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## Antagonism by haloperidol of the suppression of exploratory locomotor activity induced by the local application of (-)3-(3-hydroxyphenyl)-N-*n*-propylpiperidine into the nucleus accumbens of the rat[1]

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*Summary.* The injection of (-)3-PPP into the nucleus accumbens, 10 µg/side, produced a suppression of exploratory locomotor activity without affecting treadmill locomotion. Furthermore, the suppression of exploratory locomotor activity produced by (-)3-PPP was antagonized by the administration of haloperidol, 25–50 µg/kg i.p.

The 2 enantiomers of 3-(3-hydroxyphenyl)-N-*n*-propylpiperidine (3-PPP) are both biologically active as central dopamine (DA) receptor agonists. The (-) enantiomer selectively activates DA autoreceptors, whereas (+)3-PPP is a DA agonist at both autoreceptors and postsynaptic receptors. In addition to its actions at autoreceptors, (-)3-PPP appears also to block postsynaptic DA receptors[3]. Recently we demonstrated that the local injection of 3-PPP enantiomers into the nucleus accumbens of the rat produced a suppression of exploratory locomotor activity[4]. In agreement with biochemical and pharmacological evidence as mentioned above, (-)3-PPP was the most potent enantiomer. In the work described in the present report we investigated the specificity of the response to the local application of (-)3-PPP in 2 ways: by (1) an examination of the ability of animals thus treated to display coordinated forward locomotion on a treadmill and, (2) an attempt to antagonize the (-)3-PPP-induced suppression of exploratory locomotor activity by pretreatment with low doses of the DA receptor antagonist haloperidol (HPD)[5]. HPD may block DA autoreceptors preferentially when administered at low doses[6,7].

*Materials and methods.* Adult male Sprague-Dawley rats (Anticimex, Sollentuna, Sweden), 280–320 g, were used. The animals were housed under a constant dark-light cycle (dark 11.00–23.00 h), temperature and relative humidity, with food and water available ad libitum. The animals arrived in the laboratory at least 1 week before they were used in the experiments. Cranial cannulation for injections into the nucleus accumbens was carried out under deep anesthesia as previously described[4]. Intracerebral injections of (-)3-PPP·HCl (synthesized at Reseach and Development Laboratories, Astra Läkemedel AB) or physiological saline were made 24–30 h after surgery. Injection volume was 1 µl/side, injected over 45 sec and the cannula was left in place for an additional 30 sec before being retracted. HPD (generously donated by Janssen Leo Farma AB, Helsingborg, Sweden) was dissolved in a few drops of glacial acetic acid with 5.5% glucose added to final volume. HPD was administered i.p. in a volume of 2 ml/kg. The animals tested for motor coordination were trained to walk on a rotating drum (∅ = 166 mm) (treadmill) in 2 consecutive days (3–6 min training/day). On the following day, the animals were given a pretest and an animal which was not able to walk continuously on the treadmill for 3 min was excluded. The open field observations were made in a square arena (0.49 $m^2$) as previously described[8]. The injection site was checked by standard histological procedures after completion of the experiments. Each animal was used once only.

*Results and conclusions.* With the exception of the highest dose of (-)3-PPP, 160 µg/side, there were no statistically significant effects of local injection of (-)3-PPP into the nucleus accumbens on treadmill performance (fig. 1). This observation indicates that the decrease in exploratory locomotor activity previously observed after local injection of (-)3-PPP into the nu-

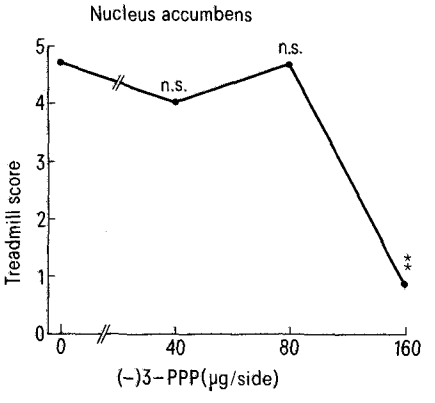


Figure 1. Effects of local injection of (-)3-PPP into the nucleus accumbens on treadmill performance in the rat. Animals trained to the criterion ( > 3 min continuous walk) were tested on the treadmill 6 min after completion of bilateral application of (-)3-PPP or saline into the nucleus accumbens. The animals were scored 0–5 according to time spent on the treadmill using a square root transformation ( > 2.25 min = maximal score). There were 5 animals/group and the figure shows median values. The data were subject to the nonparametric Kruskal-Wallis 1-way ANOVA followed by the Mann-Whitney U-test when comparing drug effects with saline controls[9]. $H(3) = 9.40$, $p < 0.05$; n.s., $p > 0.05$; ** $p < 0.02$.

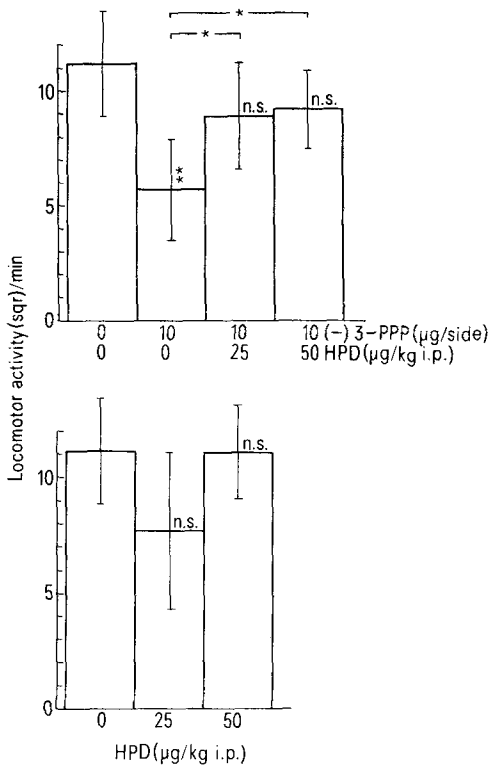


Figure 2. Antagonism by systemically administered HPD of the suppression of exploratory locomotor activity induced by the local application of (-)3-PPP into the nucleus accumbens of the rat. Naive animals were placed in the open field arena 6 min, following completion of bilateral application of (-)3-PPP, 10 µg/side, or saline, 1 µl/side. HPD, 25–50 µg/kg i.p., or 5.5% glucose pretreatment was administered 30 min before locomotor activity recording. The figure shows the exploratory locomotor activity (square root transformation, mean ± SD) of 7 animals/group during 3 min in the open field. The data were subject to an 1-way ANOVA followed by the Newman-Keul's test for individual comparisons[10]. The statistical analysis was performed on the data as grouped in the figure using the same saline controls. Top: $F(3/24) = 7.91$, $p < 0.01$; bottom: $F(2/18) = 4.02$, $p > 0.05$; n.s., $p > 0.05$; *$p < 0.05$; **$p < 0.01$.

cleus accumbens, in doses below 160 µg/side[4], is not due to a disturbance of motor coordination or other unspecific effects of the drug. Figure 2 (top) shows that, in agreement with our previous observations[4] there was a statistically significant suppression of the exploratory locomotor activity by the local injection of (-)3-PPP, 10 µg/side, into the nucleus acumbens. The effect is probably not due to diffusion to other brain areas since local injection of this or higher doses (20–80 µg/side) into the neostriatum is ineffective[4]. The suppression of the exploratory locomotor activity by (-)3-PPP was statistically significantly antagonized by i.p. injection of HPD, 25–50 µg/kg. HPD by itself had no significant effects on the exploratory locomotor activity (fig. 2, bottom). The present results show (1) that the exploratory locomotor activity suppression induced by (-)3-PPP injected locally into the nucleus accumbens is not due to any disturbance of motor coordination and (2) that the locomotor suppression is most probably due to stimulation of DA autoreceptors, since the effect can be antagonized by the administration of low doses of HPD.

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## Little effect of dimethyl sulfoxide on blood-brain barrier to dopamine[1]

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*Summary.* Rats were treated with dimethyl sulfoxide (DMSO) intraperitoneally or intravenously, and simultaneously with dopamine (DA). The presence of DMSO resulted in small or no increases in brain levels of DA or its metabolites.

Levodopa (L-DOPA), which is the principal therapeutic agent for Parkinson's disease, crosses the blood-brain barrier and is converted by DOPA decarboxylase to dopamine. L-DOPA is used because dopamine, the physiologically active neurotransmitter, does not readily cross the blood-brain barrier[3]. With long-term L-DOPA therapy many patients experience a number of fluctuations in their response such as the 'wearing-off' phenomenon, whereby the effect of L-DOPA fades after a short period of time following each dose, and the 'on-off' phenomenon, whereby the fluctuations are sudden and unpredictable[4]. Some patients with advanced Parkinson's disease become more resistant to L-DOPA and derive less benefit over time. One possible mechanism for the fluctuations and the loss of efficacy could be reduced decarboxylation of L-DOPA to dopamine in brain. DOPA decarboxylase is low in both striatum and substantia nigra in patients with Parkinson's disease as opposed to controls[5]. Hence it would be of some interest to see if it is possible to get peripheral dopamine into the brain and then utilize dopamine directly as the therapeutic agent. This paper reports an attempt to use dimethyl sulfoxide (DMSO) to facilitate the transport of dopamine across the blood brain barrier.