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Long-Term Administration of d-Amphetamine: Progressive Augmentation of Motor Activity and Stereotypy[1]

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SEGAL, D. S. AND A. J. MANDELL. *Long-term administration of d-amphetamine: progressive augmentation of motor activity and stereotypy.* PHARMAC. BIOCHEM. BEHAV. 2(2) 249–255, 1974. – The competitive relationship between d-amphetamine induced stereotypy and locomotor activity indicates the importance of their concurrent evaluation, especially during chronic studies. Repeated injection of 0.5, 1.0, 2.5, 5.0, or 7.5 mg/kg d-amphetamine for 36 successive days, in rats continuously exposed to the experimental chambers, produced a progressive augmentation in stereotypy and/or locomotion (depending on dose) during the 3–4 hr interval following injections (post-injection phase). In contrast, dark phase locomotor activity (8–20 hr after each daily injection) was maximally reduced (30–40% of controls) after the first injection of either 5.0 or 7.5 mg/kg d-amphetamine and gradually declined to this level with repeated injection of 1.0 and 2.5 mg/kg. Carry-over of both the post-injection augmentation and dark phase reduction of locomotion was revealed during amphetamine retest 8 days following discontinuation of daily d-amphetamine injections. Possible mechanisms underlying these behavioral alterations are discussed.

d-Amphetamine Tolerance Locomotor activity Stereotypy

TOLERANCE has been reported to occur to many of the physiological and behavioral effects of d-amphetamine [16,18]. However, contradictory results have been obtained regarding the effects of repeated administration on amphetamine-induced increases in locomotor activity in animals. Such studies are often inconclusive because of the relatively incomplete characterization of the various behavioral effects of amphetamine, and their interactions with situational variables. As an example of the complexity of these kinds of interactions, recent evidence indicates that conditioned locomotor activity (defined by Tilson and Rech as motor activity which is conditioned to neutral stimuli attending drug administration) can be produced by repeated injection of d-amphetamine [25]. That chronic drug effects on behavior are typically evaluated for short time periods during the peak drug response must be considered when interpreting such results. Exposure to the experimental chambers exclusively during this interval should optimize the contribution of conditioning effects and render progressive behavioral alterations in response to amphetamine difficult to interpret.

Another consideration is that various drug effects on behavior may be competitively related, in which case a relatively complete characterization of the various components of the behavioral response is required for accurate interpretation of long-term alterations. This is particularly relevant for amphetamine which has been shown, even following administration of relatively low doses in the rat (1.0 mg/kg, I.P.), to produce at least one component of stereotypy, i.e., continuous sniffing as well as enhanced locomotion [20]. After larger doses (e.g., 5.0 mg/kg), a sequence of behaviors has been described by Schiorring [22] which includes a "pre-phase" of hyperactivity, a "stereotypy phase" during which rearing and forward locomotion are absent, and an "after phase" of enhanced motor activity after which the amphetamine effect appears to subside. The duration of these 3 phases is 4–6 hr and closely corresponds to the presence of d-amphetamine in the brain [4, 8, 19, 24, 26]. The two primary behavioral characteristics of the amphetamine response (locomotion and stereotypy) seem to be competitively related, and as such the expression of each is to some extent interdependent on the other. It is, therefore, essential that both components of the amphetamine response be concurrently evaluated. This is especially relevant in chronic studies since considerable evidence suggests that different neurotransmitter systems in the brain may subserve locomotion and stereotypy. The rate and extent of change produced by

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repeated administration of amphetamine may be different for these two neural systems. In fact, it has been convincingly demonstrated that amphetamine tolerance does not develop equally for all effects [16,18]. Rapid tolerance development to the stereotypic effects of amphetamine might result in an emergence of previously masked behavioral activity. In the absence of thorough behavioral observations, such an effect might be erroneously interpreted as an augmentation of the amphetamine-induced locomotor activity or reverse tolerance. The competitive relationship between stereotypy and locomotor activity is demonstrated in the first experiment.

EXPERIMENT 1

Method

Adult, male, Sprague-Dawley rats weighing 300–350 g were obtained from Carworth Farms. Following one week of housing under standard laboratory conditions, the rats were placed individually into sound-attenuated experimental chambers (12 × 12 × 15 in.). Cross-overs from one quadrant to another were automatically measured through contacts in the floor of the chambers. Rearings were measured by touchplates set 5 in. above the floor. Both measures of locomotion were continuously monitored with the use of a Nova 1200 computer. A viewing lens allowed for regular observations without disturbing the animals. The rats were injected with saline daily at 10 a.m. and lived in the experimental chambers for at least 2 weeks prior to the initiation of drug injection. Food and water were available ad lib and a 12 hr bright light (6 a.m. to 6 p.m.)/dim light cycle was maintained. When their behavior had stabilized, the rats were injected I.P. with 100 mg/kg alpha-methyl-p-tyrosine (αMT) or with saline (n = 8 in each group). Alpha-methyl-p-tyrosine has been shown to inhibit tyrosine hydroxylase (the rate-limiting enzyme in catecholamine biosynthesis) and diminish amphetamine-induced locomotor activity and stereotypy [11, 21, 27, 28]. Three hr following the administration of αMT or saline, both groups received an I.P. injection of 3.5 mg/kg d-amphetamine (free base). Behavior was then monitored for an additional 3 hr, and the rats were periodically observed throughout the duration of the experiment.

Results and Discussion

Although αMT did not significantly affect cross-over activity when compared to saline controls, αMT pretreatment markedly altered the response to amphetamine (Fig. 1). Changes in rearings closely paralleled those observed with cross-overs. The animals initially exhibited hyperactivity for approximately 15 min after amphetamine administration followed by continuous stereotypic behavior including sniffing, chewing, gnawing, biting, licking and head swaying. During this phase, lasting approximately 1 hr, both vertical and horizontal locomotion were almost totally absent. The stereotypy phase was followed by a prolonged period of hyperactivity lasting at least 90 min. In contrast, animals pretreated with αMT did not exhibit a prolonged phase of continuous stereotypy. Rather, the predominant response was enhanced locomotion which subsided within 3 hr. Thus, when stereotypy was blocked by αMT, an increase in locomotion emerged (183 ± 23 vs. 15 ± 5, mean cross-overs ± S.E.M. for appropriate intervals; $p<0.01$). This increased activity appears in spite of the fact that αMT also reduces amphetamine-induced locomotion as indicated not only in previous studies in which locomotor activity was the predominant response [28], but also during the last half-hour of the present study during which αMT significantly lowered amphetamine-induced activity as compared to the saline pretreated group (22 ± 7 vs. 112 ± 22; $p<0.01$).

These results suggest a competitive relationship between these two components of the behavioral response to amphetamine and indicate the need for their concurrent evaluation. In the following experiment both locomotion and stereotypy were examined during the course of chronic d-amphetamine administration. To more completely characterize the drug response while minimizing the effects of contrasting situational variables, animals resided in the experimental chambers throughout the experiment.

EXPERIMENT 2

Method

The behavioral effects of repeated amphetamine administration were evaluated in 48, adult, male, Sprague-Dawley rats (Carworth Farms) following acclimation to the experimental chambers (described above). Drug treatment was initiated after stable levels of behavioral activity were achieved (approximately 2 weeks of continuous exposure). Rats were injected I.P. daily at 10 a.m. with either saline, 0.5, 1.0, 2.5, 5.0, or 7.5 mg/kg d-amphetamine (free base). All animals received injections for 36 days during which time their daytime (6 a.m. to 6 p.m.) and nighttime (6 p.m. to 6 a.m.) behavior was continuously monitored. Twenty-four hours following the 36th injection, the animals receiving saline, 0.5, 2.5 or 5.0 mg/kg d-amphetamine were sacrificed and examined for changes in regional brain catecholamine biosynthetic capacity. The results of these findings will be reported separately (Segal, Kuczenski and Mandell, manuscript in preparation). The remaining 2 groups (receiving 1.0 or 7.5 mg/kg d-amphetamine) were administered saline for seven additional days (Days 37–43) and retested with amphetamine on Day 44.

Results and Discussion

Post-injection activity. Figure 2 shows the effects of repeated amphetamine administrations for the groups receiving 1.0 mg/kg and 2.5 mg/kg. The data are presented for representative days as cross-overs during the 3 hr interval following injection. Rearing data were found to closely parallel the pattern of horizontal locomotion for all the doses examined. Animals receiving daily injections of saline showed no significant change in activity (mean cross-overs for the first 3 hr following injection ± S.E.M.) throughout the course of the experiment (50 ± 4 vs. 48 ± 4; predrug baseline and Day 36, respectively). Predrug baseline activity was comparable for all groups. Statistical significance was determined by *t*-tests for correlated observations. Data in the text is presented as mean cross-overs ± S.E.M. for 3 hr intervals following injection unless otherwise indicated.

Following the first injection of 1.0 mg/kg d-amphetamine, there was a significant increase in activity which gradually declined to predrug levels within 3–4 hr (Fig. 2). Observations of the animals indicated that while locomotion was the predominant response, the rats did exhibit some stereotypy (primarily sniffing and chewing)

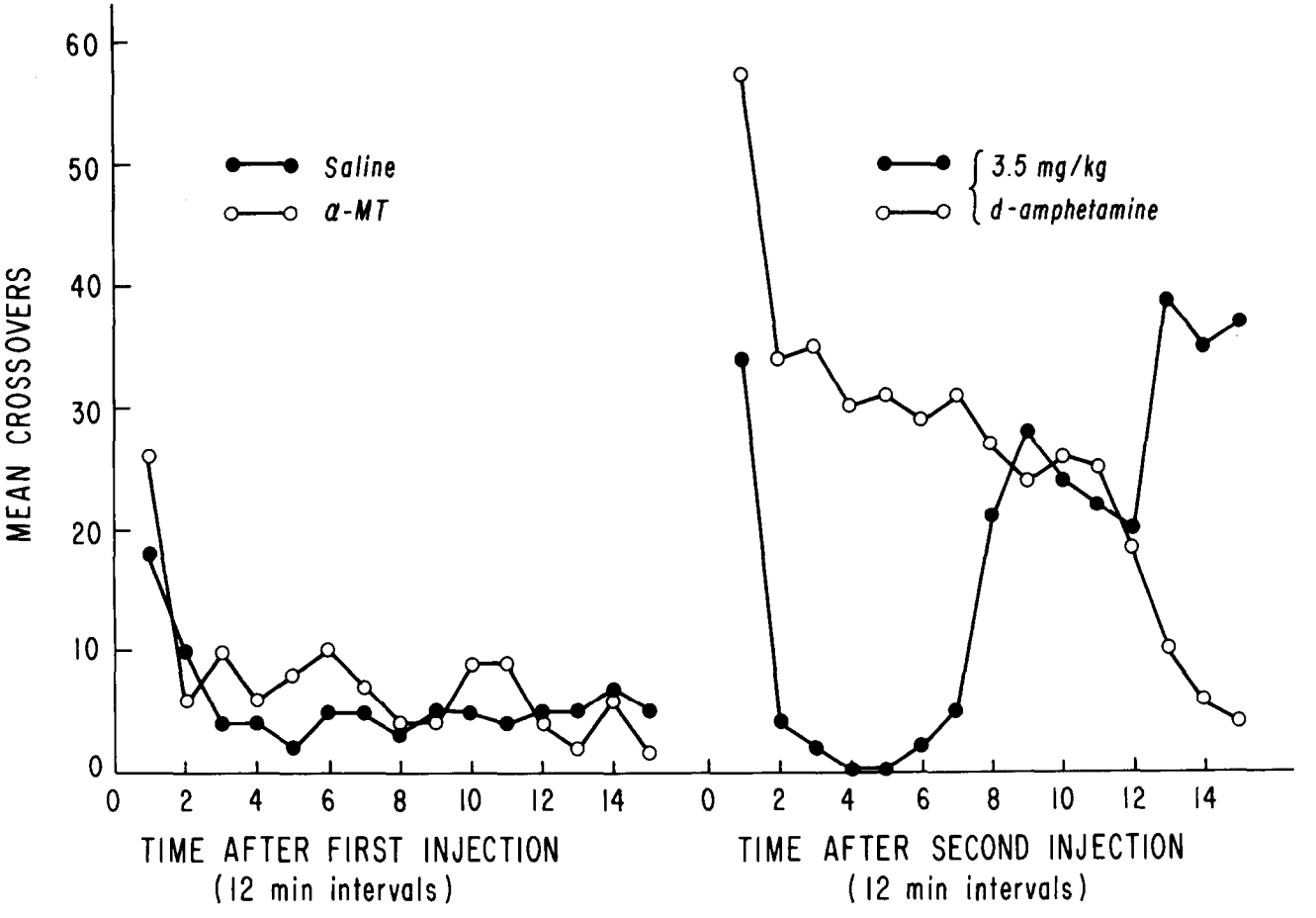

FIG. 1. Mean cross-overs during successive 12 min intervals following injection of either 100 mg/kg αMT or isotonic saline (left panel). Three hr later both groups (n = 8 in each group) were injected I.P. with 3.5 mg/kg d-amphetamine and their behavioral activity was monitored for an additional 3 hr (right panel). The competitive relationship between stereotypy and locomotion indicated by these results is described in the text.

especially during the first hour. By Day 15 there was a significant augmentation of the effect of 1.0 mg/kg d-amphetamine (322 ± 47 vs. 523 ± 74; Days 1 and 15, respectively; $p<0.01$). However, continued administration produced no further increases in locomotion. This apparent lack of a continued progressive enhancement in locomotion by Day 36 was accompanied by a marked increase in stereotypy (as compared to Day 1 and Day 15), especially within the first 90 min following each injection. During this phase of increased ambulation, the animals were engaged in continuous sniffing and to a lesser extent, chewing. Some animals showed brief episodes of stereotypy during which locomotion was absent.

This relative increase in stereotypy may have competed to some extent with the expression of locomotor activity. Consonant with this interpretation are the results obtained with the doses of 0.5 mg/kg and 2.5 mg/kg d-amphetamine. With repeated administration of 0.5 mg/kg, a progressively greater increase in locomotion was observed throughout the 36 days of experimentation (248 ± 40, 294 ± 29, 419 ± 48; for Days 1, 15 and 36, respectively); the activity on Day 36 was significantly greater than that on Days 1 and 15 ($p<0.01$ for each comparison). Since this relatively low dose does not appear within our experimental conditions to produce competitive stereotypy even after 36 days of amphetamine administration, the progressive augmentation in locomotor activity is not obscured by concurrent increases in stereotypy.

In contrast, the higher dose of 2.5 mg/kg d-amphetamine which on Day 1 produced marked increases in locomotion (248±40 [0.5 mg/kg] vs. 480±81 [2.5 mg/kg]; t-test, $p<0.01$) with accompanying sniffing and chewing, progressively elicited a multiphasic response resembling the effect produced by higher acute doses of amphetamine. By the fifteenth day an initial period of hyperactivity (12 min) was rapidly followed by a phase of continuous stereotypy which persisted for approximately 1 hr. Locomotion during this inteval (stereotypy phase) was significantly reduced (205 ± 47 [Day 1] vs. 18 ± 8 [Day 15]; $p<0.01$). During the subsequent 2 hr (after phase) the animals exhibited a marked increase in activity which progressively increased through the remainder of experimentation (233 ± 26 [Day 15] vs. 286 ± 43 [Day 36]; $p<0.05$). With the higher doses of amphetamine, 5.0 mg/kg and 7.5 mg/kg, the

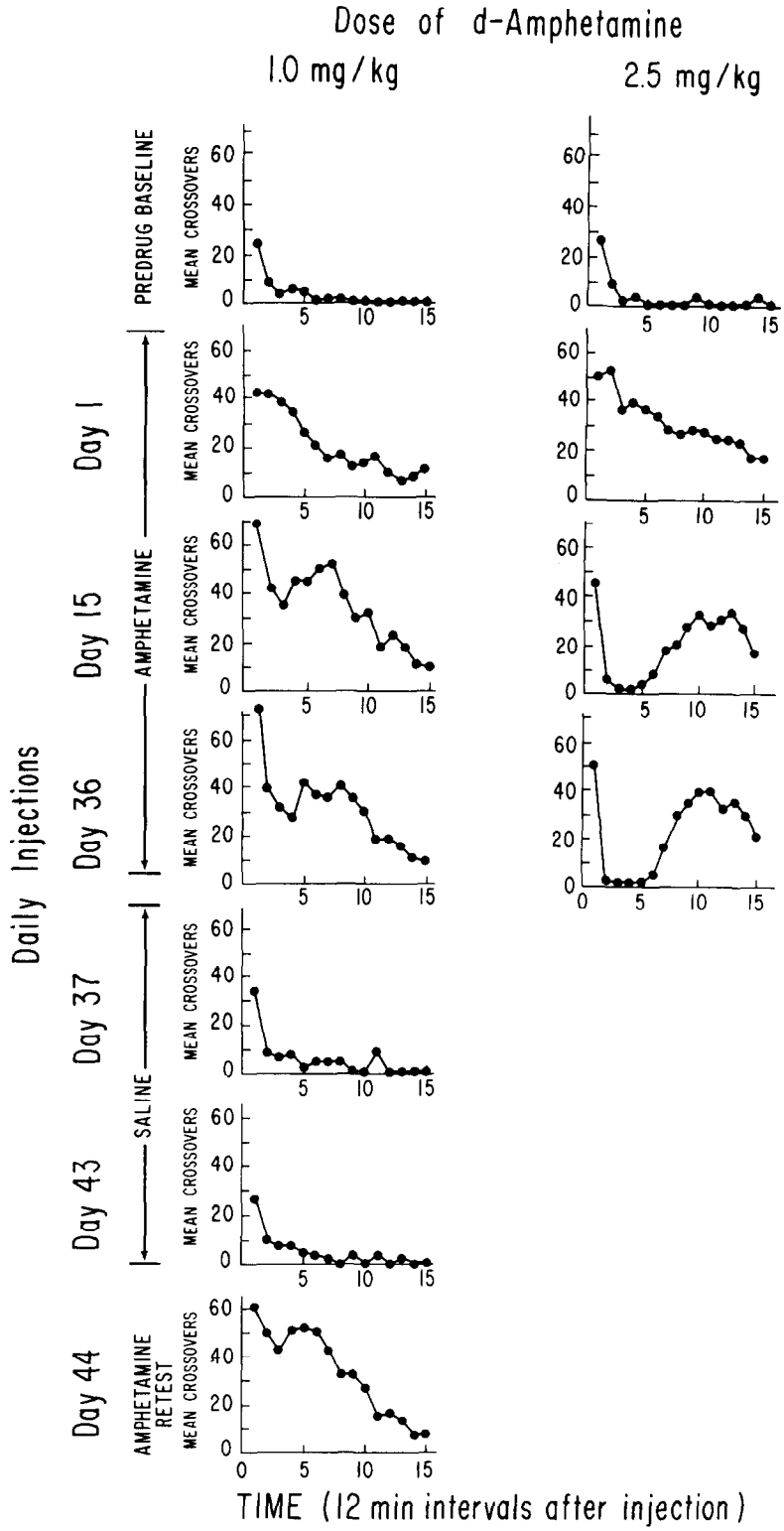

FIG. 2. Mean cross-overs during the 3 hr interval following representative daily injections of d-amphetamine (Days 1, 15, 36). Effects obtained with doses of 0.5, 5.0 and 7.5 mg/kg d-amphetamine are described in the text. Repeated administration produced a progressive augmentation in the effect of d-amphetamine with respect to both locomotor activity and stereotypy. Carry-over effects were not observed during administration of saline (Days 37–43), but were revealed by retest with d-amphetamine on Day 44.

primary change observed following repeated administration was a progressive augmentation of locomotion during the after phase.

The first injection of saline (Day 37) into animals which had received 36 days of 1.0 mg/kg d-amphetamine treatment produced a response which was not statistically greater than baseline levels for the 3 hr interval following administration (60 ± 11 vs. 88 ± 10, respectively). Six additional days of saline injection resulted in no significant alteration from baseline responding. However, retest with 1.0 mg/kg on Day 44 produced a marked increase in locomotion which was significantly greater than that following the initial injection of 1.0 mg/kg (321 ± 47 [Day 1] vs. 505 ± 65 [Day 44]; $p<0.01$). These results indicate that augmentation in response to repeated administration of amphetamine persists for at least eight days after discontinuing the chronic regimen. Similar persistence for the after phase augmentation of locomotor activity was observed with the dose of 7.5 mg/kg d-amphetamine.

Dark phase activity. Injection of d-amphetamine produced a dose and time related decrease in dark phase activity levels (Table 1). While activity of the saline control group remained relatively stable throughout the course of the experiment, the first injection of 5.0 mg/kg and 7.5 mg/kg d-amphetamine lowered activity levels by 30–40%. This reduced level of dark phase activity was maintained following each of the 36 daily injections in these animals. After administration of the lower doses (0.5, 1.0 and 2.5 mg/kg), there was no initial decrease in activity. However, with repeated administration locomotion gradually diminished, the extent of this reduction being less with 0.5 mg/kg (17%) than with either 1.0 or 2.5 mg/kg (30–40%).

The dark phase decrease in activity persisted following the first injection of saline (Day 37) in rats which had received 1.0 or 7.5 mg/kg d-amphetamine (Table 1). By the seventh injection of saline (Day 43) the activity had returned to predrug levels. Retest with d-amphetamine (Day 44) again produced a depression in night phase activity, which in the case of the 1.0 mg/kg dose was significantly below that produced following the first injection.

Unlike the augmentation of the post-injection behavioral effects produced by all doses tested, a progressive decrease in dark phase activity resulted only in those animals receiving the lower doses (0.5, 1.0, and 2.5 mg/kg). A further difference between these 2 groups is that while a progressive augmentation was observed throughout the course of the experiment, during the dark phase the effect of the doses higher than 0.5 mg/kg differed only with respect to the rate at which a 30–40% maximum reduction of activity was achieved. Furthermore, in contrast to the recovery of activity during the 3 hr immediately following the first saline injection (Day 37), the depression of dark phase activity persisted for several days before responding returned to predrug levels. Thus, the reduction of locomotion during the dark phase does not appear to be secondary to the hyperactivity produced by d-amphetamine. Finally, carry-over of both the post-injection augmentation and dark phase reduction of locomotion was revealed during the amphetamine retest. These results indicate that the mechanisms responsible for the progressive behavioral changes persist in an altered state although post-injection activity returns to predrug levels soon after the discontinuation of chronic amphetamine treatment.

It is unlikely that these effects are secondary to amphetamine-induced anorexia (recently it has been shown that starvation potentiates the behavioral effects of amphetamine [10] since the rate of weight gain in animals receiving 0.5 to 1.0 mg/kg was not significantly different from that of control animals (approximately 50 g in 36 days). Rats receiving the higher doses showed no weight gain for about 15 days after which their weight increased at a rate which paralleled that of the other groups.

TABLE 1

THE EFFECTS OF REPEATED ADMINISTRATION OF d-AMPHETAMINE ON DARK PHASE MOTOR ACTIVITY IN THE RAT. MEAN PERCENT OF PREDRUG BASELINE ACTIVITY ± S.E.M.*

Dose (mg/kg)	Predrug Baseline	Daily Injections			Saline (Withdrawal)		Amphetamine Retest
		1	15	36	37	43	44
Saline Control	100 ± 11†	100 ± 10	103 ± 9	104 ± 8			
0.5	100 ± 11	102 ± 14	83 ± 17	83 ± 6			
1.0	100 ± 10	90 ± 9	66 ± 12‡	63 ± 9§	67 ± 14‡	93 ± 15	65 ± 13‡
2.5	100 ± 7	97 ± 11	65 ± 12‡	60 ± 17‡			
5.0	100 ± 10	60 ± 16‡	57 ± 5§	63 ± 16‡			
7.5	100 ± 11	66 ± 8‡	63 ± 11‡	55 ± 13§	64 ± 15‡	97 ± 9	76 ± 9‡

*All animals received daily injections 7–8 hr prior to the onset of the dark phase.

†Mean percent of 8 rats in each subgroup averaged over the middle 8 hr of the 12-hr dark phase. Predrug activity in all groups was approximately 30 crossovers/hr.

Statistically lower than corresponding predrug baseline, *t*-test for correlated observations: ‡$p<0.05$; §$p<0.01$.

GENERAL DISCUSSION

The progressive alterations in behavior which accrue with repeated administration of d-amphetamine may be subserved by several possible mechanisms. Recently Tilson and Rech [25] have demonstrated that conditioned increases in motor activity (activity conditioned to neutral stimuli attending the drug administration) can result during the course of repeated amphetamine injection. This conditoned component of the behavioral activity was suggested by these investigators to account for the increased responsiveness produced by repeated injections of amphetamine. Although the present findings might be explained in a similar manner, several points argue against such an interpretation. For one, in contrast to the results reported by Tilson and Rech, in the present study saline injection on the day following long-term amphetamine administration produced predrug levels of activity. Therefore, it would appear that under conditions of continuous exposure to the experimental apparatus, conditioning (as reflected by the magnitude of activity during the post-amphetamine, saline test) does not significantly contribute to the behavioral effects of successive amphetamine injections. In the experiment described by Tilson and Rech there was a marked contrast between the home and experimental environments and the rats were exposed to the test chambers exclusively during the peak drug effect. These conditions appear to be more optimal for the classical conditioning of pharmacological responses.

Also difficult to explain on the basis of a conditioning model is the replacement of an ambulatory response by stereotypy after repeated amphetamine administration. For example, 2.5 mg/kg amphetamine produced enhanced locomotion during the 3–4 hr interval following the first injection, yet with continued injections this phase of hyperactivity was gradually replaced by continuous stereotypy. Since the resulting response pattern closely resembles the behavioral effects of higher acute amphetamine doses, it would appear that, at least with respect to stereotypy and locomotor activity, the effect of a given dose of amphetamine is increased with repeated treatment under the conditions described for this experiment. An enhanced potency might be expected as a consequence of alterations in the disposition of amphetamine and/or to an acquired functional change in the responsiveness of those brain systems which mediate the amphetamine-induced behavioral effects.

Although several investigators have compared the disposition of amphetamine in brains of animals receiving single or repeated injections of this drug [9, 19, 23], the evidence of an altered disposition is at present inconclusive. In fact, such changes as have been reported are more consistent with the development of tolerance than with an augmentation in responsiveness [22]. Therefore, it appears that a functional change, perhaps involving adjustive alteration in catecholamine biosynthetic capacity, may be responsible for the progressive behavioral changes observed with repeated amphetamine administration.

The response of central dopamine and norepinephrine neurons to amphetamine is different in several respects. For example, a number of investigators [15, 17, Kuczenski, Segal and Mandell, manuscript in preparation] have recently found that amphetamine produces a rapid decrease in conversion of ^{14}C-tyrosine to ^{14}C-dopamine in dopaminergic regions (neostriatum), but not in norepinephrine enriched areas such as cortex or hypothalamus. Since amphetamine allegedly facilitates synaptic transmission by promoting the release of catecholamines [5,6], the decreased biosynthetic capacity in dopamine neurons may reflect one homeostatic mechanism by which the level of transmission is maintained within some relatively restricted range. However, although amphetamine disappears rapidly from the brain (corresponding closely to the interval of behavioral hyperactivity), dopamine biosynthesis is significantly reduced for up to 18 hr (Kuczenski, Segal and Mandell, manuscript in preparation). The persistence of a compensatory decrease in biosynthetic capacity after the disappearance of amphetamine might in part be responsible for the reduced locomotion observed during the dark phase after amphetamine injection (Table 1). Furthermore, it is conceivable that a compensatory increase in biosynthesis might result in response to the prolonged post-amphetamine depression of dopaminergic activity. Thus, amphetamine which has been reported to preferentially release newly synthesized catecholamines [3] might elicit an augmented effect if catecholamine biosynthesis were elevated at the time of consecutive injection.

In central norepinephrine neurons a similar outcome may result through a different sequence of steps. In these neurons the amphetamine metabolite, p-hydroxynorephedrine, is reported to accumulate and persist (declining only slightly over 24 hr) after the disappearance of the parent compound [7,12]. This metabolite is reputed to be a false neurotransmitter substance which displaces endogenous norepinephrine and as a consequence may eventually reduce central noradrenergic tone [4]. Such a reduction in functional noradrenergic activity may contribute to both the dark phase decrease in locomotion (Table 1) and to an eventual compensatory increase in norepinephrine biosynthesis and/or receptor sensitivity. Subsequent injection of amphetamine at a time when biosynthetic capacity or receptor sensitivity had been enhanced would be expected to lead to a potentiated amphetamine-induced behavioral activation. Whether secondary compensatory increases in either dopamine and/or norepinephrine transmission occur in response to amphetamine and are responsible for the observed progressive augmentation in behavior remains for further experimentation to determine.

Recent studies indicate that chronic amphetamine administration in man can induce a behavioral pattern closely resembling paranoid schizophrenia [1, 2, 13]. These reports have provided an impetus for the development of an animal behavior model which reflects those drug actions underlying the psychotic effects in man. Such a model might facilitate the identification of neurochemical alterations involved in the pathophysiology of some forms of psychotic behavior.

Amphetamine-induced psychosis usually develops gradually with chronic high dosage [1] and therefore an appropriate animal behavior model would be expected to follow a similar pattern. Thus, the progressive augmentation in locomotion and stereotypy produced by repeated amphetamine administration in rats may represent a manifestation of the same underlying mechanisms responsible for amphetamine induction of psychosis in man.

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