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Acute and Chronic Behavioral Interactions Between Phencyclidine (PCP) and Amphetamine: Evidence for a Dopaminergic Role in Some PCP-Induced Behaviors[1]

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GREENBERG, B. D. AND D. S. SEGAL. *Acute and chronic behavioral interactions between phencyclidine (PCP) and amphetamine: Evidence for a dopaminergic role in some PCP-induced behaviors.* PHARMACOL BIOCHEM BEHAV 23(1) 99–105, 1985.—Amphetamine and phencyclidine (PCP) are both proposed to exert effects on unconditioned behavior through dopaminergic mechanisms. However, a relatively complete characterization of their effects in rats reveals markedly different response profiles. Furthermore, whereas acute co-administration of amphetamine and PCP resulted in an increase in one component of stereotypy, repetitive head movements, two measures of locomotor activation, i.e., ambulation and nonfocused sniffing, were unchanged, and rearings were reduced. In addition, the response alterations which occur with repeated administration of these drugs did not display cross-sensitization. Thus, although repeated daily injections of amphetamine, which produced progressive locomotor augmentation, sensitized animals to the locomotor-stimulating effects of PCP, repeated PCP treatment, which also resulted in locomotor augmentation, decreased the locomotor response to a challenge injection of amphetamine. These findings suggest significant differences in the mechanisms underlying the effects of acute and repeated administration of PCP and amphetamine.

Amphetamine Phencyclidine Locomotor activity Stereotypy

PHENCYCLIDINE (PCP) and amphetamine, drugs which can both induce a schizophreniform psychosis [24,32], also have a number of similar behavioral effects in animals. The two drugs produce similar changes in schedule-controlled responding [5, 25, 34], and both drugs induce hyperactivity and stereotyped behaviors [6, 29, 33]. Furthermore, repeated administration of either drug may produce an augmented locomotor response [15,31]. In addition, PCP and amphetamine are reported to have additive effects on operant [25] and unconditioned behavior [2, 9, 22].

These findings have led to the suggestion that the responses to these drugs may have common underlying mechanisms [18,21]. There are, however, significant differences in the behavioral effects of PCP and amphetamine. The two drugs have dissimilar discriminative stimulus properties, i.e., animals trained to respond to PCP as a cue do not generalize to amphetamine [26]. There are also marked qualitative differences in the patterns of PCP- and amphetamine-induced locomotion and stereotypy [16]. Although evidence that combined acute administration of PCP and amphetamine produces a more intense amphetamine-like response profile is suggestive of commonalities in their mechanisms of action, only a limited characterization of these effects is available (see below). Furthermore, although repeated administration of both drugs may produce augmented responses [6, 15, 31], there have been no attempts to determine the degree of cross-tolerance/sensitization they produce. The first objective of the present study was to further characterize the behavioral profile which results from acute co-administration of PCP and amphetamine using a relatively complete behavioral inventory and temporal analysis. Second, we investigated whether the augmented locomotor responses produced by repeated PCP and amphetamine treatment display reciprocal cross-sensitization.

GENERAL METHOD

Male Wistar rats (300–350 g; Charles River) were maintained under standard laboratory conditions for at least one week prior to experimentation, then placed individually into sound-attenuated activity chambers (30×30×38 cm) for at least 24 hours prior to and for the duration of behavioral

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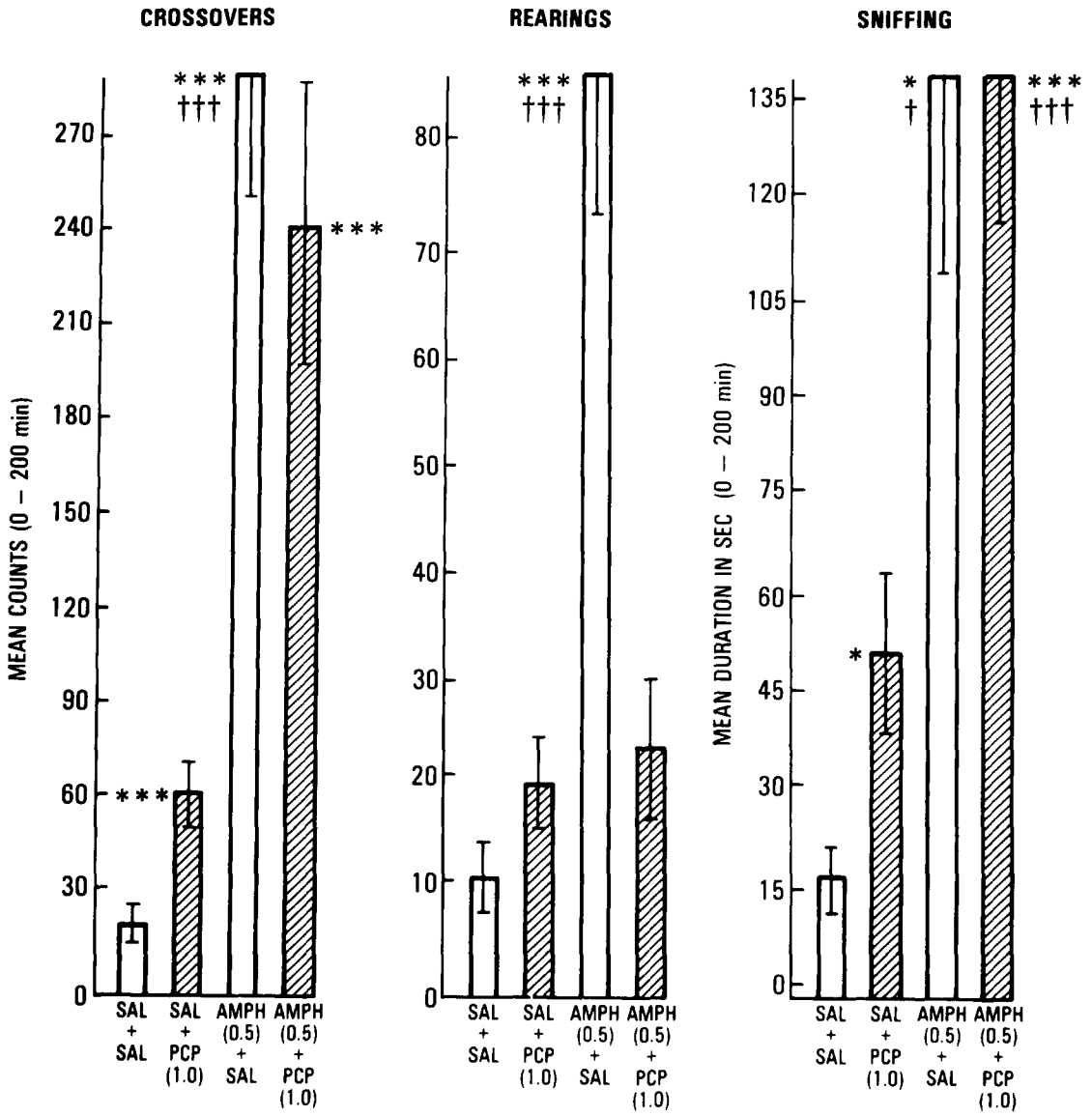

FIG. 1. Effects of combined PCP and amphetamine administration on locomotor activation in rats. Mean total crossovers and rearings, and mean total sniffing duration (in sec) during the 0–200-min period following concurrent injection of saline plus saline, saline plus PCP (1.0 mg/kg), amphetamine (0.5 mg/kg) plus saline, and amphetamine (0.5 mg/kg) plus PCP (1.0 mg/kg). Amphetamine-induced ambulation and sniffing were unchanged by PCP, whereas rearings were decreased. Significant differences from saline-saline controls: $*p<0.05$;$***p<0.01$; significant differences from the PCP-saline group: $\dagger p<0.05$; $\dagger\dagger\dagger p<0.01$; n=12 animals/group.

testing. Food and water were freely available and a 12-hour bright light (6 a.m. to 6 p.m.)/12-hour dim light cycle was maintained.

Ambulation, measured as movement from one quadrant of the cage to another (crossovers), was monitored automatically through contacts in the floor of the chamber. Rearings were measured by touchplates set 13 cm above the floor. Both measures of behavioral activity were continuously monitored with the use of a Sierra National 3000 computer. In addition, animals were observed through viewing lenses located in each experimental chamber and a closed circuit videotape system. Observations were made for 30 seconds at 10 minute intervals throughout the duration of the drug response by one rater (B.D.G.) unaware of treatment conditions.

Stereotyped behaviors, including sniffing, repetitive head movements, and oral stereotypies, both object-directed (licking and biting) and non-object-directed (chewing) were recorded as duration of occurrence of each behavior. Ataxia was rated according to the following scale: 0=normal movement; 1=misplacement of limbs; 2=impaired righting, falling; 3=hindlimbs dragging; 4=prone.

Statistical analyses used were one-way analysis of variance and the Neuman-Keuls range test for the automated measures. Observational data were analyzed using the Mann-Whitney U test.

All drug injections were subcutaneous and were given between 10–11 a.m. The drugs used were phencyclidine HCl (PCP, obtained from NIDA via Dr. Arthur Cho, Dept. of Pharmacology, UCLA), and d-amphetamine sulfate (Smith, Kline and French). PCP and amphetamine doses were calculated as the salt and as the free base, respectively. The vehicle for PCP and amphetamine was saline.

EXPERIMENT 1: ACUTE PCP/AMPHETAMINE INTERACTIONS

The acute PCP and amphetamine response profiles include some similar component behaviors. One strategy frequently used to assess possible commonalities in their underlying mechanisms is to characterize alterations in these behaviors resulting from co-administration of the two drugs [2,9]. Response components modulated by similar neuronal actions might be enhanced by the combined drug treatment at behaviorally submaximal doses of the drugs. However, although it has been reported that PCP may shift the amphetamine dose-response curve to the left [2,25], the available data are difficult to interpret, in part because changes in individual response components have not been assessed. Thus for example, combined PCP and amphetamine treatment reportedly increased one composite measure of locomotion and stereotypy [2], and also increased locomotion [9]. In contrast, one global measure of stereotypy was reported to increase [22], whereas another was unaffected [9]. Therefore, it is difficult to determine whether PCP and amphetamine co-administration produces a response similar to effects of a higher amphetamine dose, as has been speculated [2]. We characterized the response exhibited by animals administered PCP and amphetamine in combination by obtaining a relatively complete behavioral inventory for the duration of the drug response.

Method

After two days of continuous exposure to the activity chambers, animals were injected with saline or amphetamine (0.5 mg/kg). Within 30 seconds, the animals received a second injection of saline or PCP (1.0 mg/kg). The doses of amphetamine and PCP were selected because they produce submaximal levels of locomotor activation and stereotypy, thus precluding ceiling effects. Each animal was used only once. Behavioral measures were obtained as described above.

Results

As previously described [29], amphetamine (0.5 mg/kg) induced relatively pure locomotor activation consisting of ambulation, rearings, and sniffing in the absence of stereotyped behaviors. Phencyclidine (1.0 mg/kg) also stimulated ambulation and sniffing, but unlike the amphetamine response there was no parallel increase in rearings (Fig. 1). In addition, PCP produced a significant increase in repetitive head movements (Fig. 2), and mild hindlimb ataxia (Fig. 3).

Phencyclidine had no effect on amphetamine-induced ambulation or sniffing, but significantly reduced amphetamine-induced rearing (Fig. 1). In contrast, animals receiving combined PCP and amphetamine treatment displayed a supraadditive increase in repetitive head movements (Fig. 2); whereas the degree of ataxia was comparable to the effects of PCP alone (Fig. 3).

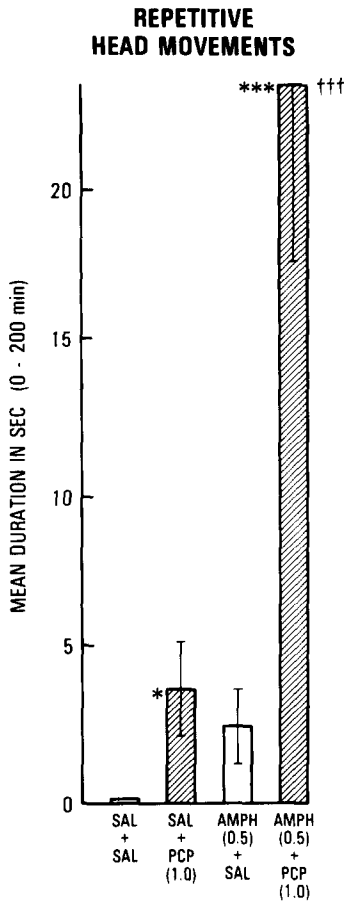

FIG. 2. Effects of combined PCP and amphetamine administration on repetitive head movements in rats. Mean repetitive head movement duration (in sec) during the 0–200-min period following concurrent injection of saline plus saline, saline plus PCP (1.0 mg/kg), amphetamine (0.5 mg/kg) plus saline, and amphetamine (0.5 mg/kg) plus PCP (1.0 mg/kg). Head movements displayed a supraadditive increase after combined PCP/amphetamine treatment. Significant differences from saline-saline controls: $*p<0.05$; $***p<0.01$; significant differences from PCP-saline group: $\dagger p<0.05$; $\dagger\dagger\dagger p<0.01$; n=12 animals/group.

Discussion

We found that amphetamine-induced ambulation was unchanged by PCP, in contrast to a previous report of enhanced ambulation after combined PCP/amphetamine treatment [9]. Methodological differences may account for this discrepancy. The previous study used a relatively high dose of amphetamine (5.0 mg/kg) which produces a complex temporal pattern of locomotion and stereotyped behaviors; however, the time course analysis was limited and therefore accurate interpretation of the response alterations is not possible [29,31]. Our findings are in accord with evidence suggesting significant differences in mechanisms modulating the locomotor responses to PCP and amphetamine. For example, amphetamine- and PCP-induced locomotion are differentially affected by the opiate antagonist naloxone [12, 15, 17, 30], and also by hippocampal lesions [14]. In addition, it was recently reported that various recombinant inbred mouse strains displayed different patterns of responsivity to

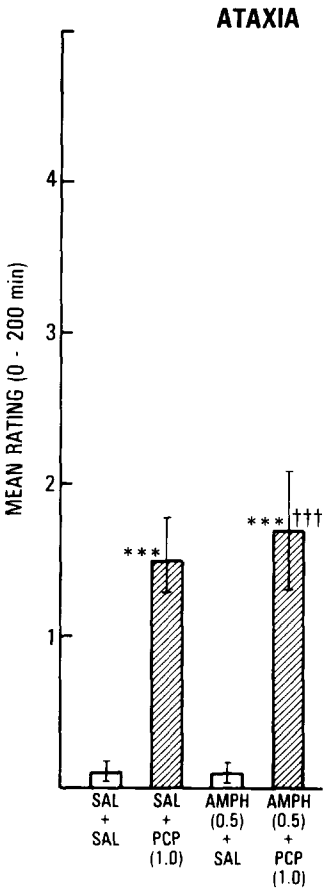

FIG. 3. Effects of combined PCP and amphetamine administration on ataxia in rats. Mean total ataxia rating during the 0–200-min period following concurrent injection of PCP (1.0 mg/kg) and amphetamine (0.5 mg/kg). Phencyclidine (1.0 mg/kg) produced significant ataxia alone or in combination with amphetamine (0.5 mg/kg). Significant differences from saline-saline control: ***$p<0.01$; significant differences from amphetamine alone: †††$p<0.01$; n=12 animals/group.

the locomotor activating effects of PCP and amphetamine [11].

We found that one component of the locomotor activating effects of amphetamine, i.e., rearings, was actually inhibited by PCP. In this regard the locomotor response to combined PCP and amphetamine administration resembled the effects of PCP alone, since PCP stimulates ambulation and sniffing in the absence of a corresponding increase in rearings typically produced by amphetamine and related stimulants [15]. It should be noted, however, that the decrease in rearing may have resulted from the PCP-induced hindlimb ataxia, rather than reflecting a mechanistic difference between amphetamine- and PCP-induced locomotor activation.

Our observation of a supraadditive increase in repetitive head movements is consistent with previous reports that combined PCP and amphetamine administration enhances stereotyped behaviors [2,22]. The present data suggest, however, that the previously reported enhancement of stereotypy may have been due primarily to elevation in this response component, in conflict with the notion that PCP- and amphetamine-induced stereotyped behaviors in general are mediated by common mechanisms [2,19]. In this regard our results are consistent with a recent report that PCP and amphetamine stereotypy are differentially antagonized by neuroleptic drugs [10]. Our findings are in accord with a recent report that repetitive head movements produced by PCP, like those induced by amphetamine, depend upon the integrity of dopamine (DA) systems in the corpus striatum [23]. It should also be noted that because of the competitive interaction between locomotion and stereotypy [29,31], the potentiation of repetitive head movements complicates interpretation of the locomotor response to combined PCP and amphetamine treatment. That is, although we found amphetamine-induced ambulation was unchanged by PCP, the increase in head movement might have interfered with the expression of a locomotor enhancement. Further studies in which stereotypy is excluded as a confounding influence (e.g., in rats with specific lesions of the corpus striatum), might better elucidate the effects of PCP/amphetamine coadministration on ambulation.

EXPERIMENT 2: EFFECTS OF REPEATED AMPHETAMINE AND PCP: CROSS-SENSITIZATION

Drugs with similar mechanisms of action may display cross-tolerance or cross-sensitization. For example, cross-tolerance (cf. [7]) and cross-sensitization (Segal, unpublished observations) have been found among amphetamine-like stimulants, and also between PCP and the sigma opiate agonist N-allylnormetazocine (NANM) [15]. Cross-augmentation observed in animals may have particular clinical relevance, since repeated administration of amphetamine- and PCP-like agents increases the probability of a schizophreniform reaction in humans [4,32].

Phencyclidine and amphetamine-like stimulants produce augmented locomotion when repeatedly administered in low to moderate doses [15, 29, 31]. Whether the enhanced locomotor responses to PCP and amphetamine display cross-augmentation has not been investigated. A reciprocal cross-augmentation between PCP and amphetamine would suggest that the response alterations observed following chronic administration of these drugs may involve common or related mechanisms. In addition, comparison of the effects of repeated amphetamine and PCP treatment may aid in further developing animal behavior models of drug-induced psychoses.

Method

Rats habituated to the residential activity chambers were injected with doses of amphetamine (0.75 mg/kg) or PCP (2.5 mg/kg) in the locomotor-augmenting range [14,29] once daily for 4 days. Separate groups of animals received 4 daily injections of saline vehicle. On the fifth day, amphetamine-treated animals received a challenge injection of PCP (2.5 mg/kg), PCP-treated animals received amphetamine (0.5 mg/kg), and vehicle-treated animals received the same doses of either drug. The PCP and amphetamine challenge doses were selected because they produce submaximal locomotor activation under our experimental conditions; any cross-augmentation would therefore be readily detectible. Behavioral measures were recorded as described above.

Results and Discussion

Consistent with previous findings [31], repeated administration of amphetamine increased the locomotor response to

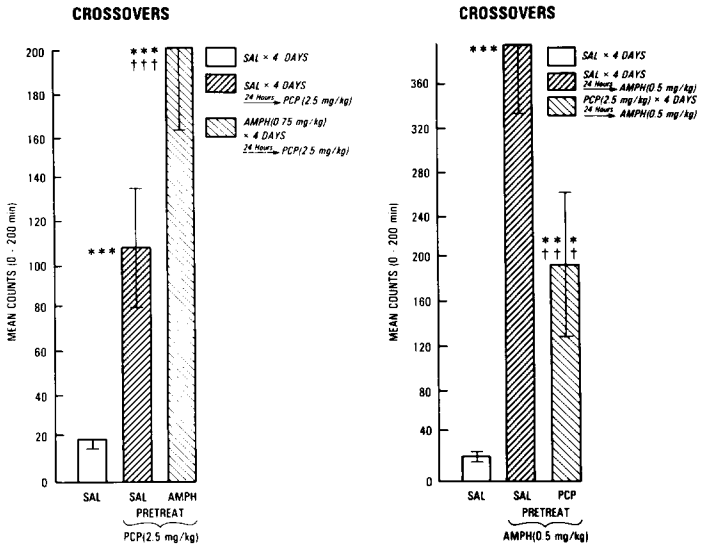

FIG. 4. PCP- and amphetamine-stimulated locomotion after repeated pretreatment with amphetamine or PCP, respectively. Mean total crossovers during the 0–200-min period after acute PCP (2.5 mg/kg) or amphetamine (0.5 mg/kg), after PCP (2.5 mg/kg) challenge in rats pretreated with amphetamine (0.75 mg/kg, once daily for 4 days), and after amphetamine (0.5 mg/kg) challenge in rats pretreated with PCP (2.5 mg/kg, once daily for 4 days). Repeated amphetamine administration produced an enhanced locomotor response to PCP challenge. Repeated PCP administration decreased the locomotor response to amphetamine challenge. Significant differences from chronic vehicle control: $***p<0.01$; significant differences from acute drug treatment: $\dagger\dagger\dagger p<0.01$; n=7 animals/group.

the drug. Ambulation was also enhanced with repeated PCP treatment, in accord with our recent results [15]. Despite the apparent similarity in these chronic effects, however, we observed an asymmetric cross-sensitization between amphetamine and PCP (Fig. 4). That is, PCP-induced ambulation was enhanced after multiple amphetamine injections, whereas amphetamine-stimulated locomotion was actually reduced in animals pretreated with PCP. Furthermore, unlike the effects of repeated treatment with either amphetamine or PCP, there were no corresponding changes in rearings in response to amphetamine or PCP challenge after pretreatment with the other drug. These results suggest that there are important differences in the processes underlying response alterations resulting from repeated administration of PCP and amphetamine.

Our finding of an asymmetric cross-sensitization involving amphetamine is consistent with some results obtained using the drug discrimination paradigm. That is, rats trained to discriminate hallucinogens such as THC and LSD do not generalize to amphetamine or to the direct DA agonist apomorphine [1,28]; in contrast, animals trained to discriminate amphetamine or apomorphine may generalize to THC or LSD [1,3]. Our results suggest an analogous asymmetry could exist for the stimulus generalization between PCP and amphetamine. That is, available evidence only shows that rats trained to discriminate PCP do not transfer stimulus control to amphetamine (e.g., [26]). The converse experiment, i.e., testing the stimulus properties of PCP in animals trained to discriminate amphetamine, has not been reported.

The enhancement of PCP-induced ambulation after repeated amphetamine pretreatment is consistent with evidence that common neuronal substrates may modulate some aspects of the locomotor responses to the two drugs. A recent study indicates that PCP-induced ambulation involves the mesolimbic DA system [13], which has also been implicated in the acute [20] as well as the chronic [30] behavioral response to amphetamine. Repeated amphetamine administration appears to increase the responsiveness of DA release mechanisms [27]; therefore, the enhanced locomotor response to PCP after chronic amphetamine pretreatment may result from an increase in the PCP-stimulated release of mesolimbic DA.

In contrast to the PCP locomotor augmentation which occurs in PCP pretreated animals, amphetamine-induced locomotion was reduced following chronic PCP administration. This finding cannot be attributed to the emergence of competing responses, as occurs with subacute administration of moderate to high doses of amphetamine [29], since our observations revealed no qualitative change in the amphetamine response profile. Our previous findings suggested that an alteration in sigma receptor mechanisms may be responsible for the locomotor augmentation associated with chronic PCP administration [15]. The present results suggest the possibility that the repeated interaction of PCP with sigma receptors may reduce the sensitivity of dopaminergic mechanisms which modulate amphetamine-induced locomotion.

GENERAL DISCUSSION

Although the behavioral effects of PCP are similar in some respects to those of amphetamine and related stimulants [2, 18, 21], these drugs produce significantly different

acute response profiles. With regard to the behaviors which appear to be similar, combined administration of PCP and amphetamine produced no alteration in ambulation, and enhanced only one component of stereotypy, i.e., repetitive head movements. These findings argue against the interpretation, based on global behavioral ratings, that combined PCP and amphetamine administration produces a higher dose amphetamine profile [2].

While both PCP and amphetamine produce enhanced locomotion with repeated administration, the lack of reciprocal cross-augmentation suggests that different mechanisms underlie the respective augmentation effects. These results are consistent with the clinical observation that PCP-induced psychotic reactions in normal human subjects may result from single acute low doses [8], while amphetamine-induced psychosis is typically associated with chronic high dose drug exposure. However, that PCP-induced locomotion was enhanced by chronic amphetamine pretreatment is consonant with the involvement of DA mechanisms in the locomotor response to PCP. Furthermore, regardless of possible differences in underlying mechanisms, the finding that repeated administration of either drug alone produces behavioral sensitization may be relevant to the clinical observations that the likelihood of a schizophreniform reaction to either amphetamine or PCP increases with chronic treatment [4,32].

REFERENCES

1. Appel, J. B., F. J. White and A. M. Holoheam. Analyzing mechanisms of hallucinogenic drug action with drug discrimination procedures. *Neurosci Biobehav Rev* **6:** 529–536, 1982.
2. Balster, R. L. and L. D. Chait. The effects of phencyclidine on amphetamine stereotypy in rats. *Eur J Pharmacol* **48:** 445–450, 1978.
3. Bueno, O. F. A., E. A. Carlini, E. Finklefarb and J. S. Suzuki. Delta(9)-tetrahydrocannabinol, ethanol, and amphetamine as discriminative stimuli—generalization tests with other drugs. *Psychopharmacologia* **46:** 235–242, 1976.
4. Burns, R. S. and S. E. Lerner. The effect of phencyclidine in man: A review. In: *PCP (Phencyclidine): Historical and Current Perspectives*, edited by E. F. Domino. Ann Arbor, MI: NPP Books, 1981, pp. 449–469.
5. Byrd, L. D. Comparison of the behavioral effects of phencyclidine, ketamine, d-amphetamine and morphine in the squirrel monkey. *J Pharmacol Exp Ther* **220:** 139–144, 1982.
6. Castellani, S. and P. Adams. Acute and chronic phencyclidine effects on locomotor activity, stereotypy, and ataxia in rats. *Eur J Pharmacol* **73:** 143–154, 1981.
7. Demellweek, C. and A. J. Goudie. Behavioral tolerance to amphetamine and other psychostimulants: The case for considering behavioral mechanisms. *Psychopharmacology (Berlin)* **80:** 287–307, 1983.
8. Domino, E. F. and E. D. Luby. Abnormal mental states induced by phencyclidine as a model of schizophrenia. In: *PCP (Phencyclidine): Historical and Current Perspectives*, edited by E. F. Domino. Ann Arbor, MI: NPP Books, 1981, pp. 401–418.
9. Fessler, R. G., R. D. Sturgeon and H. Y. Meltzer. Effects of phencyclidine and methylphenidate on d-amphetamine-induced behaviors in reserpine pretreated rats. *Pharmacol Biochem Behav* **13:** 835–842, 1980.
10. Freed, W. J., L. A. Bing and R. J. Wyatt. Effects of neuroleptics on phenycyclidine (PCP)-induced locomotor stimulation in mice. *Neuropharmacology* **23:** 175–181, 1984.
11. Freed, W. J., S. Crump and D. V. Jeste. Genetic effects on PCP-induced stimulation in recombinant inbred strains of mice. *Pharmacol Biochem Behav* **21:** 159–162, 1984.
12. Freed, W. J., D. R. Weinberger, L. A. Bing and R. J. Wyatt. Neuropharmacological studies of phencyclidine (PCP)-induced behavioral stimulation in mice. *Psychopharmacology (Berlin)* **71:** 291–297, 1980.
13. French, E. D. and G. Vantini. Phencyclidine-induced locomotor activity in the rat is blocked by 6-hydroxydopamine lesion of the nucleus accumbens: Comparisons to other psychomotor stimulants. *Psychopharmacology (Berlin)* **82:** 83–88, 1984.
14. Glick, S. D., R. C. Meibach, R. D. Cox and S. Maayani. Phencyclidine-induced rotation and hippocampal modulation of nigrostriatal asymmetry. *Brain Res* **196:** 99–108, 1980.
15. Greenberg, B. D. and D. S. Segal. Evidence for multiple opiate receptor involvement in different phencyclidine-induced unconditioned behaviors in rats. *Psychopharmacology (Berlin)*, in press, 1984.
16. Greenberg, B. D., D. S. Segal and B. L. Jacobs. Phencyclidine. In: *Psychopharmacology 2*, edited by D. G. Grahame-Smith, H. Hippius and G. Winokur. Amsterdam: Excerpta Medica, 1985, in press.
17. Holtzman, S. G. Behavioral effects of separate and combined administration of naloxone and amphetamine. *J Pharmacol Exp Ther* **198:** 51–60, 1974.
18. Johnson, K. M. Phencyclidine: Behavioral and biochemical evidence against the anticholinergic hypothesis. *Pharmacol Biochem Behav* **17:** 53–57, 1982.
19. Johnson, S., P. E. Haroldson, B. J. Hoffer and R. Freedman. Presynaptic dopaminergic activity of phencyclidine in rat caudate. *J Pharmacol Exp Ther* **229:** 322–332, 1984.
20. Kelly, P. H., P. W. Seviour and S. D. Iversen. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. *Brain Res* **94:** 507–522, 1975.
21. Meltzer, H. Y., R. D. Sturgeon, M. Simonovic and R. G. Fessler. Phencyclidine as an indirect dopamine agonist. In: *PCP (Phencyclidine): Historical and Current Perspectives*, edited by E. F. Domino. Ann Arbor, MI: NPP Books, 1981, pp. 207–242.
22. Murray, T. F. and A. Horita. Phencyclidine-induced stereotyped behavior in rats: Dose-response effects and antagonism by neuroleptics. *Life Sci* **24:** 2217–2226, 1979.
23. Nabeshima, T., K. Yamaguchi, K. Yamada, M. Hiramatsu, H. Furkawa and T. Kameyama. Phencyclidine-induced stereotyped behaviors in the rat following specific neurotoxin lesions of the striatum. *Eur J Pharmacol* **93:** 229–234, 1983.
24. Pearlson, G. D. Psychiatric and medical syndromes associated with phencyclidine abuse. *Johns Hopkins Med J* **148:** 25–33, 1981.
25. Poling, A., J. Cleary, K. Jackson and S. Wallace. d-Amphetamine and phencyclidine alone and in combination: effects on fixed-ratio and interresponse-time-greater-than-t responding in rats. *Pharmacol Biochem Behav* **15:** 357–361, 1981.
26. Poling, A. D., F. J. White and J. B. Appel. Discriminative stimulus properties of phencyclidine. *Neuropharmacology* **18:** 459–468, 1979.
27. Robinson, T. E. and J. B. Becker. Behavioral sensitization is accompanied by an enhancement in amphetamine-stimulated dopamine release from striatal tissue in vitro. *Eur J Pharmacol* **85:** 253–265, 1982.
28. Schechter, M. D. and J. A. Rosecrans. Lysergic acid diethylamide (LSD) as a discriminative cue: drugs with similar stimulus properties. *Psychopharmacologia* **26:** 313–319, 1972.
29. Segal, D. S. Behavioral and neurochemical correlates of repeated d-amphetamine administration. In: *Neurobiological Mechanisms of Adaptation and Behavior*, edited by A. J. Mandell. New York: Raven Press, 1975, pp. 247–266.
30. Segal, D. S., P. H. Kelly, G. Koob and D. C. S. Roberts. Nonstriatal dopamine mechanisms in the response to repeated d-amphetamine administration. In: *Catecholamines: Basic and Clinical Frontiers*, edited by E. Usdin and J. Barcas. New York: Pergamon Press, 1979, pp. 1672–1674.

31. Segal, D. S. and A. J. Mandell. Long-term administration of amphetamine: Progressive augmentation of motor activity and stereotypy. *Pharmacol Biochem Behav* **2:** 249–254, 1974.
32. Segal, D. S. and M. A. Schuckit. Animal models of stimulant-induced pyschosis. In: *Stimulants: Neurochemical, Behavioral and Clinical Perspectives,* edited by I. Creese. New York: Raven Press, 1983, pp. 131–167.
33. Sturgeon, R. D., R. G. Fessler and H. Y. Meltzer. Behavioral rating scales for assessing phencyclidine-induced locomotor activity, stereotyped behavior, and ataxia. *Eur J Pharmacol* **59:** 169–179, 1979.
34. Thompson, D. M. and J. M. Moerschbaecher. Phencyclidine in combination with d-amphetamine: Differential effects on acquisition and performance of response chains in monkeys. *Pharmacol Biochem Behav* **20:** 619–627, 1984.