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Amphetamine Discrimination: Onset of the Stimulus

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SILVERMAN, P. B. AND B. T. HO. *Amphetamine discrimination: Onset of the stimulus.* PHARMAC. BIOCHEM. BEHAV. 12(2) 303–304, 1980.—Rats were trained to discriminate 1.0 mg/kg (+)-amphetamine sulfate from saline in a two-lever operant procedure. The normal injection-to-session interval was fifteen minutes. When tested with amphetamine immediately after intraperitoneal injection, rats initially responded on the lever paired with saline in training, but quickly shifted to the lever paired with amphetamine in training. When tested with saline immediately after injection, animals responded appropriately for the saline treatment throughout the extinction test. The results show that (+)-amphetamine exerts discriminative response control within five minutes of intraperitoneal injection.

Drug discrimination (+)-Amphetamine

(+)-AMPHETAMINE is an effective agent for discriminative control of behavior. The discriminative stimulus properties of amphetamine have been fairly well defined [4,10]. The temporal aspects of discriminative response control by amphetamine in operant tasks have been investigated in several studies [5, 6, 8]. These studies were primarily concerned with the duration of amphetamine's stimulus as related to dose. Relatively unexamined is the onset of the amphetamine stimulus. Jones *et al.* [6] found that rats, injected with the same dose of (+)-amphetamine as that utilized in training, made 50 to 60% of their responses on the amphetamine appropriate lever when tested for a ten minute period beginning immediately after injection. Kuhn *et al.* [8], on the other hand, made an attempt to measure the onset of the amphetamine stimulus and reported that rats made their initial responses on the drug lever immediately after IP injection. Such a finding very strongly suggests a peripheral locus for the amphetamine stimulus, since absorption from the peritoneal cavity, transport to the central nervous system and subsequent central activity are all time-dependent. The bulk of data available on the stimulus properties of amphetamine suggest instead that amphetamine's stimulus is central (see [4,10] for review). The purpose of the study presented here was to examine more closely the onset of the amphetamine stimulus.

METHOD

Adult male Sprague-Dawley rats (Simonsen Labs, Gilroy, CA) were deprived to 80% of their free feeding weight and were trained to bar press for 45 mg food pellets (Noyes) in a two-lever operant chamber (Scientific Prototype). Fifteen minutes prior to each daily 20 min sessions, rats were injected (IP) with 1.0 ml/kg saline or 1.0 mg/kg (+)-amphetamine sulfate (Sigma). For any individual rat, saline injection was paired with availability of reinforcement for operating one lever, while (+)-amphetamine injection was paired with availability of reinforcement for operating the opposite lever. Reinforcement was delivered in accordance with a VI-30 sec-FR-5 tandem schedule. Responses on the incorrect lever during the interval portion of the schedule had no consequence; during the ratio portion of the schedule, incorrect responses reset the ratio response requirement. The rats used in this experiment (n=13) were chosen at random from a larger group of animals trained as described above. Subjects used here had over six months of experience in the discrimination procedure and always made ≥90% correct responses in the training conditions.

Rats were injected (IP) with 1.0 mg/kg (+)-amphetamine sulfate (n=6) or 1.0 ml/kg saline (n=7) and immediately placed in the operant chambers. The extinction test lasted ten minutes. The number of responses on the lever paired in training with (+)-amphetamine, divided by the total number of responses, was calculated for each one minute interval of the test.

RESULTS

The percentage of responses on the amphetamine lever for each minute is shown in Fig. 1. When injected with (+)-amphetamine, rats immediately responded on the saline lever, responded "randomly" three to four min postinjection, and responded primarily on the drug lever thereafter. Rats injected with saline responded appropriately for saline treatment throughout the test. The fact that rats injected with amphetamine changed levers, while those injected with saline did not, demonstrates that the shift to the drug lever is not a result of extinction induced response probing.

DISCUSSION

The results show that, while very rapid, the onset of the

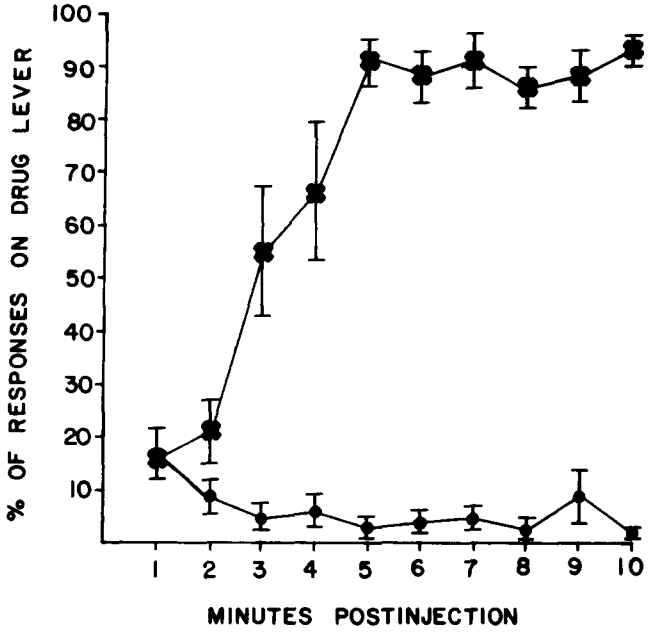

FIG. 1. Mean ± SEM percentage of responses made on the lever paired with (+)-amphetamine in training following injection of (+)-amphetamine (x; n=6) or saline (●; n=7).

amphetamine stimulus is not instantaneous. Amphetamine is apparently "detectable" three to four min postinjection and reaches a sufficient level at its site of recognition to generalize with the drug training condition within five min. The data thus show good agreement with those of Jones *et al.* [6], who found that rats made 50 to 60% of their total responses on the amphetamine lever during the first ten minutes postinjection. Because these authors used a DRL schedule in training and testing, it was probably not possible to analyze their data on a minute-by-minute basis due to low response rates. Any shift of responding from the saline lever to the drug lever was thus obscured. The VI-FR tandem schedule used here seems ideal for determining stimulus onset since it results in moderately high rates along with resistance to extinction.

The data presented here do not show agreement with the finding of Kuhn *et al.* [8] that rats made their initial responses on the amphetamine lever immediately following IP injection. Such a finding suggests a peripheral cue. Colpaert *et al.* [2] found that rats could discriminate 0.16 mg/kg (±)-amphetamine from saline and concluded that this was a peripheral phenomenon. They also concluded that the stimulus resulting from this very low dose of amphetamine was qualitatively unlike that resulting from larger doses which probably induce a central stimulus. Further, Colpaert *et al.* [2] utilized the subcutaneous route of administration, and the possibility of the local anesthetic action of amphetamine serving as the stimulus cannot be ruled out.

The bulk of evidence resulting from discrimination training with larger (0.8 to 4.0 mg/kg) doses of (+)-amphetamine suggest a central locus for the amphetamine stimulus. Thus (+)-amphetamine is a more potent stimulus than (−)-amphetamine despite equipotency in the periphery [7,9]. *p*-Hydroxyamphetamine, which has peripheral activity but, due to its poor penetration of the blood brain barrier, no appreciable central activity, does not generalize with (+)-amphetamine and is not an effective stimulus itself [7]. Centrally administered (+)-amphetamine generalizes with systemically administered (+)-amphetamine and is more efficacious on a mg/kg basis [4]. The present data are consistent with the contention that the (+)-amphetamine stimulus is a central phenomenon.

In single unit recording studies in rats, central effects of amphetamine are apparent within 30 sec of intravenous administration [1] and within five min of IP administration [3]. The present experiment demonstrates a behavioral effect of amphetamine with similar onset.

REFERENCES

1. Bunney, B. S., J. R. Walters, R. H. Roth and G. K. Aghajanian. Dopaminergic neurons: Effect of antipsychotic drugs and amphetamine on single cell activity. *J. Pharmac. exp. Ther.* **185**(3): 560–571, 1973.
2. Colpaert, F. C., J. J. Kuyps, C. J. E. Niemegeers and P. A. J. Janssen. Discriminative stimulus properties of a low *dl*-amphetamine dose. *Archs int. Pharmacodyn.* **223:** 34–42, 1976.
3. Groves, P. M., G. V. Rebec and D. S. Segal. The action of *d*-amphetamine on spontaneous activity in the caudate nucleus and reticular formation of the rat. *Behav. Biol.* **11:** 33–47, 1974.
4. Ho, B. T. and P. B. Silverman. Stimulants as discriminative stimuli. In: *Stimulus Porperties of Drugs: Ten Years of Progress*, edited by F. C. Colpaert and J. A. Rosecrans. Amsterdam: Elsevier/North-Holland Biomedical Press, 1978, pp. 53–68.
5. Huang, J.-T. and B. T. Ho. Discriminative stimulus properties of *d*-amphetamine and related compounds in rats. *Pharmac. Biochem. Behav.* **2:** 669–673, 1974.
6. Jones, C. N., L. D. Grant and D. M. Vospalek. Temporal parameters of *d*-amphetamine as a discriminative stimulus in the rat. *Psychopharmacologia* **46:** 59–64, 1976.
7. Jones, C. N., H. F. Hill and R. T. Harris. Discriminative response control by *d*-amphetamine and related compounds in the rat. *Psychopharmacologia* **36:** 347–356, 1974.
8. Kuhn, D. M., J. B. Appel and I. Greenberg. An analysis of some discriminative properties of *d*-amphetamine. *Psychopharmacologia* **38:** 57–66, 1974.
9. Schechter, M. D. Stimulus properties of *d*-amphetamine as compared to *l*-amphetamine. *Eur. J. Pharmac.* **47:** 461–464, 1978.
10. Silverman, P. B. and B. T. Ho. Characterization of discriminative response control by psychomotor stimulants. In: *Discriminative Stimulus Properties of Drugs*, edited by H. Lal. New York: Plenum Press, 1977, pp. 107–119.