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Blockade of Amphetamine but not Opiate-Induced Locomotion Following Antagonism of Dopamine Function in the Rat

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VACCARINO, F. J., M. AMALRIC, N. R. SWERDLOW AND G. F. KOOB. *Blockade of amphetamine but not opiate-induced locomotion following antagonism of dopamine function in the rat.* PHARMACOL BIOCHEM BEHAV **24**(1) 61–65, 1986.—The effects of pharmacological blockade of dopamine (DA) receptors or 6-OHDA lesions of mesolimbic DA fibers on the locomotor-activating properties of systemic amphetamine (0.35 mg/kg) and heroin (0.5 mg/kg) were examined. Pharmacological blockade of DA receptors or lesions of mesolimbic DA neurons blocked amphetamine but not heroin-induced locomotion. These results show that the opiate receptors essential for opiate-induced locomotor activation are not located on mesolimbic DA neurons. It appears that DA plays a primary role in stimulant-induced locomotion, but may have only a secondary role in opiate locomotion.

Heroin Amphetamine Locomotion Mesolimbic system Nucleus accumbens Alpha-flupenthixol 6-OHDA

AT low doses, systemic administration of opiates in rats produces analgesia and locomotor activation and, at higher doses, a state of immobility followed by an increase in locomotor activity [2]. The locomotor activation observed in rats following systemic opiate treatment can be reproduced by intraventricular injections of endorphins and is believed to be a reflection of the "mood-altering" properties of opiates [2,12]. In recent years a number of studies have been directed at identifying the central substrates for opiate-induced locomotor activation. These studies have depended primarily on intracerebral injection techniques in which the locomotor response to direct intracerebral injections of opiates or opioid peptides was measured [3, 6, 8, 9, 16, 17, 19]. Using this method, it has been suggested that the mesolimbic dopamine (DA) system is critical for the expression of opiate-induced locomotor activation [3, 8, 11]. This notion was based largely on two findings. Firstly, microinjections of morphine or opioid peptides into the ventral tegmental area (VTA), source of the mesolimbic DA cell bodies, produce an increase in locomotor activity which resembles that observed following systemic stimulant treatment [3, 8, 11]. Secondly, 6-OHDA lesions of the mesolimbic DA system or microinjections of DA receptor antagonists block the locomotor activation induced by intra-VTA microinjections of opiates [11,19].

Recently, however, Kalivas *et al.* [9] have provided evidence for the presence of a DA-independent substrate of opioid-induced locomotor activation. They found that microinjections of D-Ala^2-Met^5-enkephalinamide (DALA, a peptidase-resistant synthetic enkephalin analogue) into the nucleus accumbens (N.Acc) produced locomotor activation which was not attenuated by destruction of the mesolimbic DA system [9]. Moreover, while intra-VTA DALA injections resulted in an increased DOPAC/DA ratio, a positive index of DA neuronal activity [5,18], intra-N.Acc DALA injections had no such effect [9]. Based on these findings the authors suggested that while activation of opiate receptors in the VTA appears to produce a DA-dependent locomotor activation, activation of opiate receptors in the N.Acc produces a DA-independent locomotor activation [9]. Also, earlier work in mice showed that injection of haloperidol into the N.Acc blocked the locomotor activating properties of amphetamine but not morphine [20].

Taken together, the results of the above studies make it difficult to assess the extent to which the locomotor activation observed following systemic opiate treatment is DA-dependent. The present study, then, was designed to investigate the role of the mesolimbic DA system in the expression of locomotor activation induced by systemic heroin administration. To this end, the effects of systemic neuroleptic

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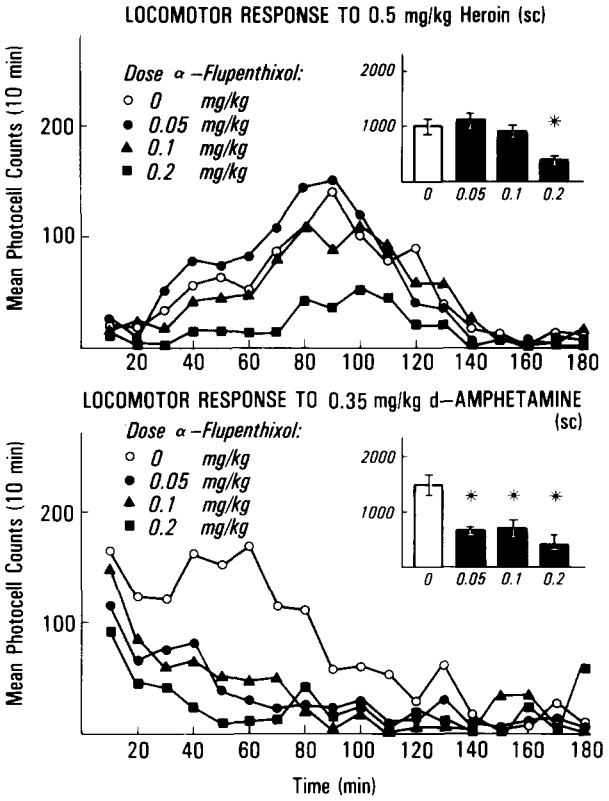

FIG. 1. Top Graph. Effects of alpha-flupenthixol on the locomotor response after SC injection of heroin (0.5 mg/kg). Rats were pretreated with alpha-flupenthixol and, 60 minutes later, habituated to the photocell cages. Ninety minutes later the rats were injected with heroin. Bottom Graph. Effects of alpha-flupenthixol on the locomotor response after SC injection of amphetamine (0.35 mg/kg). Rats were pretreated and tested as in the top graph. *Significantly different from saline, $p<0.05$, Duncan Multiple Range *a posteriori* test shows the mean total counts for 180 min±S.E.M. The present data are based on an independent group design. N=8 in each group.

treatment and mesolimbic 6-OHDA lesions on heroin and amphetamine-induced locomotor activation were investigated.

EXPERIMENT 1

This experiment was aimed at investigating the effects of systemic alpha-flupenthixol (a DA antagonist) [15,21] on heroin-induced locomotor activation. It was hypothesized that if increased DA activity plays a critical role in mediating opiate-induced locomotion, then blockade of DA receptors should attenuate heroin-induced locomotor activation in doses which also block amphetamine-induced locomotor activation (a DA-dependent phenomenon) [7, 10, 13].

METHOD

Subjects

Sixty-four male Wistar rats weighing 260–280 grams at the time of testing were used. Rats were group-housed in a temperature and light controlled environment, lights on 0700–1900 hr. The present experiment was carried out using an independent group design. Each group reported in this experiment contained eight naive rats.

Apparatus

The testing apparatus was a bank of 16 photocell cages, each cage measuring 20 cm by 25 cm by 36 cm with a wire mesh floor. Two infrared photocell beams were situated across the long axis 2 cm above the floor. Interruption of a beam registered a count on an Acorn computer situated in an adjoining room. Readings were totalled every 10 minutes.

Procedure

To measure the locomotor response to heroin and amphetamine, the rats were first pre-exposed to the photocell cages for 3 hours at least 2 days prior to a test day to overcome the potential stressful nature of a novel environment. On the test day, rats were pretreated intraperitoneally with one of the following doses of alpha-flupenthixol: 0, 0.05, 0.1 and 0.2 mg/kg, 1.0 hour before being placed in the photocell cages. The rats were then placed in the photocell cages for a habituation period of 1.5 hours, after which they were injected with either d-amphetamine (0.35 mg/kg) subcutaneously (SC) or heroin (0.5 mg/kg) SC and monitored for another 3 hours. Pilot studies revealed that 0.35 mg/kg d-amphetamine and 0.5 mg/kg heroin produced similar overall levels of locomotor-activation.

Drugs

All drugs were dissolved in saline vehicle and injected in a volume of 1 ml/kg.

RESULTS

Heroin-Induced Locomotor Activation

Heroin, injected SC at a dose of 0.5 mg/kg produced an initial "catatonic"-like state lasting 10 to 30 minutes which was followed by a period of increased locomotor activation which lasted approximately 90–120 minutes. The increased locomotor activation reached a peak at about 90 minutes after the heroin injection. The saline pretreated rats in Fig. 1 (top graph) show this trend. Consistent with this trend, a two factor analysis of variance (ANOVA) comparing alpha-flupenthixol dose × time revealed a significant effect of time, $F(17,476)=18.860$, $p<0.05$.

Examining the effects of alpha-flupenthixol, the two factor ANOVA also revealed a significant main dose effect, $F(3,28)=9.637$, $p<0.05$. It can be seen in Fig. 1 (top graph) that alpha-flupenthixol had little effect on heroin locomotion at the 0 (saline), 0.05 and 0.1 mg/kg doses, but produced an attenuation at the 0.2 mg/kg dose. Individual group comparisons using the Duncan Multiple Range *a posteriori* test at the 0.05 level of significance revealed that rats pretreated with 0.2 mg/kg alpha-flupenthixol had significantly lower overall locomotor scores than rats pretreated with 0 (saline), 0.05 or 0.1 mg/kg alpha-flupenthixol (Fig. 1, top bar graph insert). With 0.2 mg/kg alpha-flupenthixol, a significant drug × time interaction also was found, $F(51,476)=1.428$, $p<0.05$, which was consistent with a locomotor blockade over the whole three hour testing period.

Amphetamine-Induced Locomotor Activation

Amphetamine, injected subcutaneously at a dose of 0.35 mg/kg produced the same overall amount of locomotor activation, but with a different time course from that observed with heroin. As can be seen in Fig. 1 (bottom graph), rats receiving amphetamine and pretreated with saline showed an

TABLE 1

NUCLEUS ACCUMBENS (N.Acc), ANTERIOR CAUDATE (AC) AND POSTERIOR CAUDATE (PC) DEPLETION LEVELS FOLLOWING INJECTIONS OF 6-OHDA INTO THE NUCLEUS ACCUMBENS

Site		Dopamine	DOPAC
N.Acc	Sham 6-OHDA (n=5)	86.97 ± 11.08	52.14 ± 7.61
	6-OHDA (n=8)	17.26 ± 2.85*	17.25 ± 3.23*
	% depletion	80%	67%
AC	Sham 6-OHDA (n=5)	107.04 ± 10.68	23.76 ± 2.37
	6-OHDA (n=8)	31.64 ± 6.05*	10.33 ± 3.69*
	% depletion	70%	57%
PC	Sham 6-OHDA (n=5)	100.93 ± 14.57	12.97 ± 1.3
	6-OHDA (n=8)	65.18 ± 4.72*	10.35 ± 0.8
	% depletion	35%	20%

Values are in ng/mg protein, mean ± S.E.M.
*Significantly different from sham 6-OHDA group, $p<0.05$, Student's t-test.

immediate increase in locomotion which lasted for approximately 40–60 minutes after amphetamine injection. The maximal activity level was observed at the 60 minute interval with a mean±SEM of 168±34 counts. This level was similar to the mean±SEM maximal activity observed at the 90 minute interval with heroin (152±19 counts). After the initial increase a steady decline over the remainder of the session was observed. Consistent with this trend, two factor ANOVA revealed a significant effect of time, $F(17,476)=17.753$, $p<0.05$.

Examining the effects of alpha-flupenthixol, the ANOVA also showed a significant main dose effect, $F(3,28)=8,597$, $p<0.05$. It can be seen in Fig. 1 (bottom graph) that in contrast to the saline pretreated group (0 mg/kg dose), alpha-flupenthixol attenuated amphetamine locomotion at all three doses (0.05, 0.1 and 0.2 mg/kg). Individual group comparisons using the Duncan Multiple Range *a posteriori* test at the 0.05 level of significance revealed that rats pretreated with 0.05, 0.1 or 0.2 mg/kg alpha-flupenthixol had significantly lower overall locomotor scores than rats pretreated with 0 mg/kg (saline) (Fig. 1, bottom bar graph insert). Consistent with the difference over time observed between the saline pretreated group and the remaining alpha-flupenthixol pretreated groups, a significant group × time interaction was found, $F(51,476)=2.619$, $p<0.05$.

DISCUSSION

The results of Experiment 1 show that alpha-flupenthixol, a DA antagonist, blocked amphetamine-induced locomotion at all three doses tested. This finding is consistent with numerous other studies indicating that amphetamine-induced locomotion is dependent on DA function [7, 10, 13]. In contrast to amphetamine, heroin-induced locomotion was not significantly affected by alpha-flupenthixol, except at the highest dose tested (0.2 mg/kg). The fact that alpha-flupenthixol had no effect on heroin locomotion at doses that blocked amphetamine locomotion (0.05 and 0.1 mg/kg), suggests that DA systems do not play a primary role in the expression of heroin-induced locomotion.

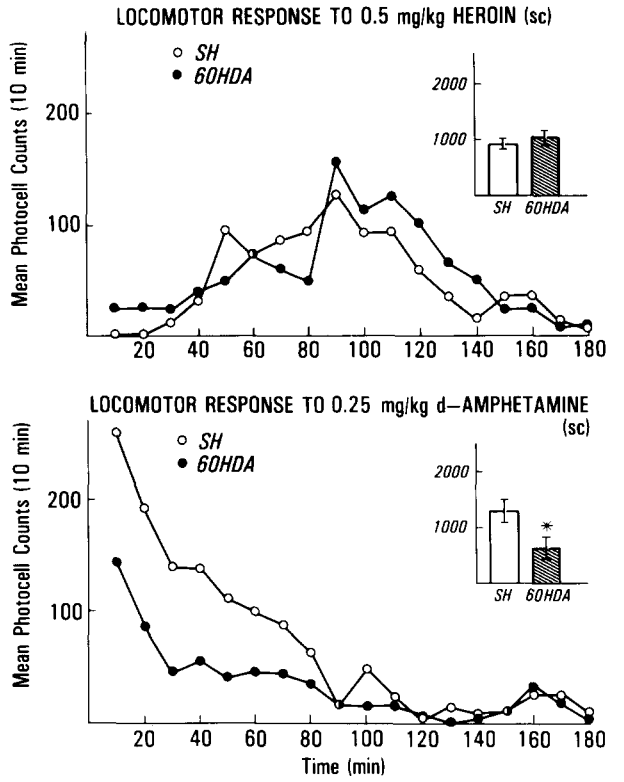

FIG. 2. Top Graph. Effects of 6-OHDA lesions of the N.Acc on the locomotor response after SC injection of heroin (0.5 mg/kg). Rats were habituated to the photocell cages for 90 minutes after which they were injected with heroin. Bottom Graph. Effects of 6-OHDA lesions of the N.Acc on the locomotor response after SC injection of amphetamine (0.25 mg/kg). Rats were tested as in the top graph. *Significantly different from sham lesion group, $p<0.05$, main effect ANOVA. Inserts show the mean total counts for 180 min±S.E.M. for eight rats in the sham and lesion group, respectively.

EXPERIMENT 2

This experiment was aimed at investigating the effects of 6-OHDA lesions of the mesolimbic DA system on heroin and amphetamine-induced locomotion. Based on the results of Experiment 1, it was hypothesized that destruction of mesolimbic DA fibers, which are known to be critical for the expression of amphetamine locomotion [7, 10, 13], should result in a blockade of amphetamine locomotion but have little effect on heroin locomotion.

METHOD

Subjects

Sixteen male Wistar rats weighing 280–300 grams at the time of surgery were used. Rats were housed as in Experiment 1.

Surgery

Animals were divided into two groups of eight. One group received bilateral injections of 6-OHDA (8 μg/2 μl, expressed as free base) dissolved in saline containing ascorbic acid (0.1 mg/ml; 6-OHDA group). The other group received bilateral injections of saline-ascorbic acid vehicle alone (sham group). Rats were anesthetized with pentobarbital [50

mg/kg, intraperitoneally (IP)] and secured in a Kopf stereotaxic instrument with the toothbar 5 mm above the interaural line. Injections were made into the N.Acc through a 30 ga cannula at a rate of 1 μl per 3 minutes at coordinates: AP +3.2 (from bregma), ML ±1.7, DV −7.8 (from skull surface).

Apparatus

As in Experiment 1.

Procedure

Eight days following surgery rats were first pre-exposed to the photocell cages for 3 hours to habituate them to the novel environment. The following day rats were placed in the photocell cages for a habituation period of 1.5 hours, after which they were injected with heroin (0.5 mg/kg) SC and monitored for an additional 3 hours. Seventy-two hours later animals were tested for their locomotor response to d-amphetamine (0.25 mg/kg) SC, using the same procedure. Drugs were injected in a volume of 1 ml/kg.

Following completion of behavioral testing, most rats were decapitated and their brains were removed. Forebrain structures including the anterior striatum, frontal cortex, olfactory tubercles and N.Acc were removed from coronal slices as previously described [7] and stored at −40°C until assayed for DA using electrochemical detection following separation by high pressure liquid chromatography.

RESULTS

Biochemistry

Biochemical analysis of all 6-OHDA injected animals revealed an 80% depletion of DA, and a 67% depletion of DOPAC, recorded as ng/mg protein in the N.Acc compared to vehicle injected animals, $t(11)=7.516$, $p<0.05$; DOPAC, $t(11)=4.860$, $p<0.05$, Student's t. Biochemical analysis of the anterior caudate and posterior caudate revealed a 70% and 35% depletion of DA, respectively, and a 57% and 20% depletion of DOPAC, respectively. See Table 1.

Heroin-Induced Locomotor Activation

As in Experiment 1, heroin injected SC at a dose of 0.5 mg/kg produced an initial catatonic phase (10–30 minutes) which was followed by a period of increased locomotor activation which lasted approximately 90–120 minutes. As can be seen in Fig. 2 (top graph, sham group), the increased locomotor activation reached a peak at about 90 minutes after the heroin injection. Consistent with this trend, a two factor ANOVA comparing 6-OHDA lesion × time revealed a significant effect of time, $F(17,238)=15.049$, $p<0.05$. Examining the effects of 6-OHDA lesions, the two factor ANOVA revealed no significant main lesion effect, $F(1,14)=0.446$, n.s. It can be seen in Fig. 2 (top graph) that 6-OHDA lesions of the N.Acc had little effect on heroin locomotion.

Amphetamine-Induced Locomotor Activation

Amphetamine injected SC at a dose of 0.25 mg/kg produced locomotor activation with a different time course from that observed with heroin as in Experiment 1, as can be seen in Fig. 2 (bottom graph) sham rats treated with amphetamine showed an immediate increase in locomotion which declined steadily throughout the session. Consistent with this trend, a two factor ANOVA comparing 6-OHDA lesion × time revealed a significant effect of time, $F(17,238)=2.856$, $p<0.05$.

Examining the effects of 6-OHDA lesions, a two factor ANOVA revealed a significant main lesion effect, $F(1,14)=5.181$, $p<0.05$ (Fig. 2). It can be seen in Fig. 2 (bottom graph) that 6-OHDA lesions produced an attenuation of amphetamine-induced locomotor activation. Consistent with this effect a significant lesion × time interaction was also found, $F(17,238)=2,856$, $p<0.05$. It can be seen in Fig. 2 (bottom graph) that the sham group showed an initial increase with a steady decline which lasted approximately 90–110 minutes. In contrast, 6-OHDA rats showed a less dramatic initial increase and a more rapid decline (i.e., 30 minutes).

DISCUSSION

The results of Experiment 2 show that 6-OHDA lesions of the mesolimbic system blocked amphetamine-induced locomotion. This finding is in agreement with numerous other studies showing that stimulant-induced locomotion is dependent, to a large extent, on the mesolimbic DA system. In contrast, heroin-induced locomotion was not significantly altered by mesolimbic 6-OHDA lesions. The finding that 6-OHDA lesions block amphetamine, but not heroin locomotion, suggests that the mesolimbic DA system is not critical for the expression of heroin-induced locomotion.

GENERAL DISCUSSION

The finding that low doses of alpha-flupenthixol block amphetamine-induced locomotion, while only high doses block heroin-induced locomotion suggests that DA does not play a primary role in the locomotor activating properties of systemic opiates. In addition, the fact that destruction of DA-ergic terminals in the N.Acc significantly attenuates amphetamine but not heroin locomotion indicates that mesolimbic DA fibers are not essential for the expression of opiate-induced locomotion.

Studies with intracerebral opiate injections suggested that activation of both VTA or N.Acc opiate receptors can produce locomotor activation. 6-OHDA lesions of the mesolimbic DA system blocked locomotion produced by injections of opioid peptides or opiates into the VTA, but had no effect on locomotion produced by injection of opioid peptides into the N.Acc [9, 11, 19]. These results indicated that the locomotion produced by opiate injection into the VTA was DA-dependent while the locomotion produced by opiate injection into the N.Acc was DA-independent [9]. The present finding that pharmacological blockade of DA transmission (low doses of alpha-flupenthixol) did not block locomotion produced by heroin suggests that DA activation does not play a critical role in locomotion following systemic opiate treatment. Similar results have been observed in mice where intra-accumbens injection of haloperidol blocked systemic amphetamine but not systemic morphine induced locomotor activity [20].

However, it is still possible that opiate receptors in the N.Acc may be involved in mediating the locomotor-activating properties of systemic opiates. In support of this notion, it was recently reported that the locomotor-activating properties of systemic heroin could be blocked by injections of low doses of methylnaloxonium chloride, a quaternary opiate antagonist, into the N.Acc. Similar injections of methylnaloxonium chloride into the VTA failed to

block heroin-stimulated locomotion [1]. This finding was taken to suggest that opiate receptors in the region of the N.Acc play the primary role in mediating the locomotor activation observed following systemic opiate treatment [1]. The fact that destruction of DA-ergic terminals in the present study does not block heroin locomotion further suggests that the N.Acc opiate receptors critical for opiate-induced locomotion must be located postsynaptic to the DA terminals. These opiate receptors may be located on the same postsynaptic neurons as the DA terminals, however, the observation that electrolytic lesions of the posterior N.Acc attenuate amphetamine, but not morphine locomotor activity suggest that this is not the case [20].

It should be noted that while the present results strongly suggest that N.Acc DA function is not necessary for opiate-induced locomotor activation, it is apparent that DA systems, if sufficiently blocked, can produce an attenuation of opiate-induced locomotion. This is evidenced by the fact that at high doses (0.2 mg/kg), alpha-flupenthixol was able to block heroin-induced locomotion in the present study. Since this dose is higher than the ED50 for alpha-flupenthixol-induced catalepsy, the locomotor blockade observed with high doses of alpha-flupenthixol is presumably due to the cataleptic effects of a widespread interference with DA function throughout the CNS [14,15].

In conclusion, the present data indicate that while DA plays a central role in mediating the locomotor-activating effects of systemic stimulant treatment, DA plays only a secondary role in mediating the locomotor-activating effects of systemic opiate treatment. More specifically, it appears that in contrast to the importance of mesolimbic fibers in mediating stimulant-induced locomotion, the mesolimbic DA system is not essential for the expression of opiate-induced locomotion. Taken together, the present experiments suggest that the neurochemical substrates underlying the behavioral-activating properties of stimulants and opiates are, at the present level of analysis, non-congruent.

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