rigidity, thus providing a pharmacological model of parkinsonism (Colpaert, 1987). We also observed the effects of (−)-BPAP on rotational behavior in unilaterally 6-hydroxydopamine-lesioned rats. This model, termed "the hemi-parkinsonian rat", is widely used to evaluate the potential antiparkinson activity of therapeutic agents (Costall and Naylor, 1975; Ungerstedt, 1976; Fuxe and Ungerstedt, 1976; Silverman, 1993). In addition, the role of the dopaminergic system in the behavioral effects of (−)-BPAP was investigated, using the dopamine D1 and D2 receptor antagonists, *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH 23390) and sulpiride, respectively.

2. Materials and methods

2.1. Animals

Male Wistar rats (10-weeks-old, Nihon SLC, Shizuoka, Japan) were maintained in a humidity- ($55 \pm 10\%$) and temperature- (23 ± 2°C) controlled facility under a 12/12 h light/dark cycle (light on at 7:00 a.m.) with free access to food (MF, Oriental Yeast, Tokyo, Japan) and water. The rats were allowed to adapt for 1 week before testing.

The study was approved by Institutional Committee of Institute of Research and Development of Fujimoto Pharmaceutical. All animal procedures were in accordance with the Institutional Guideline of Care and Use of Laboratory Animals.

2.2. Compounds

The following compounds were used: amantadine hydrochloride (HCl), apomorphine HCl, 6-hydroxydopamine hydrobromide, imipramine HCl, SCH 23390 HCl (Research Biochemicals International, Natic, MA, USA), reserpine and sulpiride (Sigma, St. Louis, MO, USA). (−)-BPAP HCl, the formula of which is shown in Fig. 1, was synthesized by the Institute of Research and Development of Fujimoto Pharmaceutical (Osaka, Japan). Reserpine was dissolved in acetic acid and distilled water.

2.3. Locomotor activity

Locomotor activity was assessed using an infrared (Model NS-AS01)-linked activity sensor system (Model AB system-24A, Neuroscience, Tokyo, Japan). Counts of motor activity were recorded on a computer system during consecutive 5-min intervals.

The rats, which were not adapted to the test cages, were used to determine the effects of test substances on locomotor activity during a 2-h observation period, including an active exploration period. The effects of (−)-BPAP HCl were measured immediately after treatment with this compound. The effects of compounds on reserpine-induced hypolocomotion were measured 24 h after i.v. administration of reserpine (1 mg/kg). Reserpine-model rats were placed in the cage immediately after treatment with (−)-BPAP HCl, and locomotor activity was measured.

2.4. Testing of rotation

Rats were anesthetized with sodium pentobarbital (50 mg/kg i.p.), and 8 μg of 6-hydroxydopamine, in 4 μl of vehicle (saline containing 0.1% ascorbic acid), was injected into the substantial nigra pars compacta ($A = -5.6$ mm, $L = 1.6$ mm from bregma and $H = -7.6$ mm from the surface of the skull) at a rate of 0.8 μl/min. Imipramine

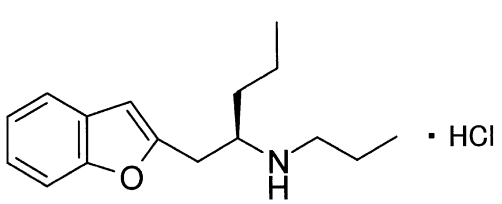

Fig. 1. Structure of *R*-(−)-1-(benzofuran-2-yl)-2-propylaminopentane hydrochloride [(−)-BPAP HCl].

HCl was administered at a dose of 10 mg/kg i.p. 30 min prior to the 6-hydroxydopamine lesion. Ten to eleven days after surgery, the rats were injected with 0.2 mg/kg s.c. of apomorphine HCl and placed in plastic cages. The rotations (360°) were scored for 1 h. Rats showing 100 rotations/h or more were selected for further experiments.

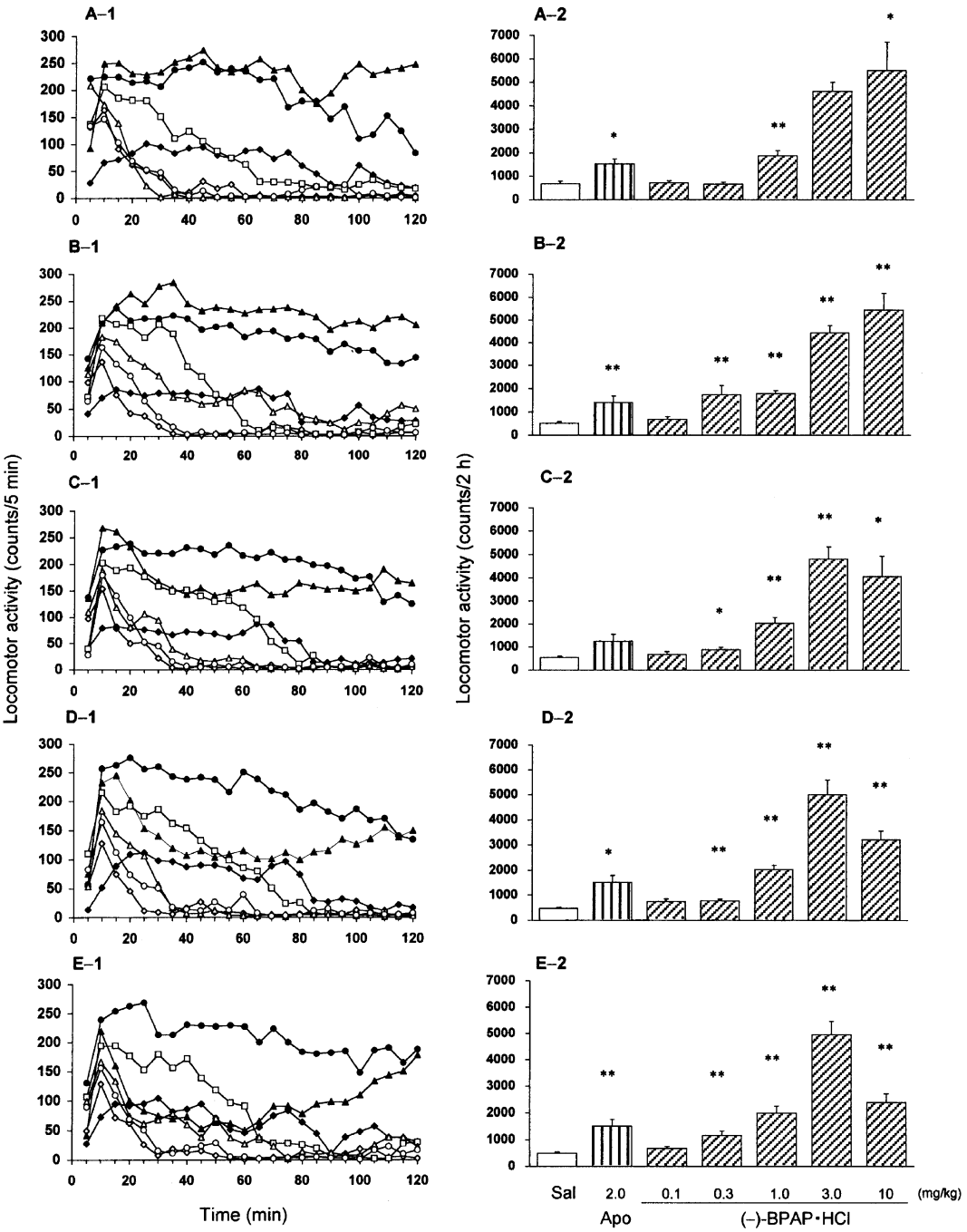

Fig. 2. Effects of (−)-BPAP HCl and apomorphine HCl on locomotor activity in non-habituated rats. Rats were treated with the compounds once a day for five consecutive days. Motor activity during the 2-h observation period was measured starting immediately after injection of each compound every day. A, B, C, D and E represent the respective motor activity in the experiments on five consecutive days. A-1, B-1, C-1, D-1 and E-1 represent the time courses of action of compounds. Open diamonds (◇), closed diamonds (◆), open circles (○), open triangles (△), open squares (□), closed circles (●) and closed triangles (▲) represent saline, 2 mg/kg s.c. apomorphine HCl (Apo), 0.1, 0.3, 1, 3 or 10 mg/kg s.c. (−)-BPAP HCl-treated group, respectively. Data are presented as the averages of locomotion taken at each 5-min interval, over a period of 2 h after administration of the compounds. S.E.M. are not shown for the sake of clarity. A-2, B-2, C-2, D-2 and E-2 represent cumulative motor activity for 2 h in the rats after treatment with each compound. $^{*}P < 0.05$ and $^{**}P < 0.01$ vs. saline-treated control. Each value represents an average score for a group of seven rats except for the first day, and vertical bars represent S.E.M. On the first day, numbers of values for statistical analyses in each group were 4, 4, 7, 3, 7, 3 and 4 for saline, Apo, 0.1, 0.3, 1.0, 3.0 or 10 mg/kg s.c. (−)-BPAP-treated group, respectively.

Table 1
Hypolocomotion in rats 24 h after administration of reserpine
Cumulative locomotor activity of reserpine-treated rats was recorded for 2 h immediately after placement in the test cage.

Treatment	Dose (mg/kg i.v.)	*n*	Counts of locomotor activity (mean ± S.E.M.)
Control	–	10	538.9 ± 57.3
Reserpine	0.3	10	312.6 ± 34.7[a]
	1	10	279.0 ± 86.4[a]
	3	10	88.6 ± 11.2[a]

[a] $P < 0.01$ vs. control rats.

These rats, 18–19 days after surgery, were then injected s.c. with (−)-BPAP HCl and tested for ipsilateral rotations for 1 h.

2.5. Ptosis scoring in reserpine-treated rats

The scoring system of Janssen et al. (1965) was used to evaluate the degree of ptosis in reserpine-treated rats. Score 4, eyes completely closed; score 2, half-open eyes; and score 0, wide-open eyes; scores 1 and 3, intermediate values.

2.6. Statistics

The experimental data were evaluated with the Kruskal–Wallis' analysis of variance followed by post hoc Wilcoxon's test (SAS preclinical package version 4.0, SAS Institute, Cary, NC, USA). Only the experimental data in Fig. 7 for the 6-hydroxydopamine-model were analysed with the paired *t*-test. $P < 0.05$ was considered significant.

3. Results

3.1. Effects of (−)-BPAP in locomotor activity in non-habituated normal rats

Fig. 2 shows the locomotor stimulant effect of (−)-BPAP HCl. The animals injected with vehicle alone displayed locomotion related to active exploration during the initial phase that was usually followed by a decline in activity due to habituation (Fig. 2A-1, open diamonds). The (−)-BPAP HCl-treated animals displayed pronounced locomotor activity (Fig. 2). Regarding cumulative locomotor activity, 0.1–10 mg/kg s.c. (−)-BPAP HCl caused increases in locomotor action in a dose-dependent manner,

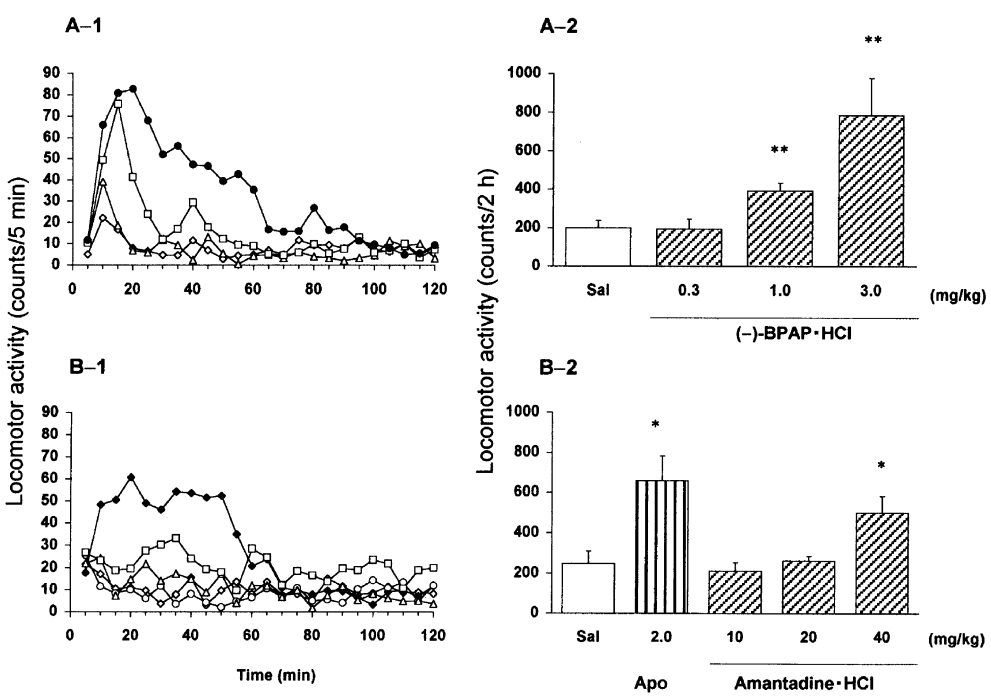

Fig. 3. Effects of (A) (−)-BPAP and (B) apomorphine and amantadine on reserpine-induced hypolocomotion in rats. Reserpine (1 mg/kg i.v.) was given 24 h before administration of the compounds. The locomotor activity of each rat was measured for 2 h after administration of compounds. A-1 and B-1 show time courses of the actions of compounds. In A-1, open diamonds (◇), open triangles (△), open squares (□) and closed circles (●) represent saline, 0.3, 1 or 3 mg/kg s.c. (−)-BPAP, respectively. In B-1, open diamonds (◇), closed diamonds (◆), open circles (○), open triangles (△) and open squares (□) show saline-treated control, 2 mg/kg s.c. apomorphine HCl (Apo), 10, 20 or 40 mg/kg s.c. amantadine HCl, respectively. Data are presented as average locomotion from each 5-min interval over a period of 2 h after administration of the compounds. S.E.M. are not shown for the sake of clarity. A-2 and B-2 show the cumulative motor activities for 2 h in the rats treated with compounds. $^{*}P < 0.05$ and $^{**}P < 0.01$ vs. saline-treated control. Each value represents an average score for a group of 10 rats, and the vertical bars represent S.E.M.

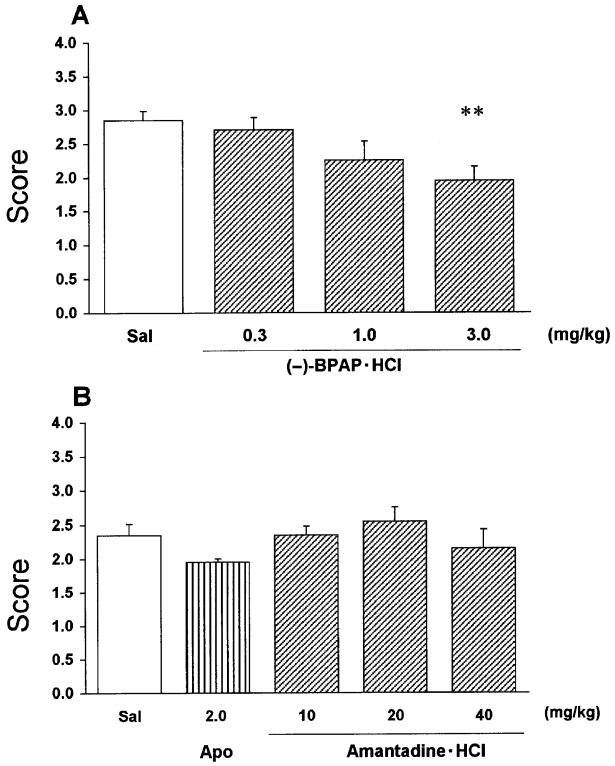

Fig. 4. Effects of (A) (−)-BPAP and (B) apomorphine and amantadine on reserpine-induced ptosis in rats. Reserpine (1 mg/kg i.v.) was given 24 h before treatment with the compounds, and the level of ptosis of each rat was scored 2 h after administration of drugs. $^{**}P < 0.01$ vs. saline-treated control. Each value represents an average score for a group of 10 rats, and the vertical bars represent S.E.M.

with a minimal effective dose of 0.3 mg/kg (Fig. 2A-2–E-2). It should also be noted that a significant increase in locomotion was observed even at a lower dose, 0.1 mg/kg, during some observation periods (Fig. 2A-1–E-1, open circles). Lower doses (0.1, 0.3 and 1 mg/kg s.c.) of (−)-BPAP HCl preferentially potentiated locomotor activity during the initial phase of active exploration. At higher doses such as 3 or 10 mg/kg, (−)-BPAP HCl-treated animals showed long-lasting enhancement of locomotor activity until 2 h later. Although rats treated with the dopamine agonist, apomorphine, displayed an increase in cumulative locomotor activity for 2 h (Fig. 2A-2–E-2), there was a decrease in locomotor activity with 2 mg/kg s.c. apomorphine HCl during the initial phase of active exploration (Fig. 2A-1–E-1, closed diamonds). In the initial phase, 2 mg/kg s.c. apomorphine HCl caused more stereotypic behavior and less forward locomotion than did (−)-BPAP HCl.

3.2. Effects of (−)-BPAP in locomotor activity in reserpine-treated rats

A marked reduction in locomotor activity was observed 24 h after intravenous injection of 0.3–3 mg/kg reserpine, in a dose-dependent manner (Table 1). Active exploration during the initial phase, although to a lesser degree, was still observed in 1 mg/kg reserpine-treated rats (Fig. 3A-1,B-1).

As shown in Fig. 3B-1,B-2, reserpine-induced hypolocomotion was reversed by 2 mg/kg apomorphine HCl and by 40 mg/kg amantadine HCl, a dopamine-releaser (Scatton et al., 1970; Von Voigtlander and Moore, 1971). (−)-BPAP HCl also reversed reserpine-induced hypolocomotion at doses of 1–3 mg/kg. Note that locomotor activity during the initial phase was markedly potentiated by (−)-BPAP HCl in reserpine-treated animals, apparently

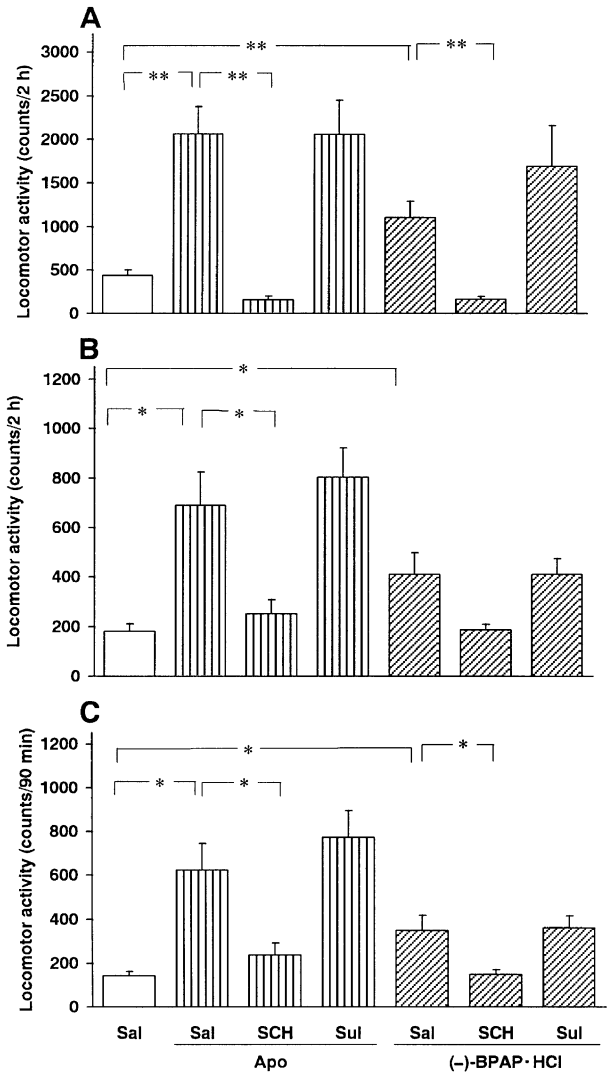

Fig. 5. Effects of dopaminergic antagonists on the hyperlocomotor actions of (−)-BPAP HCl or apomorphine HCl on normal rats (A), or reserpine-treated rats (B and C). (A) Locomotor activities of normal rats were measured immediately after administration of compounds. (B and C) Reserpine (1 mg/kg i.v.) was given 24 h before treatment with the compounds, and locomotor activity of each rat was measured for 2 h (B) or 90 min (C) after administration of compounds. (−)-BPAP HCl or apomorphine HCl was administered at doses of 1 and 2 mg/kg s.c., respectively. SCH 23390 HCl (SCH; 0.1 mg/kg s.c.) or sulpiride (Sul; 20 mg/kg s.c.) were administered simultaneously with (−)-BPAP HCl or apomorphine HCl. $^{*}P < 0.05$ and $^{**}P < 0.01$ vs. saline-treated control (Sal). Each value represents an average for a group of 10 rats, and the vertical bars represent S.E.M.

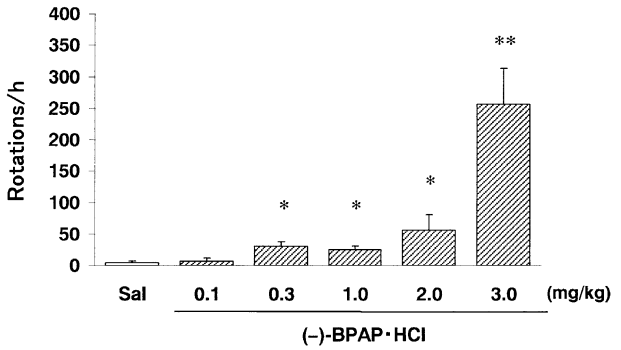

Fig. 6. Dose-dependent effects of (−)-BPAP HCl on ipsilateral rotations in unilaterally 6-hydroxydopamine-lesioned rats. The number of rotations was counted for 1 h immediately after the subcutaneous administration of (−)-BPAP HCl. Each value represents an average for a group of eight rats, and the vertical bars represent S.E.M. $^{*}P < 0.05$ and $^{**}P < 0.01$ vs. saline-treated control group (Sal).

with restoration of the activity pattern observed in non-habituated normal rats.

Moreover, although ptosis was observed in 1 mg/kg reserpine-treated rats, this symptom was significantly improved by treatment with 3 mg/kg (−)-BPAP HCl ($P < 0.01$, Fig. 4A). In contrast, 2 mg/kg apomorphine HCl and 10–40 mg/kg amantadine HCl failed to improve reserpine-induced ptosis (Fig. 4B).

3.3. Effects of dopamine antagonists against (−)-BPAP-enhanced locomotor activity in normal or reserpine-treated rats

To determine if the effects of (−)-BPAP are mediated by activation of the dopaminergic system, we utilized subtype-specific dopamine receptor antagonists, SCH 23390 HCl and sulpiride. As shown in Fig. 5A, the dopamine D1 receptor-selective antagonist, SCH 23390 HCl, at a dose of 0.1 mg/kg, completely inhibited (−)-BPAP- and apomorphine-enhanced locomotor activity in normal rats. In contrast, the dopamine D2 receptor-selective antagonist, sulpiride (20 mg/kg), had no significant effect.

SCH 23390 HCl at 0.1 mg/kg also significantly inhibited apomorphine HCl-enhanced locomotor activity in reserpine-treated rats. We found no significant inhibitory effects of SCH 23390 HCl on 1 mg/kg s.c. (−)-BPAP HCl-enhanced locomotor activity, with regard to the cumulative motor activity over the 2-h observation period (Fig. 5B). As the locomotor enhancement by (−)-BPAP HCl in reserpine-treated rats was relatively selective for the initial phase of active exploration, we also analyzed the cumulative motor activity data for the initial 90 min. In this case, significant inhibition by SCH 23390 HCl of (−)-BPAP HCl-enhanced locomotor activity in reserpine-treated rats was observed (Fig. 5C). In either measure of the initial 90 min or 2-h observation periods, 20 mg/kg sulpiride did not show any significant effect on (−)-BPAP HCl- or apomorphine HCl-enhanced locomotor activity in reserpine-treated rats (Fig. 5B,C).

3.4. Rotational behavior in rats with unilateral 6-hydroxydopamine lesion of the dopaminergic nigrostriatal pathway

In unilateral 6-hydroxydopamine-lesioned rats, 0.1–3.0 mg/kg s.c. (−)-BPAP HCl caused ipsilateral rotations in

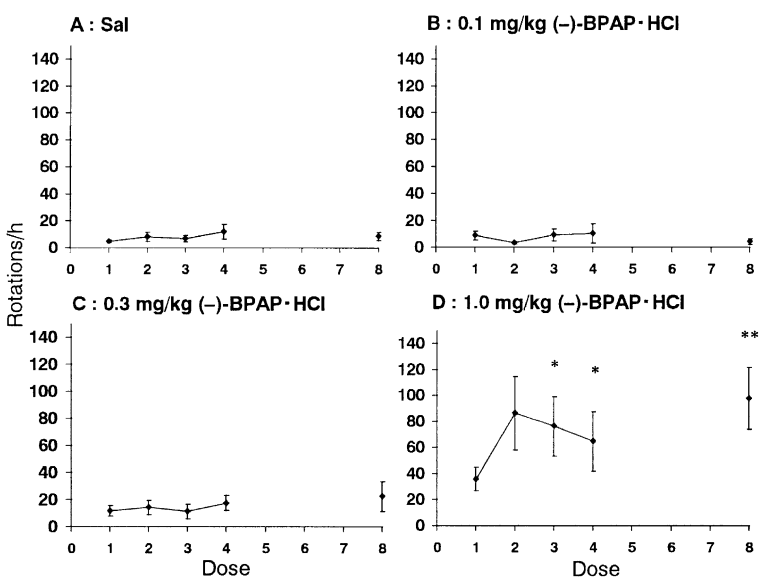

Fig. 7. Effects of repeated treatment with (−)-BPAP HCl on ipsilateral rotations in unilaterally 6-hydroxydopamine-lesioned rats. A, B, C and D show saline (Sal), 0.1, 0.3 and 1.0 mg/kg s.c. (−)-BPAP HCl-treated groups, respectively. Eight doses of (−)-BPAP HCl were given to 6-hydroxydopamine-lesioned rats at 1–3-day intervals within 10 days. Rotation was counted during a 1-h period immediately after treatment with (−)-BPAP HCl, at doses 1, 2, 3, 4 and 8. Each point represents mean cumulative activity from five successive experiments, and vertical bars represent S.E.M. ($n = 8$). Statistical analyses were performed with a paired t-test. $^{*}P < 0.05$ and $^{**}P < 0.01$ vs. the value after the first dose.

a dose-dependent manner (Fig. 6). The minimum dose of (−)-BPAP HCl that induced a significant number of rotations was 0.3 mg/kg.

In addition, unilateral 6-hydroxydopamine-lesioned rats were treated with (−)-BPAP HCl eight times at 1–3-day intervals (Fig. 7). Although 0.1 and 0.3 mg/kg (−)-BPAP HCl induced no significant changes at the dose of 1 mg/kg, the rotation behavior was significantly increased after three, four and eight doses, as compared to that after the first dose ($P < 0.05$, Fig. 7).

4. Discussion

The present study demonstrated that (−)-BPAP HCl, which is a novel compound showing the "catecholaminergic and serotoninergic activity enhancer" effect (Knoll et al., 1999; Yoneda et al., 2001), produces a dose-dependent increase in locomotor activity of non-habituated rats. Moreover, (−)-BPAP HCl was demonstrated to produce a dose-dependent antiparkinsonian response in a reserpine model of Parkinson's disease. This is the first demonstration of the effectiveness of a "catecholaminergic and serotoninergic activity enhancer" compound in an acute animal model of Parkinson's disease.

These behavioral effects of (−)-BPAP HCl are considered to be mediated by dopamine release through its "catecholaminergic activity enhancer" effect, because (−)-BPAP HCl induced ipsilateral rotations in unilateral 6-hydroxydopamine-lesioned rats, and the (−)-BPAP HCl-induced locomotor activity was completely inhibited by the dopamine D1 receptor antagonist, SCH 23390 HCl. These results suggested that the "catecholaminergic activity enhancer" effect is more important than the "serotoninergic activity enhancer" effect, in the light of the improvement of motor deficits in the models of Parkinson's disease. Repeated administration of 1 mg/kg (−)-BPAP HCl increased the response to this compound in unilaterally 6-hydroxydopamine-lesioned rats, which may have been due either to sensitization, resembling the effects of several dopamine receptor agonists (Klug and Norman, 1993; Kostrzewa, 1995), or to pharmacokinetic mechanisms involving accumulation of the compound in the brain.

The dopamine D2 receptor antagonist, sulpiride, failed to inhibit locomotor enhancement by (−)-BPAP HCl and apomorphine HCl. Several investigators have also reported that sulpiride does not inhibit the hyperlocomotion induced by dopaminergic activation. Fritts et al. (1997, 1998) reported that amphetamine-, dexbenzetimide- or scopolamine-induced hyperlocomotion and stereotypy were decreased by the dopamine D1 receptor antagonist, SKF 83566, but not by the dopamine D2 receptor antagonist, sulpiride. However, other studies showed that the dopamine D2 receptor antagonists, raclopride and eticlopride, reduced the locomotor stimulation by *d*-amphetamine, phencyclidine and diazepam (Lapin and Rogawski, 1995), and by the nicotinic cholinergic agonist, SIB-1765F (Menzaghi et al., 1997a,b), respectively. Thus, although dopamine D2 receptor antagonism may reduce the hyperlocomotion induced by various substances, the action of sulpiride may be complex, compared with that of other D2 receptor antagonists.

In normal non-habituated rats, (−)-BPAP HCl increased motor activity during the entire 2-h observation period. On the other hand, apomorphine decreased motor activity during the period of active exploration because of stereotypy. In the treatment of Parkinson's disease, the benefits of dopamine agonists on motor functions are due to their ability to activate dopaminergic receptors on postsynaptic neurons. Amantadine stimulates dopamine release from dopaminergic terminals (Scatton et al., 1970; Von Voigtlander and Moore, 1971). On the other hand, although "catecholaminergic activity enhancer" compounds are also able to induce dopamine release from dopaminergic terminals, this effect seems to be dependent on the degree of firing activity of presynaptic axons (Knoll et al., 1996a,b,c). Such unique actions were also observed in vivo in animal model systems. Using the two-way shuttle box, Knoll et al. (1996a,b,c) showed that treatment of tetrabenazine-induced depression model rats, with "catecholaminergic activity enhancer" compounds such as (−)-PPAP and (−)-BPAP, significantly increased a conditioned avoidance response (Knoll et al., 1996a, 1999). However, "catecholaminergic activity enhancer" compounds did not induce a significant increase in intersignal reactions. It has been reported that amphetamine significantly increased intersignal reactions, as well as a conditioned avoidance responses, in a conditioned avoidance task (Knoll et al., 1992). It was also reported that methamphetamine and spocolamine facilitated the avoidance response with an increase in the response rate in Sidman avoidance (Kuribara, 1982).

Furthermore, in the present study, (−)-BPAP HCl improved reserpine-induced ptosis, a parameter widely used in evaluation of antidepressant action (Claassen et al., 1977; Miyamoto et al., 1996), while two antiparkinsonian agents, apomorphine and amantadine, failed to affect this parameter. Non-motor symptoms of Parkinson's disease, such as depression unresponsive to antiparkinsonian drugs (Fibiger, 1984; Mayberg and Solomon, 1995), may not be related only to dopaminergic deficits, but also to noradrenergic and serotoninergic deficits (Agid et al., 1984; Gerlach et al., 1994). In this context, the effects of (−)-BPAP on noradrenergic and serotoninergic systems are likely to be important for the non-motor symptoms in animal models of Parkinson's disease, an aspect which should be studied in detail in future.

In conclusion, (−)-BPAP HCl showed motor-stimulant effects in rats, and reversed hypolocomotion in reserpine-induced acute Parkinson's model rats. These effects were

dependent on the dopamine receptor activation subsequent to dopamine release due to "catecholaminergic activity enhancer" effects. In addition, "catecholaminergic and serotoninergic activity enhancer" compounds are expected to show different pharmacological profiles from those of established dopamine agonists in clinical trials for Parkinson's disease.

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