*Pharmacology Biochemistry & Behavior*, Vol. 24, pp. 1409–1415, 1986. © Ankho International Inc. Printed in the U.S.A. 0091-3057/86 $3.00 + .00

# Involvement of Extrapyramidal Motor Mechanisms in the Suppression of Locomotor Activity by Antipsychotic Drugs: A Comparison Between the Effects Produced by Pre- and Post-Synaptic Inhibition of Dopaminergic Neurotransmission

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Received 29 April 1985

AHLENIUS, S. AND V. HILLEGAART. *Involvement of extrapyramidal motor mechanisms in the suppression of locomotor activity by antipsychotic drugs: A comparison between the effects produced by pre- and post-synaptic inhibition of dopaminergic neurotransmission.* PHARMACOL BIOCHEM BEHAV **24**(5) 1409–1415, 1986.—The effects of two proposed dopaminergic autoreceptor agonists, (−)3-(3-hydroxyphenyl)-N-*n*-propylpiperidine (3-PPP) and the azepine derivative B-HT 920, on spontaneous locomotor activity, treadmill locomotion, and catalepsy in the rat have been compared with the effects produced by the postsynaptic dopamine (DA) receptor blocking agent haloperidol. It was found that the threshold dose for suppression of exploratory locomotor activity was 0.5, 0.005 and 0.2 mg/kg for (−)3-PPP, B-HT 920 and haloperidol, respectively. The corresponding doses for suppression of treadmill locomotion were 8.0, 5.12 and 0.2 mg/kg, respectively. Furthermore, (−)3-PPP and B-HT 920, in contrast to haloperidol, did not produce any catalepsy. Thus, using exploratory locomotor activity as an index of limbic forebrain DA functions and treadmill locomotion and catalepsy as indices of extrapyramidal DA functions, the DA autoreceptor agonists, in contrast to the postsynaptic antagonist, show a difference in the doses required to produce these effects. The designation of the behavioral functions as "limbic" or extrapyramidal is supported by the finding that scopolamine, 0.8 mg/kg, antagonized the haloperidol-induced suppression (0.2 mg/kg) of treadmill locomotion, but not the suppression of exploratory locomotor activity.

Dopamine Autoreceptors Locomotor activity Extrapyramidal motor effects Rat

IT has been shown in animal experiments that apomorphine, which at low doses activates dopamine (DA) autoreceptors, has sedative properties [18,34], while apomorphine or norpropylapomorphine administered to man in low doses may produce antipsychotic effects [17, 37, 38]. This antipsychotic effect is probably due to autoreceptor activation. Clinical use of these drugs, however, is limited, as postsynaptic DA receptors are activated with increasing doses resulting often in emesis and possibly exacerbation of the psychotic symptoms (see [8]).

Two new compounds, the (−)enantiomer of 3-(3-hydroxyphenyl)-N-*n*-propylpiperidine (3-PPP) and the azepine derivative B-HT 920 appear to inhibit central DA neurotransmission by selective stimulation of the DA autoreceptors [7, 9, 25]. Theoretically, these compounds should be useful in the treatment of schizophrenia. Preclinical experiments show that fewer extrapyramidal side effects are found [2,15] and, in contrast to classical antipsychotic agents, no increase in plasma levels of prolactin have been seen in rats treated with 3-PPP or B-HT 920 [12, 19, 20, 28].

Extrapyramidal motor disturbances are side effects commonly associated with antipsychotic drugs in current use. In fact, it can be questioned whether extrapyramidal signs and clinical efficacy can be separated (see [11]). The mechanism of action is inhibition of the central post-synaptic DA and, possibly, noradrenaline (NA) receptors (see [13]).

The effects of exploratory locomotor activity and on extrapyramidal motor mechanisms are thought to be mediated via different brain areas. Drugs with different mechanisms of action may influence these areas differently. The suppres-

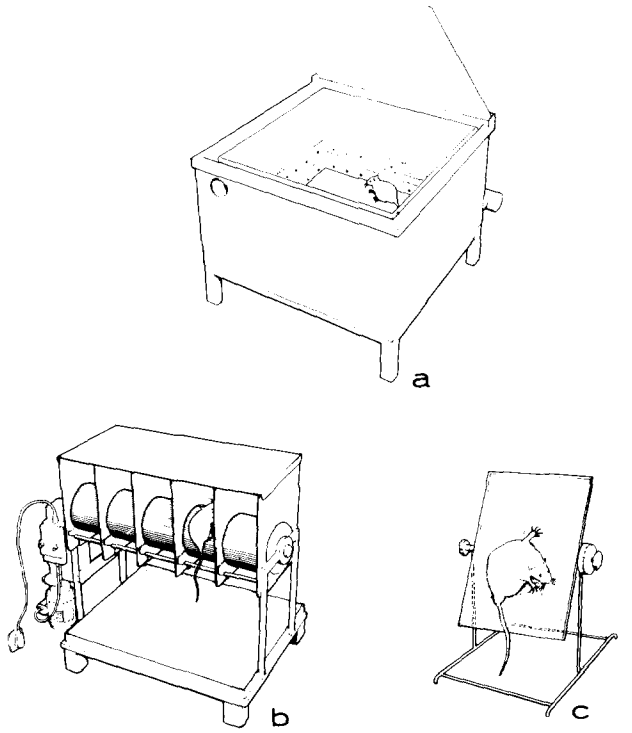


FIG. 1. Schematic drawings of the equipment used for measuring (a) spontaneous motor activity, (b) treadmill performance and (c) catalepsy. For further details see text.

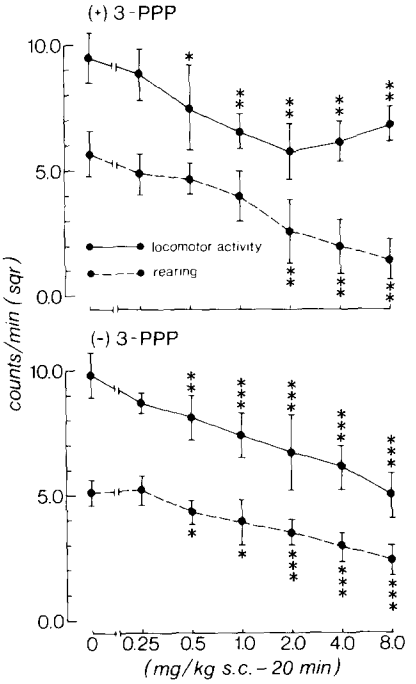


FIG. 2. Effects of 3-PPP enantiomers on spontaneous motor activity. (+) and (−)3-PPP were administered in different doses and tested 20 min after the injection. The results are based on the performance of 5–6 animals/dose and are represented as means±S.D. *Locomotor activity:* $F(6,28)=9.05$, $p<0.001$ [(+)3-PPP]; $F(6,35)=17.61$, $p<0.001$ [(−)3-PPP]. *Rearing:* $F(6,28)=13.86$, $p<0.001$ [(+)3-PPP]; $F(6,35)=17.24$, $p<0.001$ [(−)3-PPP]. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

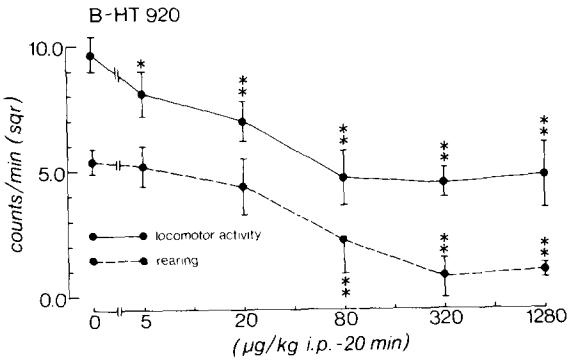


FIG. 3. Effects of B-HT 920 on spontaneous motor activity. B-HT 920 was administered in different doses and tested 20 min after the injection. The results are based on the performance of 5 animals/dose and are represented as means±S.D. in the figure. *Locomotor activity:* $F(5,24)=27.07$, $p<0.001$; *Rearing:* $F(5,24)=29.91$, $p<0.001$. $^{*}p<0.05$, $^{**}p<0.01$.

sion of exploratory locomotor activity in the rat by low doses of apomorphine or DA, as well as by the antipsychotic agent *cis*-flupenthixol, is mediated via interactions with dopaminergic receptors in the nucleus accumbens of the limbic forebrain [24, 31, 35]. These effects may be homologous with the clinical effects produced by antipsychotic drugs. The extrapyramidal effects produced by antipsychotic drugs in animals and in man have been ascribed to a blockade of postsynaptic DA receptors in the neostriatum. Clinical and laboratory findings support this contention. It is well known that extrapyramidal side effects, induced by antipsychotics, can be counteracted by concomitant administration of anticholinergics (see [11,33]). Secondly, the increase in neostriatal (but not limbic) DA turnover induced by haloperidol can be antagonized by anticholinergics [4,5].

In the following experiments we have investigated to which extent extrapyramidal effects contribute to the suppression of exploratory locomotor activity by the DA receptor blocking agent haloperidol [6] and made a comparison with the effects produced by (−)3-PPP and B-HT 920. Exploratory locomotor activity has been monitored in an open field arena equipped with photocells, and the extrapyramidal effects have been evaluated by observing treadmill locomotion and catalepsy.

## METHOD

### *Animals*

Male Sprague-Dawley rats (Anticimex, Sollentuna, Sweden), 280–320 g, were used. The animals arrived from the breeder at least one week before being used in experiments, and were housed under constant conditions of temperature (21°C), relative humidity (50–60%) and light/dark cycle (dark 06.00–18.00). Food (R3, Ewos, Södertälje, Sweden) and tap water was available ad lib. Experiments were performed between 09.00 and 18.00.

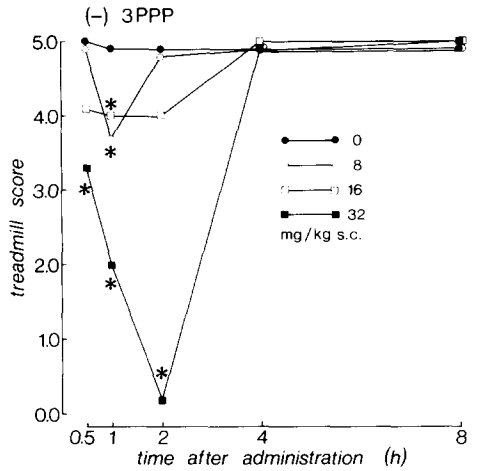


FIG. 4. Effects of (−)3-PPP on treadmill performance. (−)3-PPP was administered in different doses at time 0 min and tested at various time intervals as indicated in the figure. The dose of 4 mg/kg did not differ from saline controls at any time interval and these results are not shown in the figure. The results are based on the performance of 9–11 animals/dose and the results are represented as medians. Kruskal-Wallis two-way ANOVA: $H(4)=14.7$, $p<0.01$ (0.5 hr); $H(4)=10.0$, $p<0.05$(1 hr); $H(4)=1.9$, n.s. (2 hr); $H(4)=5.4$, n.s.(4 hr); $H(4)=1.90$, n.s. (8 hr). $^{*}p<0.05$.

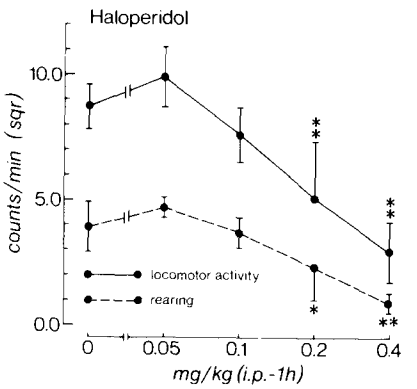


FIG. 5. Effects of haloperidol on spontaneous motor activity. Haloperidol was administered in different doses and tests were performed 1 hr after the injection. The results are based on the performance of 5 animals/dose and are represented as means±S.D. in the figure. *Locomotor activity:* $F(4,20)=20.83$, $p<0.001$. *Rearing:* $F(4,20)=16.08$, $p<0.001$. $^{*}p<0.05$, $^{**}p<0.01$.

*Spontaneous Motor Activity*

The animals were observed in a square open field arena (680×680×450 mm) equipped with two rows of 8 infralight sensitive photocells placed 40 and 125 mm above the floor of the pen, respectively. The photocells were spaced 90 mm apart and the last photocell in a row was spaced 25 mm from the wall (see Fig. 1a). Interruptions of photocell beams were collected by means of a microcomputer and allowed the recording of the following variables: *Locomotor activity* (all horizontal activity as measured by the entire lower row of photocells); *Peripheral activity* (activity along the walls as measured by the photocells spaced 25 mm from the wall only); *Rearing* (vertical activity as measured by the upper row of photocells). The data were fed on-line to VAX 11-780 equipment (Digital Equipment Corporation, Maynard, MA). Time (1–99 min), and the number of cycles recorded (1–99), were preset by the experimenter. The open field was enclosed in a ventilated, sound-attenuating box with a Plexiglas top. Two sets of equipment were housed together in a dark room.

*Treadmill, Motor Activity*

The animals were trained to walk on a drum (diameter: 166 mm) rotating at a speed of 8 rpm (Fig. 1b). This was found to be the lowest speed that ensured continuous forward locomotion (4 m/min). The rats were trained to walk for 3 min twice a day for two days. Additional 3 min tests were provided on the second day for those rats unable to walk unaided in the last test that day.

On the day of experimentation, a pretest was performed, and only those rats that were able to walk unaided for 3 min were used in the experiments. Tests were performed for a maximal time of 2.5 min preceeded by a 0.5 min warm-up. Treadmill performance was scored from 0–5 according to the time (square root transformation), the animals walked on the drum (min): 0=0–0.08, 1=0.09–0.35, 2=0.36–0.80, 3=0.81–1.42, 4=1.43–2.24, 5=>2.25 min.

*Catalepsy*

Animals were placed on an inclined (60°) grid (Fig. 1c) and, excluding the first 30 sec, the time the rat remained in the same position was measured for a maximum of 2.5 min. The catalepsy was scored in the same manner as the treadmill performance (see above), i.e., if the rat remained immobile for >2.25 min it was scored as 5, etc.

*Drugs*

The following drugs were used: 3-(3-hydroxyphenyl)-N-*n*-propylpiperidine·HCl (3-PPP) enantiomers (Astra Läkemedel AB, Södertälje, Sweden), 6-allyl-2-amino-5,6,7,8-tetra-hydro-4H-thiazolo-[4,5-d] azepin·2HCl (B-HT 920, Boehringer Ingelheim KG, Ingelheim am Rhein, GFR), haloperidol (Janssen Leo Farma AB, Helsingborg, Sweden), (−) scopolamine·HBr (Sigma, St. Louis, MO). 3-PPP enantiomers, B-HT 920 and scopolamine were dissolved in 0.9% NaCl. Haloperidol was dissolved in a minimal quantity of glacial acetic acid and diluted to the final volume with distilled water. 3-PPP enantiomers were administered subcutaneously, whereas all the other drugs were given intraperitoneally. The injected volume was kept constant at 2 ml/kg. Controls received the solvent vehicle.

*Statistics*

The *Spontaneous motor activity* data were subjected to a square root (sqr) transformation and analysed by means of a one-way ANOVA followed by the Dunnett's *t*-test for comparisons with saline treated controls [39]. Treadmill motor activity and catalepsy data were analysed by means of the

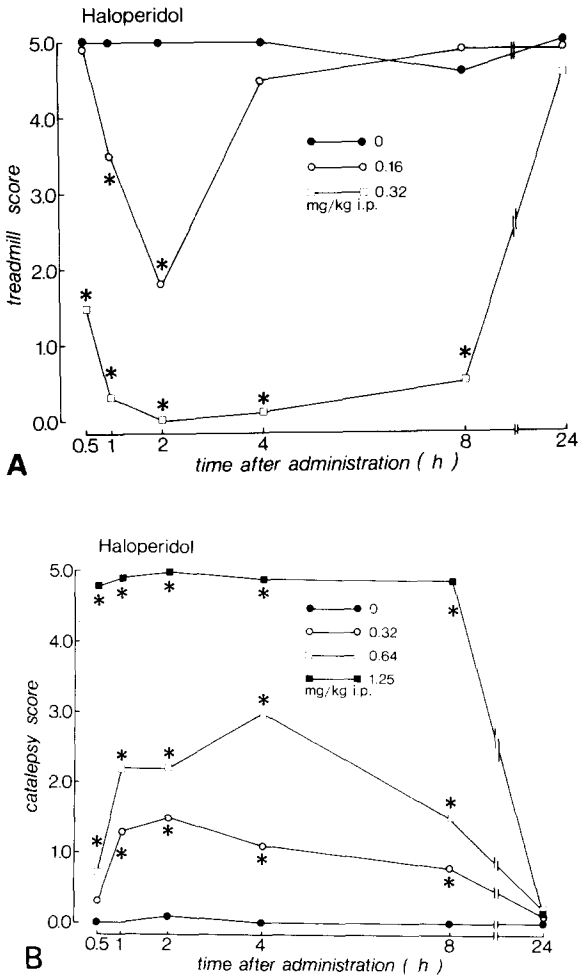


FIG. 6. Effects of haloperidol on treadmill performance (A) and on catalepsy (B). Haloperidol was administered in different doses at time 0 hr as indicated in the figures. A: Two more doses, 0.08 and 0.64 mg/kg were included in the experiment. The effects of these doses did not differ from controls and 0.32 mg/kg, respectively, and are not shown in the figure. Kruskal-Wallis two-way ANOVA: $H(4)=38.8$, $p<0.01$ (0.5 hr), $H(4)=45.9$, $p<0.01$ (1 hr); $H(4)=46.2$, $p<0.01$ (2 hr); $H(4)=42.9$, $p<0.01$ (4 hr); $H(4)=30.5$, $p<0.01$ (8 hr); $H(4)=15.7$, $p<0.01$ (24 hr). B: In addition to the doses shown in this figure, 2.5 mg/kg was administered. However, the results from this dose did not differ from the 1.25 mg/kg dose and are not shown in the figure Kruskal-Wallis two-way ANOVA: $H(4)=28.6$, $p<0.01$ (0.5 hr); $H(4)=32.7$, $p<0.01$ (1 hr); $H(4)=36.8$, $p<0.01$ (2 hr); $H(4)=38.5$, $p<0.01$ (4 hr); $H(4)=41.2$, $p<0.01$ (8 hr); $H(4)=1.5$, n.s. (24 hr). The results presented in the figure are based on the performance of 12 animals/dose, which were tested repeatedly at the different time intervals shown; and the results are represented as medians. $^*p<0.05$.

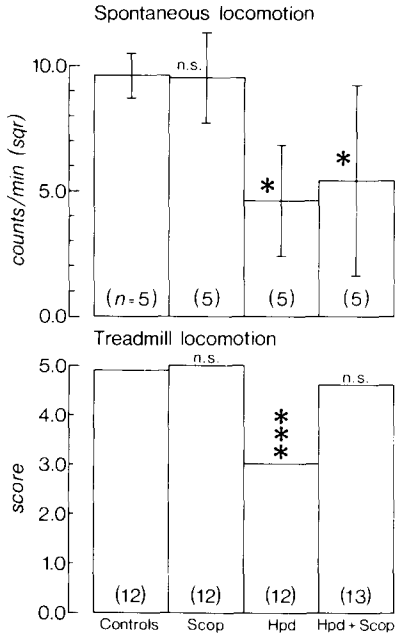


FIG. 7. Effects of scopolamine (scop) on haloperidol (hpd)-induced suppression of spontaneous locomotion and on treadmill locomotion. Haloperidol, 0.2 mg/kg IP, was administered 1 hr and scopolamine, 0.8 mg/kg IP, 30 min before the behavioral observations. Top: The spontaneous locomotor activity is represented by the *Locomotor activity*: $F(3,16)=5.93$, $p<0.01$. Shown are the means ± S.D. Bottom: $H(3)=14.16$, $p<0.01$. Shown are the medians. n.s. $p>0.05$, $^*p<0.05$, $^{***}p<0.01$.

TABLE 1

| | Drug (threshold dose mg/kg) | | |
|---|---|---|---|
| | HPD | (−)-3-PPP | B-HT 920 |
| Treadmill (TM) | 0.2 | 8.0 | >5.12 |
| Locomotor activity (LMA) | 0.2 | 0.5 | 0.005 |
| TM/LMA | 1 | 16 | >1000 |

Kruskal-Wallis two-way ANOVA and followed by the Mann-Whitney U-test for individual comparisons [32]. $p>0.05$ was considered as statistically not significant (n.s.).

## RESULTS

### *Effects of Stimulation of Dopaminergic Autoreceptors on Spontaneous Motor Activity*

*3-PPP enantiomers (Fig. 2).* The *Locomotor activity* was significantly reduced by 0.5 mg/kg SC and higher doses of (+)3-PPP. There was a tendency that the effect was reversed at doses above 2 mg/kg. The *Rearing* activity, however, showed a dose-dependent reduction. (−)3-PPP (0.5–8.0 mg/kg SC) produced a dose-dependent suppression of both the *Locomotor activity* and of *Rearing*. The maximal suppression

by either enantiomer was about 50% of the spontaneous motor activity displayed by saline treated controls.

*B-HT 920 (Fig. 3).* Therre was a statistically significant effect with the administration of 5 μg/kg (IP) of B-HT 920 and there was a dose-dependent suppression of the *Locomotor activity* and *Rearing* up to 80–320 μg/kg IP. In agreement with results obtained with 3-PPP enantiomers, the maximal suppression was about 50% of the activity displayed by saline treated controls.

*Effects of Stimulation of Dopaminergic Autoreceptors on Treadmill Locomotion and Catalepsy*

*(−)3-PPP (Fig. 4).* A dose of 8 mg/kg SC was needed to significantly suppress treadmill locomotion and the effect increased in a dose-dependent manner, 8.0–32.0 mg/kg SC. The effect was maximal 1–2 hr after the injection, and all animals had recovered completely by 4 hr. It was not possible to induce catalepsy with doses up to 32 mg/kg, SC.

*B-HT 920.* There was a slight but not statistically significant effect at the 5.12 mg/kg IP dose of B-HT 920, in comparison with saline treated controls at the 30 min time interval (treadmill score 4.0 and 4.8 respectively). There was no evidence of effects with lower doses and there were no signs of catalepsy in doses up to 5.12 mg/kg IP.

*Effects of Haloperidol on Spontaneous Motor Activity, Treadmill Locomotion and Catalepsy*

There was a slight tendency for an increase in the *Locomotor activity* by the lowest dose used, 0.05 mg/kg IP, whereas higher doses produced a dose-dependent suppression of the *Locomotor activity* and of *Rearing* (Fig. 5). Treadmill locomotion was significantly suppressed by 0.16 mg/kg IP and a complete suppression of the performance was obtained with 0.32 mg/kg IP, 2–4 hr after the injection (Fig. 6A). The effect was maximal 2–8 hr after the injection depending on dose. Catalepsy was produced by 0.32 mg/kg IP and increased in a dose-dependent manner up to 1.25 mg/kg IP at which dose maximal catalepsy was obtained (Fig. 6B). The effect lasted for at least 8 hr and all animals had recovered by 24 hr.

*Antagonism by Scopolamine of the Haloperidol-Induced Suppression of Treadmill Locomotion but not Spontaneous Locomotion*

In agreement with the experiments described above, there was a statistically significant suppression of *Locomotor activity* (Fig. 7, top) and of treadmill locomotion (Fig. 7, bottom) by 0.2 mg/kg IP of haloperidol. The suppression of treadmill locomotion was antagonized by the administration of 0.8 mg/kg IP of scopolamine. The *Locomotor activity*, however, was still significantly suppressed by haloperidol in the presence of scopolamine. Scopolamine (0.8 mg/kg IP) by itself produced no statistically significant effects on *Locomotor activity* or on treadmill locomotion.

## DISCUSSION

The initial (15 min) locomotor activity and the number of rearings in a novel environment have been taken as indices of exploratory locomotor activity. In these experiments we see that (−)3-PPP and B-HT 920 [7,9,25], like the postsynaptic DA receptor antagonist haloperidol, suppress the exploratory locomotor activity of rats. At the same time, the drugs differ markedly in their ability to produce catalepsy and to suppress treadmill motor activity. In fact, (−)3-PPP and B-HT 920 do not produce any catalepsy at all. Furthermore, in comparison with haloperidol, high doses of (−)3-PPP are needed to suppress a conditioned avoidance response (CAR), which also may be considered an index of extrapyramidal side effects [2,15].

It is well known that extrapyramidal side effects of antipsychotic drugs can be counteracted by the administration of anticholinergic agents (see Introduction). Furthermore, catalepsy or a suppression of CAR performance in the rat can be antagonized by anticholinergics [23,29]. The findings in the present experiments that the suppression of treadmill performance in rats, but not exploratory locomotor activity, was antagonized by scopolamine, shows that treadmill performance may be a measure of extrapyramidal motor functions.

A number of experiments have shown that spontaneous locomotor activity is mediated via dopaminergic mechanisms in the limbic forebrain, particularly the nucleus accumbens [26,30], whereas extrapyramidal motor mechanisms are mediated via the neostriatum (see[21,27]). Limbic dopaminergic areas of the forebrain are probably important in the effects produced by haloperidol since the suppression of treadmill performance, but not the suppression of exploratory locomotion, was counteracted by scopolamine treatment. Our experiments indicate, however, that exploratory locomotor activity and treadmill performance were suppressed by about the same dose and a clear separation of these effects is not possible. In contrast, (−)3-PPP and B-HT 920 produce a suppression of exploratory locomotor activity at doses which do not produce any signs of extrapyramidal effects (Table 1). There is direct evidence that the suppression of exploratory locomotor activity by (−)3-PPP or B-HT 920 administration is, at least partially, due to inhibition of DA neurotransmission in the nucleus accumbens [1,36] and thus indicates the antipsychotic potential of these drugs. It should not be excluded, however, that effects by these drugs in the neostriatum may also contribute to the suppression of locomotion after systemic administration. It is well known that clinical efficacy and the incidence of extrapyramidal symptoms are correlated.

Another interesting aspect of (−)3-PPP and B-HT 920 is their inability to produce increases in plasma prolactin levels. Both drugs actually suppress plasma prolactin levels in reserpine-treated animals [20,28]. A possible explanation for this effect, that at least applies to (−)3-PPP, is partial agonist properties of the drug [16,22]. This would also explain emetic, and other agonist properties of (−)3-PPP as seen, e.g., in denervated preparations [10]. The apparent autoreceptor selectivity in normal animals may be due to a greater sensitivity at the autoreceptor as compared to the postsynaptic receptor. In this respect the DA receptor at the lactotroph and in the emetic chemotrigger zone of the area postrema are similar to the autoreceptor [14].

In conclusion, an activation of central DA autoreceptors by (−)3-PPP or B-HT 920 produces a suppression of exploratory locomotor activity in the rat, as has also been shown for a number of antipsychotic drugs that block postsynaptic DA receptors. However, much higher doses of the apparent DA autoreceptor agonist are needed to produce signs of extrapyramidal motor effects in comparison with the classical antipsychotic DA receptor blocking agents. This indicates a preferential action of the autoreceptor agonists in limbic as compared to striatal dopaminergic areas. The explanation for this apparent selectivity, however, awaits further investigation.

ACKNOWLEDGEMENTS

The open field apparatus was built by Mr. Ulf Jonsson and Mr. Roland Elgh, Indivent AB, Mölndal, Sweden. The treadmill and catalepsy equipment were built by Mr. Tage Andersson, Astra Läkemedal AB, Södertälje, Sweden. Figures 2–7 were prepared by Ms. Madelene Kröning at the Department of Psychology, University of Göteborg, Sweden and Fig. 1 by Mr. Lars Johansson, Södertälje, Sweden. We thank Ms. Rybbina Svärd for revising the language and Ms. Kerstin Norman for help in typing and editing the manuscript. The generous supply of drugs by Boehringer Ingelheim KG and Janssen Leo Farma AB is gratefully acknowledged. It is a special pleasure to acknowledge the efforts of Ms. Kicki Norén and Ms. Gun Pettersson in this project.

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