

Drug-Induced Modulation of Locomotor Hyperactivity Induced by Picrotoxin in Nucleus Accumbens

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MORGENSTERN, R., T. MENDE, R. GOLD, P. LEMME AND W. OELSSNER. *Drug-induced modulation of locomotor hyperactivity induced by picrotoxin in nucleus accumbens*. PHARMACOL BIOCHEM BEHAV 21(4) 501-506, 1984.—Locomotor hyperactivity was induced in rats by bilateral injection of picrotoxin (PIC) into the nucleus accumbens (NAC) followed by intraperitoneal (IP) or intra-accumbens (IA) injection of agents affecting dopamine (DA), acetylcholine, serotonin, or GABA receptors. IP injection of haloperidol and diazepam attenuated PIC-induced hypermotility in a dose-dependent manner. Low (sedative) doses of the DA agonists apomorphine (APO) and lisuride, or pretreatment with reserpine abolished PIC-induced hypermotility. Independent of a preceding IA injection of PIC, higher IP doses of APO produced the well-known locomotor effect. LSD, and the atypical neuroleptic, sulpiride, potentiated PIC-induced hypermotility strongly whereas clozapine was ineffective. IA injection of carbachol or haloperidol, in doses which antagonized hypermotility induced by APO IP, did not influence PIC-induced hypermotility. The atypical neuroleptics, clozapine and sulpiride, and the benzodiazepine, diazepam, inhibited PIC-induced hypermotility. The results suggest that there is a complex involvement of GABA, DA and serotonin functions in the effectuation of PIC-induced hypermotility and that PIC-induced hypermotility may be affected by DA-sensitive structures situated outside the NAC.

Nucleus accumbens	Picrotoxin	Locomotor activity	Haloperidol	Clozapine	Sulpiride	LSD
Apomorphine	Carbachol	Lisuride	Diazepam			

THE nucleus accumbens (NAC) and its mesolimbic dopamine (DA) projections from the midbrain have been implicated in the initiation of locomotor activity and in the induction of antipsychotic actions of neuroleptic drugs [1, 4, 9, 13, 23]. Injections into the NAC of DA agonists produce locomotor hyperactivity which can be antagonized by DA antagonists [10, 24, 31, 34, 35]. In addition to DA, a number of other putative neurotransmitters in the NAC were reported to contribute to the control of locomotor activity. Thus, it was shown that the NAC receives serotonin (5-HT) projections from the raphe nuclei and it was suggested that locomotor hyperactivity induced by DA agonists is modulated by this 5-HT input [19, 21, 30]. Furthermore, there is much evidence for the existence of acetylcholine (ACh) interneurons (see [27]) and of several neuronal systems in the NAC that utilize GABA:

(1) The prominent efferent projection from the NAC to the substantia innominata as the ventral part of the globus pallidus probably contains a heavy contingent of GABA fibers [44]. (2) The high density of terminals of GABA interneurons in the medial NAC seems to coincide with the most dense ACh and DA innervation, thus forming a center for possible GABA/ACh/DA interaction [44]. (3) A rather sparse GABA projection from the NAC to the mesencephalon was described to terminate in the rostral ventral tegmental area

(VTA) whereas the majority of GABA fibers from the NAC to the mesencephalon terminate in the medial substantia nigra [33,45].

There is a considerable body of data on GABA involvement in the induction of locomotor activity after systemic administration of various drugs in the literature. An involvement of the NAC in these locomotor effects was demonstrated by several microinjection experiments: Intra-accumbens (IA) injection of GABA or GABA agonists in higher doses caused locomotor hypoactivity and sedation [2, 16, 40, 43] which are potentiated by inhibitors of the GABA metabolizing enzyme [43], whereas the injection of lower doses of GABA agonists was found to be ineffective [38,40] or even to cause hyperactivity [25,43]. On the other hand, IA injection of the GABA antagonist picrotoxin (PIC) was shown to induce a very pronounced locomotor hyperactivity [25,43].

The locomotor hyperactivity after DA microinjection into the NAC was suppressed by IA injection of GABA [37], IA or intraperitoneal (IP) administration of γ -acetylenic GABA [32], and IA ethanolamine-O-sulfate [36]. Furthermore, the ergometrine-induced locomotor hyperactivity was suppressed by non-sedative doses of IA muscimol [39]. Systemically induced apomorphine (APO) [40,43] or amphetamine [36,37] hypermotilities were strongly inhibited by

IA GABA [37,43], uptake inhibitors of GABA [37], non-sedative doses of muscimol [40], and ethanolamine-O-sulfate [36].

The hypermotility induced by IA injection of PIC, however, is less well characterized in the literature. Jones *et al.* [25] observed that the PIC-induced hypermotility is potentiated by IA injection of DA.

The present experiments were performed to investigate the effects of different psychotropic drugs on locomotor hyperactivity induced by IA injection of PIC. It is the aim of this study to characterize this hypermotility regarding the mode of interaction of DA, ACh, and GABA transmission systems within the NAC and to test whether the IA-induced PIC hypermotility is a useful model for differentiating typical and atypical neuroleptics.

METHOD

Animals

The experiments were performed on male Wistar rats (VEB Versuchstierproduktion Schonwalde) weighing 150 ± 10 g. They were housed in groups of 10 per cage at a room temperature of $22 \pm 2^\circ\text{C}$ and a 12 hr light-dark schedule. The rats received standard food and water, ad lib.

Intracerebral Injection Technique

Bilateral injections into the NAC were made by means of platforms with two vertically fixed guide cannulae [47]. The rats were anaesthetized with sodium hexobarbitone, 140 mg/kg IP, and the platforms were screwed on the skull. On the next day an injection cannula with an outer diameter of 0.23 mm was inserted slowly through the guide cannulae into the NAC. The coordinates of the injection cannulae were, according to König and Klippel [26], for NAC A=9.4, L=1.2, and DV=-1.0. Drugs or 0.9% NaCl were administered to conscious hand-held animals by means of a Hamilton CR 700-20 μl syringe in a volume of 1 μl bilaterally over 30 sec with a further 30 sec for deposition of drug.

Rats were used only once and killed after the experiment for histological examination.

Measurement of Locomotor Activity

The behavioral experiments were carried out between 8.00 a.m. and 11.00 a.m. and between 2.00 p.m. and 4.00 p.m. in a sound-proofed room. The rats were allowed to adapt to this room for 2 hr. Immediately after drug administration the rat was returned to its home cage for a period depending on the drug injected (see below) and then transferred to the middle of an open-field cage. The white open-field cage consisted of a 1×1 m area divided into 36 squares and surrounded by a 40 cm high wall. The whole area of the cage was diffusely lighted by a 40 Watt white fluorescent tube. Infrared lightbeams were connected with a processing system providing a selective, automatic counting of squares crossed by the animal during a 5 min observation period, without counting light beam crossings due to other behaviors not contributing to ambulation such as stereotypies.

Drugs

For IA or IP injections picrotoxin (FLUKA)—PIC, apomorphine-HCl (SPOFA)—APO, carbachol (JENAPHARM)—CARB, lisuride hydrogenmaleate (SCHERING)—LIS, lysergic acid diethylamide (SPOFA)—LSD, re-

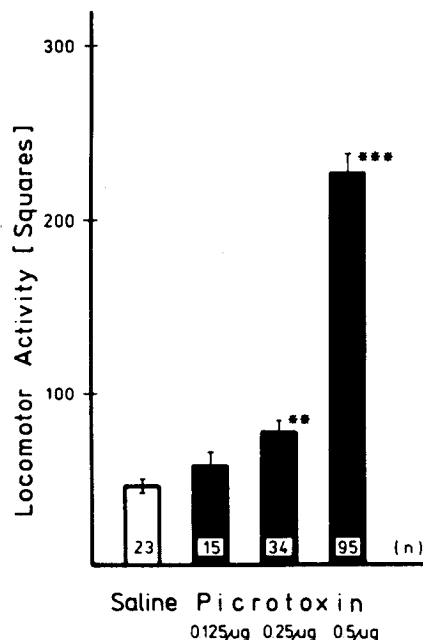


FIG. 1. Bilateral IA injection of PIC induces a dose-dependent increase of locomotor activity. Vertical bars represent the means $\pm$ S.E.M. of (n) animals. ** $p < 0.005$, *** $p < 0.001$ vs. saline (Mann-Whitney).

serpine (AWD)—RES (injectible form) were dissolved in 0.9% NaCl. Haloperidol (ORION)—HALO and sulpiride (SCHÜRHOFF)—SULP were dissolved in 0.9% NaCl by adding minor amounts of acetic acid, clozapine (SANDOZ)—CLOZ by adding minor amounts of 0.3% tartaric acid, and diazepam (AWD)—DIAZ by adding a drop of 1 N HCl.

PIC, APO and LSD are commercial products, all the other drugs are generous gifts from the respective firms.

For IP injections the drugs were administered in a volume of 1 ml per 100 g body weight. Controls were treated IA and/or IP with 0.9% NaCl or vehicle. All drug solutions were prepared freshly. All doses were calculated as the salt. The interval between application of the drugs and the open-field test was 30 min usually, excepting APO and CARB (7 min) or LSD and LIS (20 min), i.e., animals receiving the combination of PIC and CARB received PIC at 0 min, CARB at 23 min and they were tested at 30 min. Corresponding controls were treated in the same way. In preliminary studies these intervals were found to be sufficient to produce maximum responses to the given doses of drugs.

Values are presented as the mean $\pm$ standard error of the mean (SEM). Significance was assessed using the non-parametric Mann-Whitney test.

RESULTS

Animals receiving saline IA and/or IP crossed about 47 squares per 5 min. Bilateral IA injection of PIC in doses ranging from 0.125 to 0.5 μg induced a dose-dependent and long-lasting increase of locomotor activity (Fig. 1). After the highest dose of PIC the animals were extremely hyperactive and sensitive to noise and touch. Frequently and rapidly changing the direction of movement, they ran across the area

TABLE 1

EFFECT OF IP INJECTION OF HALO, DIAZ, LSD AND SULP ON LOCOMOTOR HYPERACTIVITY INDUCED BY IA INJECTION OF PIC (0.5 μ g, BILATERALLY)

IP Treatment	Locomotor Activity (Squares)
Saline	226.7 $\pm$ 12.2 (n=95)
HALO 0.06 mg/kg	105.9 $\pm$ 25.7 $\ddagger$ (n=14)
0.13 mg/kg	54.0 $\pm$ 19.2 $\ddagger$ (n=10)
0.25 mg/kg	13.6 $\pm$ 2.1 $\ddagger$ (n= 8)
DIAZ 1.0 mg/kg	89.0 $\pm$ 36.6 $\ddagger$ (n= 5)
2.0 mg/kg	39.7 $\pm$ 21.1 $\ddagger$ (n= 7)
4.0 mg/kg	4.8 $\pm$ 3.4 $\ddagger$ (n= 4)
LSD 0.1 mg/kg	376.4 $\pm$ 62.9* (n=13)
SULP 10.0 mg/kg	322.0 $\pm$ 31.6 $\ddagger$ (n= 9)

HALO, DIAZ and SULP were injected immediately after the IA injection of PIC, i.e., about 30 min before the commencement of testing, and LSD was injected 10 min after the injection of PIC.

Values are means $\pm$ S.E.M.

* p <0.02, $\ddagger p$ <0.01, $\ddagger p$ <0.001 vs. saline (Mann-Whitney).

of the open-field cage throughout the observation period. In some cases general convulsions or forelimb tremor were detected. Those animals were discarded from the experiments.

HALO IP administered immediately after the IA injection of PIC (0.5 μ g, bilaterally) produced a dose-dependent inhibition of the PIC-induced locomotor hyperactivity (Table 1). The lowest dose of HALO (0.06 mg/kg) inhibited the PIC-induced hypermotility by about 50 percent. DIAZ in doses ranging from 1.0 to 4.0 mg/kg IP produced a dose-dependent inhibition of the PIC-elicited hypermotility. The highest dose produced an inhibition below control (Table 1).

The atypical neuroleptic drug CLOZ in doses between 0.25 and 2.0 mg/kg IP did not influence the PIC-elicited hypermotility (not shown).

SULP (10 mg/kg IP) potentiated the PIC-induced hypermotility strongly. In these experiments the animals ran extremely fast and nearly without any interruption throughout the 5 min observation period (Table 1). A similar but somewhat stronger potentiation of motility was produced when the animals were treated with LSD (0.1 mg/kg IP), 10 min after the injection of PIC (Table 1). Injection of the DA agonist APO in doses known to inhibit (0.25 mg/kg IP) or stimulate (1 mg/kg IP) the locomotor activity of naive animals, inhibited the PIC-induced hypermotility (Table 2). The inhibitory action of APO 0.25 mg/kg, however, was stronger than that of APO 1.0 mg/kg. In each case the resulting effect was similar to the locomotor activity induced by the corresponding dose of APO given alone. LIS (0.1 mg/kg IP) which is known to inhibit spontaneous locomotor activity in naive animals suppressed the PIC-induced hypermotility completely (Table 2).

Pretreatment with reserpine (10 mg/kg IP, 24 hr before) resulted in a catatonic state with marked suppression of locomotor activity. In these animals bilateral IA injection of PIC produced no locomotor hyperactivity. After RES pretreatment, saline IA treated animals crossed 17.0 ± 11.5 (n=5) (p <0.05 vs. NaCl) squares whereas the PIC IA animals crossed 8.3 ± 4.0 (n=6) (p <0.005 vs. NaCl) squares.

After combined IA injection of PIC (0.5 μ g, bilaterally) plus HALO (0.4 μ g, bilaterally) the PIC-induced hypermotility remained unchanged (Fig. 2). CLOZ IA (1.0 μ g, bilaterally) suppressed the PIC-induced hypermotility by more than 50 percent and DIAZ IA (0.5 μ g, bilaterally) decreased motility below control (Fig. 2). SULP IA in doses between 0.01 and 0.4 μ g, bilaterally, produced a dose-dependent inhibition of the PIC-induced hypermotility (Fig. 2).

CARB IA (1.0 μ g, bilaterally) given 23 min after the IA injection of PIC had only a very weak inhibitory influence on the PIC-induced hypermotility. However, hypermotility induced by APO IP (1 mg/kg) was antagonized by simultaneous IA injection of CARB (1 μ g, bilaterally) below control (Fig. 3).

DISCUSSION

There is a considerable body of data in the literature reporting on GABA involvements in the induction of locomotion.

TABLE 2

EFFECT OF IP INJECTION OF APO OR LIS ON LOCOMOTOR ACTIVITY AND HYPERACTIVITY OF RATS INJECTED WITH SALINE IA AND PIC IA (0.5 μ g, BILATERALLY), RESPECTIVELY

Treatments	Saline IA	PIC IA
Saline IP	46.6 $\pm$ 3.9 (23)	226.7 $\pm$ 12.2 $\ddagger$ (95)
APO IP 0.25 mg/kg	23.5 $\pm$ 2.0 $\ddagger$ (36)	50.4 $\pm$ 9.0 $\S$ ** (20)
0.5 mg/kg	71.9 $\pm$ 14.4* (8)	74.7 $\pm$ 11.8 $\S$ ¶ (6)
1.0 mg/kg	154.6 $\pm$ 14.2 $\ddagger$ (7)	140.0 $\pm$ 28.4 $\ddagger$ ¶ (6)
LIS IP 0.1 mg/kg	20.9 $\pm$ 2.1 $\ddagger$ (7)	51.2 $\pm$ 5.3 $\S$ †† (10)

APO and LIS were injected 23 min after the injection of PIC which was injected 30 min before the commencement of testing.

Results are expressed as squares (means $\pm$ S.E.M. of (n) animals).

* p <0.05, $\ddagger p$ <0.001 vs. saline IA plus saline IP; $\ddagger p$ <0.05, $\S p$ <0.001 vs. PIC IA plus saline IP; ¶n.s., ** p <0.02 vs. saline IA plus corresponding APO IP; †† p <0.05 vs. saline IA plus LIS IP. (Mann-Whitney).

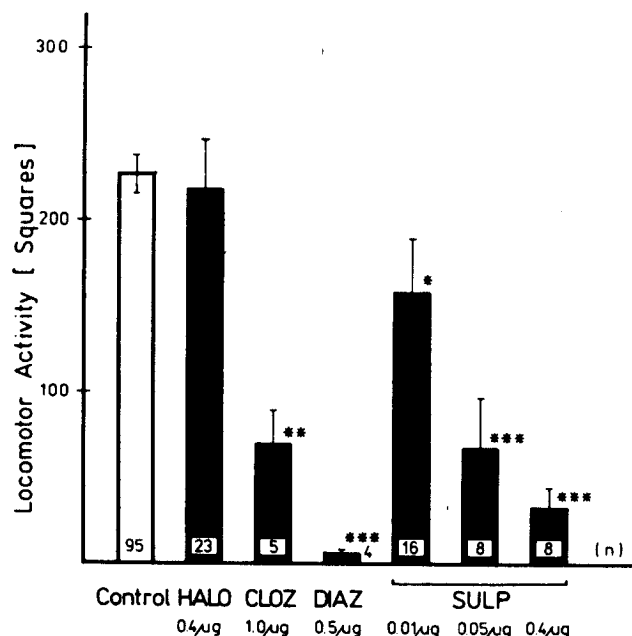


FIG. 2. Effects of HALO, CLOZ, DIAZ and SULP injected IA on locomotor hyperactivity induced by IA injection of PIC (0.5 µg, bilaterally) (Control). HALO, CLOZ, DIAZ and SULP were injected immediately after the injection of PIC which was injected 30 min before the commencement of testing. Vertical bars represent the means $\pm$ S.E.M. of (n) animals. * p < 0.02, ** p < 0.002, *** p < 0.001 vs. control (Mann-Whitney).

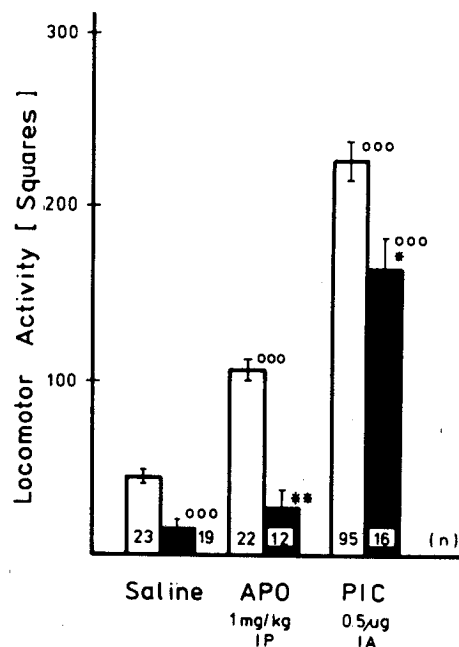


FIG. 3. Effect of IA injection of CARB (1 µg, bilaterally) (shaded bars) on locomotor hyperactivity after APO IP (1 mg/kg) or PIC IA (0.5 µg, bilaterally) (open bars). CARB was injected 23 min after the injection of PIC which was injected 30 min before the commencement of testing. APO was injected immediately after the injection of CARB, about 7 min before the commencement of testing. Controls were treated in the same way. Vertical bars represent the means $\pm$ S.E.M. of (n) animals. * p < 0.05 vs. PIC alone; ** p < 0.005 vs. APO alone; *** p < 0.001 vs. saline alone (Mann-Whitney).

tor activity [3, 7, 12, 32, 41, 43]. IA injection of the GABA antagonist PIC has been described to produce pronounced locomotor hyperactivity in rats [25,44].

In the present study locomotor activity was recorded for the first five minutes after introducing the rat to an unfamiliar test environment, i.e., during the exploratory phase. This procedure differs from that used in many studies of locomotor activity which have been based on records made over a period of more than one hour [2, 9, 10, 11, 32, 36, 37, 39, 43]. However, in previous studies we could demonstrate that the method used is very sensitive and suitable to study interactions of transmission systems and the mode of action of psychotropic drugs after both systemic administration [17, 19, 29, 30] and intracerebral microinjection [18, 20, 21, 31] of various agents.

Confirming the data in the literature [25,43], in our experiments IA injection of PIC induced a dose-dependent and long-lasting locomotor hyperactivity in rats. In preliminary studies we found no significant difference between the locomotor activities measured 5 min or 30 min after the administration of PIC. Therefore we used the 30 min interval between IA PIC and the commencement of testing to reduce the number of handlings.

IP or IA injections of DIAZ antagonized the PIC-induced hypermotility, indicating that GABA sensitive structures of the NAC are involved in the induction of this hypermotility.

Systemic administration of the DA antagonist HALO, of low doses of APO (0.25 mg/kg IP) or LIS (0.1 mg/kg IP) [5, 22, 46] which activate DA autoreceptors, and pretreatment

with RES strongly inhibited the PIC-induced hypermotility. Therefore, it is concluded that DA sensitive mechanisms are involved in the mediation of the PIC-induced hypermotility.

Furthermore, the higher doses of APO IP produced the well-known stereotyped running which in quality and quantity appeared to be independent of the IA injection of PIC prior to the IP injection of APO. This suggests that APO-induced and PIC-induced hypermotilities are competing behaviors.

IA injection of HALO has previously been shown to inhibit locomotor activity in naive animals and locomotor hyperactivity induced by APO IP [31]. Therefore, it was rather unexpected that in the present study IA injection of HALO did not influence the PIC-induced hypermotility. This result indicates that the PIC-induced hypermotility is modulated by DA sensitive structures situated outside the NAC.

IP injection of LSD produced a strong potentiation of the PIC-induced hypermotility. Similar LSD-induced potentiation effects were demonstrated for APO IP-induced hypermotility, amphetamine IP-induced hypermotility [19], and scopolamine IP-induced hypermotility [17]. In the case of the DA agonist-induced hypermotility the results led us to the suggestion that this LSD effect is evoked at somatodendritic 5-HT receptors within the median raphe nucleus. A decreased 5-HT input into the NAC seems to be responsible for the potentiation effect [21] (see also [6,11]). The LSD-induced potentiation of the PIC-induced hypermotility might be based on a comparable mode of action, but other expla-

nations are possible.

ACh mechanisms have been reported to be involved in the modulation of locomotor effects in the NAC. The ACh agonists CARB [25] and oxotremorine [15] increased locomotor hyperactivity induced by IA injection of DA. Under our experimental conditions CARB IA inhibited locomotor activity of naive animals and APO-induced (1 mg/kg IP) hypermotility. The PIC-induced hypermotility, on the other hand, was completely unaffected by CARB IA, indicating that the PIC-induced hypermotility is relatively independent of the function of cholinergic mechanisms whereas cholinergic mechanisms are closely involved in the mediation of DA agonist-induced hypermotility.

Opposite actions of CARB on DA or APO-induced locomotor hyperactivities might be based on differences of the modes of action of the two DA agonists:

It is generally accepted that APO acts at postsynaptic DA receptors to produce its short lasting locomotor stimulant effect and that this effect is relatively independent of the function of presynaptic DA terminals. On the other hand, it seems most plausible that DA IA to produce its long lasting effect [25] acts at postsynaptic DA receptors too, however, mainly after it being stored in and released from DA nerve terminals [42]. The release of DA from nerve terminals in the NAC is increased by ACh agonists [14]. This effect is consistent with the action of CARB [25] or oxotremorine [15] to enhance the DA-induced hypermotility and with an inhibition of this ACh agonist-induced enhancement by 6-OH-DA lesion of the NAC [15].

The inhibitory effect of CARB on the APO IP response as shown in this paper may not depend on intact DA terminals within the NAC and, therefore, may be located somewhere functionally "downstream" the DA presynapses. We think that this effect is comparable with the inhibitory locomotor effect of ACh agonists on the DA response [8] whereas the transient and insignificant initial increase of DA-induced locomotor hyperactivity described by Costall *et al.* [8] might be caused by ACh agonist-induced actions at the DA terminals as described above.

Of particular interest may be the results with the atypical neuroleptics CLOZ and Sulp which are thought to primarily affect 5-HT or presynaptic DA functions, respectively [20, 28, 30]. Systemic administration of CLOZ in doses which were shown to affect locomotor activity strongly [30], did not influence the PIC-induced hypermotility. IA injection of CLOZ (1 μ g, bilaterally) produced inhibition of the PIC-induced hypermotility. Since it was shown that 5-HT antagonists in the NAC or decreased 5-HT input into the NAC stimulate locomotor activity [6, 11, 21], that the ACh antagonist methylatropine was without any effect on locomotor activity in naive animals and on the PIC-induced hypermotility [31] and that both IP and IA injected DIAZ strongly attenuated the PIC-induced hypermotility, the conclusion can be drawn that a benzodiazepine-like (functionally GABA agonist) property of CLOZ may be responsible for the inhibition of the PIC-induced hypermotility. However, this effect is weaker than that of DIAZ. Recently we could show that IP injection of Sulp potentiates different types of locomotor hyperactivity. This effect has been discussed as a presynaptic DA antagonist effect [28,30]. The PIC-induced hypermotility was also potentiated by Sulp IP. This result is in agreement with the findings of Jones *et al.* [25] who found that DA injection into the NAC enhanced the PIC-induced hypermotility. On the other hand, IA injection of Sulp antagonized the PIC-induced hypermotility dose-dependently. It seems to us that further experiments are needed to explain this finding in connection with the finding that HALO IA was ineffective. Summarizing, the results indicate a complex involvement of DA, ACh, GABA and 5-HT transmission systems in the mediation of locomotor activity. Contrary to the mediation of the DA agonist-induced hypermotility the mediation of the PIC-induced hypermotility does not involve ACh sensitive structures of the NAC. The results indicate further than the PIC-induced hypermotility may be strongly affected by DA sensitive structures situated outside the NAC.

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