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# Following Several Days of Continuous Administration *d*-Amphetamine Acquires Hallucinogenlike Properties

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**Abstract.** Rats injected with LSD or mescaline show the behavioral syndrome which has been previously reported following injections of hallucinogens in higher mammals: limb flicks and whole body shakes. Although these behaviors are not elicited by acute injections of amphetamine, they are present in rats which have been pretreated for 108 h with a slow-release amphetamine pellet, given a 12 h rest period, and then injected with *d*-amphetamine. Such pellet-pretreated animals also groom their body surface excessively. We propose that this novel syndrome which follows continuous amphetamine administration can serve as an animal model of the type of amphetamine psychosis that is produced by a similar drug regimen in humans.

**Key words:** Continuous amphetamine – Hallucinogens – Limb flicks – Shakes – Grooming – Model psychosis – Rat

One close model of schizophrenia is the type of amphetamine psychosis that can be elicited in human volunteers if frequent doses of *d*-amphetamine are administered every few hours for a number of days (Snyder et al., 1974; Griffith et al., 1972; Angrist et al., 1974; Kramer et al., 1967). To simulate this continuous regimen of drug administration we have developed slow-release silicone pellets that continuously release *d*-amphetamine for up to 10 days when implanted subcutaneously (Huberman et al., 1977). Implantation of these pellets produces unique effects on behavior (Ellison et al., 1978a; Nelson and Ellison, 1978) and biochemistry (Ellison et al., 1978b; Nielsen et al., 1978). Rats housed in social colonies and implanted with these pellets go through several stages of alterations in behavior, culminating 5 days after implantation in a 'late stage' characterized by socially disruptive behaviors and heightened startle responses (Ellison et al., 1978a). Monkeys with similar slow-release pellets also enter a late stage commencing about 5 days after implantation during which they show rapid picking movements by the hands directed at various parts of the body, which is suggestive of parasitosis, and other hallucinatory behaviors such as capturing movements of the hands in midair or spontaneous fleeing behaviors (Lyon and Nielsen, 1979).

The appearance of these distinctive behaviors during the late stages of continuous amphetamine administration suggest that their closer study and quantification could lead to a useful animal model of amphetamine psychosis. In further studies we recorded on videotape the behavior of rats during the 7 days following amphetamine pellet implantation. We observed that the rats initially entered into intense and continuous motor stereotypies, as reported previously (Huberman et al., 1977), but at 3–5 days after pellet implantation these behaviors waned and the rats were inactive most of the time. However, when active they began to show periods of intense grooming directed towards various parts of the body, wet-dog shakes, and spontaneous flicking movements of the forelimbs. These behaviors seemed of theoretical importance, for limb flicks occur in cats and monkeys injected with hallucinogens such as LSD and mescaline but not with acute amphetamine (Schlemmer et al., 1977; Jacobs et al., 1976) and the type of grooming observed, involving biting the skin with the teeth, also occurs in rats infected with skin parsites such as mites. This suggested that these behaviors might provide a way of quantifying in rats what might be parallel to the hallucinatory and parasitoticlike behaviours observed in humans and monkeys undergoing amphetamine psychosis.

These behaviors observed in rats, however, occurred at unpredictable times and considerable time was spent observing TV tapes. In further experiments we found that these behaviors could be evoked at a high frequency if the amphetamine pellet was removed

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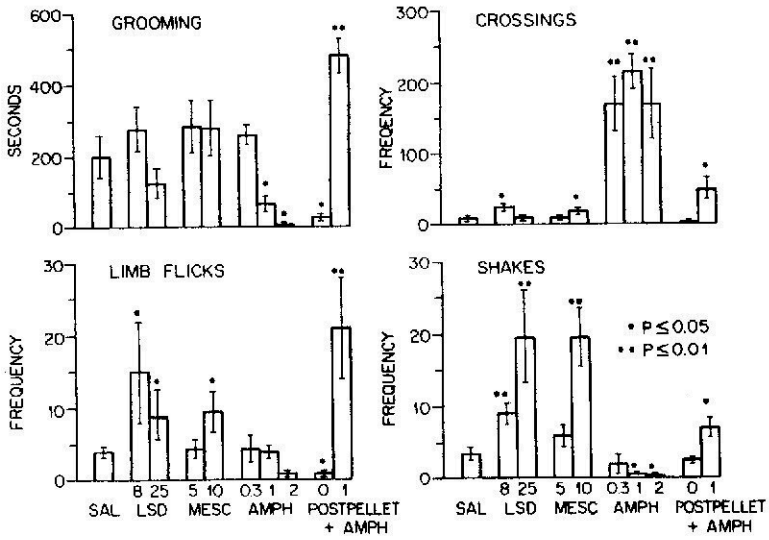


**Fig. 1**
Average duration of grooming and frequency of cage crossings, limb flicks, and wet-dog shakes following injections to drug-naive animals of saline, LSD (8 or 25 µg/kg), mescaline (5 or 10 mg/kg), or amphetamine sulphate (0.3, 1 or 2 mg/kg), and to amphetamine-pellet pretreated animals of saline or 1 mg/kg amphetamine. Statistical tests are two-tailed $t$-tests based on $N = 8$/group

108 h after implantation, a 12 h rest period given, and the animal then was administered an injection of amphetamine. We then compared the behavioral effects of such injections of amphetamine in the postpellet animals with those of injections of amphetamine or hallucinogens into control rats.

## Materials and Methods

The 106 female albino rats (Simonsen's Lab., Gilroy, California, USA), weighing 220 – 230 g, were individually housed in metal cages at 21 °C room temperature. The lights were turned off from 7:00 p.m. until 7:00 a.m. Food and water was available ad lib. throughout the experiment. Amphetamine pellets were implanted using procedures previously described (Huberman et al., 1977), and control animals were implanted with pellets containing only the polyethyleneglycol (PEG) 300 vehicle. The amphetamine pellets contain 50 mg of amphetamine base of which 26 mg is released in the first 5 days following implantation. Brain amphetamine levels produced by this pellet are equivalent to those produced by a 1.5 mg/kg acute injection of amphetamine sulphate (Huberman et al., 1977). To control for possible artifacts due to the presence of laboratory mites, all animals in this experiment were immersed once weekly for a month in a parasite disinfectant, gamma benzene hexachloride, prior to testing.

All pellets were removed 108 h after implantation and the rats, housed in 29 × 20 × 20 cm cages with transparent fronts, were placed in a soundproof room with dim red lighting. Twelve hours later the control animals received IP injections of either saline, LSD (8 or 25 µg/kg), mescaline hydrochloride (5 or 10 mg/kg), or amphetamine sulphate (0.3, 1 or 2 mg/kg). The behavior was scored for 50 min commencing 10 min after drug injections by trained observers who were not informed of treatment conditions. The observers operated keyboards (with pushbuttons for each behavior) connected to a computer which registered the time and frequency. The following behaviors were scored: body washing (grooming with the forelimbs and licking of the fur); body biting (with the teeth biting the hindflank, tail, or paws); hind-limb scratching (rapid scratch of flank region with hind limbs); wet-dog shakes (including head twitches); limb flicks (rapid flicking movement of forepaw); treading (or weaving with forepaws); cage crossings (the whole body crossing the centerline of the TV monitor); and motor stereotypies (continuous sniffing or licking the cage floor or walls). At 108 h after implantation, amphetamine pellet animals had lost 10 – 15 g body wt. but were otherwise healthy, with minimal signs of self-mutilation.

## Results

Figure 1 shows that there were different patterns of behavior observed in the different groups. The rats injected with LSD at doses of 8 or 25 µg/kg, or with mescaline at a dose of 10 mg/kg, showed the behavioral syndrome which has previously been reported to be specifically induced by injections of hallucinogens in cats or monkeys: increased limb flicks and wet-dog shakes together with normal levels of locomotor activity. Limb flicks and wet-dog shakes were not increased over control levels in the rats injected acutely with amphetamine (0.3, 1, or 2 mg/kg), and in fact these behaviors were decreased in a dose-dependent manner. These animals acutely injected with amphetamine were active and exploratory, however, and showed more cage crossing than any of the other groups.

The rats pretreated with slow-release amphetamine pellets for 4.5 days and then injected 12 h later with saline were generally inactive, showing few of the rated behaviors throughout the session. However, when similarly pellet-pretreated animals were injected with amphetamine sulphate (1 mg/kg) just prior to testing, they showed a novel behavioral syndrome. The stimulatory effect of amphetamine on locomotion was considerably attenuated in these animals, but the number of limb flicks and wet-dog shakes characteristic of hallucinogens increased. This was striking because both behaviors were decreased in a dose-dependent manner by injections in drug-naive animals. Another behavior was increased in the pellet-pretreated rats injected with amphetamine: heightened grooming of the body. Two separate measures were taken – body washing and body biting. On both measures the pellet-pretreated animals injected with amphetamine showed more grooming than all other groups (for both measures greater than controls $P < 0.01$). This was again striking because 1 and 2 mg/kg injections of amphetamine decreased these grooming behaviors in drug-

**Table 1.** Effects on four behaviors of saline or amphetamine injections following different durations of amphetamine pellet pretreatment (48 or 108 h) and different rest periods following pellet removal (12, 36, and 50 h). The behavioral syndrome consisting of heightened limb flicks, body shakes, and grooming is maximal after 108 h of pellet pretreatment and 12 h rest. Data are expressed as means ± SEM, based on a 50-min observation period with 6–8 rats/group. * $P < 0.05$; means compared to saline control ($t$-test); ** $P < 0.01$

| Pretreatment duration | Control pellet 108 h | | Amphetamine pellet 48 h | Amphetamine pellet 108 h | | |
|---|---|---|---|---|---|---|
| Rest period; injected with | 12 h Saline | 12 h Amphetamine | 12 h Amphetamine | 12 h Amphetamine | 36 h Amphetamine | 50 h Amphetamine |
| Limb flicks (no) | 3.8 ± 1.2 | 4.0 ± 1.2 | 11.1 ± 5.1* | 21.5 ± 7.1** | 8.6 ± 3.0* | 3.3 ± 2.6 |
| Shakes (no) | 3.3 ± 0.6 | 0.3 ± 0.2 | 1.4 ± 0.5* | 6.7 ± 1.7 | 6.6 ± 2.6 | 1.4 ± 0.6* |
| Crossings (no) | 7.4 ± 1.9 | 215 ± 24** | 55 ± 29** | 50 ± 19** | 105 ± 33** | 194 ± 44** |
| Grooming (s) | 198 ± 60 | 64 ± 24 | 340 ± 110 | 482 ± 46** | 313 ± 50 | 276 ± 197 |

naive animals. The excessive grooming by these pellet-pretreated, amphetamine-injected animals had several distinctive features. Normal washing of the body by the forepaws and tongue alternated with episodes of intense biting at the skin, especially around the hind-flanks, and of picking up the tail with the teeth and carrying it. Frequent episodes of biting the forepaw toenails were also observed. These episodes of intense grooming were quite different in appearance from that sometimes observed at higher, stereotypy-inducing doses of amphetamine in that they were directed towards various parts of the body surface, rather than becoming focused on a certain spot. Furthermore, this grooming was performed in rapid alternation with locomotion and other behaviors and was not directed towards the site of pellet implantation which was generally inaccessible.

## Supplementary Observations

In additional experiments we found that flicks, shakes, and grooming behaviors were not generally present in animals which had received the pellet-pretreatment for only 48 h and then 12 h later were injected with 1 mg/kg of amphetamine (Table 1). The ability of amphetamine injections to produce this syndrome decreased markedly in animals pretreated with the pellet for 108 h and then injected 36 or 50 h after pellet removal. By 50 h after pellet removal, a 1-mg/kg injection of amphetamine elicited normal levels of limb flicks and shakes, although some heightened grooming was still present. This novel behavioral syndrome was also present following a 2 mg/kg injection of amphetamine in pellet-pretreated animals, although variability between animals was increased. At higher doses (3 mg/kg or more), motor stereotypies such as sniffing the cage wall began to predominate and limb flicks, shakes, and excessive grooming decreased (no data shown).

## Discussion

One finding of the present experiment is that the behavioral syndrome consisting of wet-dog shakes and limb flicks elicited by hallucinogens in monkeys and cats (Siegel et al., 1974; Jacobs et al., 1976) is also present in rats injected with the hallucinogens LSD or mescaline. Several details may have been responsible for our ability to observe these behaviors in rats, such as the administration of low doses of hallucinogens to rats which had been housed for 12 h in a dim, quiet environment and the use of closed circuit TV providing a minimum of distraction to the animals.

These hallucinogen-specific behaviors, however, were present at a low rate in rats which had been subjected to 5 days of continuous amphetamines, and could be elicited at a high frequency in animals which had been pretreated with a slow-release amphetamine pellet for 4.5 days (108 h), given a 12 h rest period, and then injected with a low dose of amphetamine. These results indicate that continuous amphetamine intoxication produces an alteration in the behavioral response to the drug. Whereas the initial effects of amphetamine in the drug-naive animal are stimulation and, at higher doses, stereotypies, the effects of amphetamine during the late stage of continuous amphetamine intoxication are attenuated locomotor stimulation, heightened grooming, and the appearance of other behaviors which are usually hallucinogen-specific.

We propose that this novel behavioral syndrome which follows continuous amphetamine administration in rats can serve as a useful animal model of amphetamine psychosis with possible advantages over other existing models. First, the behavioral syndrome appears in the late phase of the drug regimen which similarly produces delayed psychotic symptoms in human volunteers. Second, like amphetamine psy-

chosis in humans (Angrist et al., 1969), it rapidly disappears when the continuous amphetamine regimen is discontinued. Third, this behavioral syndrome uses behavioral measures which are valid in rats, cats, and monkeys and have theoretical importance. The fact that the same behaviors which are normally elicited only by hallucinogens appear following continuous amphetamine administration makes an extension to animal models of psychotic behavior more tenable, while the other behavior observed following continuous amphetamines, excessive grooming of the body, might be a parallel to the frantic grooming episodes observed in monkeys following amphetamine pellet implantation and the parasitosis observed during amphetamine psychosis in humans (Ellinwood, 1972). Last, this model is based on measures which are reliable, quantifiable, and easily observed.

Some of the elements of the behavioral syndrome reported here, such as limb flicks and body shakes, can also be observed in cats and monkeys injected with very large doses of amphetamine or cocaine once or twice daily for a number of weeks (Ellinwood and Kilbey, 1977). Amphetamine pellet implantation thus differs from repeated injections of massive doses of amphetamines with respect to the induction of these 'end-stage' behaviors: less amphetamine must be administered as a pretreatment, the syndrome appears much sooner, and it appears at a reliable point in time. Furthermore, following amphetamine pellet pretreatment this syndrome is elicited by low doses of amphetamine, whereas the similar behaviors observed following massive repeated doses require further large doses of amphetamine. Such large doses in humans induce elements of a toxic psychosis, which has been reported to differ in symptomatology from those of schizophrenic psychoses (Snyder et al., 1974). Finally, injections of amphetamines administered once daily leads to a progressive augmentation of motor stereotypies (Segal and Mandell, 1974), whereas amphetamine pellet implantation leads to a diminution of motor stereotypies (Nelson and Ellison, 1978). This makes it likely that large amphetamine injections repeated once or twice daily will lead to a behavioral syndrome which contains elements of both heightened motor stereotypies and of 'end-stage' behaviors, whereas the latter behaviors will mainly be observed following pellet implantation.

It may thus be of considerable relevance for models of psychosis to learn why the response of the nervous system to amphetamine after the continuous amphetamine intoxication differs from the initial effects. Although there are long-lasting changes in dopaminergic innervations of the caudate nucleus following amphetamine pellet treatment (Ellison et al., 1978b), these changes are probably not solely responsible for the syndrome described here. The changes are still present 110 days after pellet removal, but the behavioral syndrome described here can only be elicited for a few days thereafter.

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