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Apparent Tolerance to Some Aspects of Amphetamine Stereotypy with Long-Term Treatment

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REBEC, G. V. AND D. S. SEGAL. *Apparent tolerance to some aspects of amphetamine stereotypy with long-term treatment.* PHARMAC. BIOCHEM. BEHAV. 13(6) 793–797, 1980.—Previous reports have demonstrated that long-term amphetamine treatment results in a progressive augmentation of locomotion and focused stereotypy in the rat. A series of experiments were conducted to determine whether an increase in dopamine receptor sensitivity is the primary mechanism underlying the behavioral alterations associated with multiple amphetamine injections. Detailed observations of the focused stereotyped behaviors produced by amphetamine revealed that although some components were enhanced with long-term treatment, others were reduced. Thus, whereas repeated administration of 2.5 mg/kg d-amphetamine produced a progressive increase in repetitive head and limb movements, long-term treatment with 5.5 mg/kg d-amphetamine resulted in a reduction of licking and biting behaviors (oral stereotypies). These results, which suggest that different mechanisms mediate the various components of focused stereotypy, argue against the supersensitivity hypothesis. In fact, the apparent tolerance that develops to oral stereotypies may reflect a decrease in dopamine receptor sensitivity since repeated amphetamine administration also reduces the oral stereotypies produced by 0.5 or 2.0 mg/kg apomorphine, a direct acting dopamine agonist. Thus, the behavioral alterations produced by repeated amphetamine injections cannot be explained solely by an increase in receptor sensitivity.

d-Amphetamine Apomorphine Stereotypy Tolerance

LONG-TERM administration of d-amphetamine produces a progressive augmentation of locomotion and focused stereotypy in the rat [31, 35, 36]. This behavioral augmentation, which typically consists of several distinct phases, follows a dose-dependent pattern. Thus, repeated daily administration of a relatively low dose (0.5 mg/kg) increases both the magnitude and duration of the locomotor activity characteristic of an acute injection, whereas with a moderate dose (1.0 mg/kg) the locomotion is gradually replaced by progressively longer episodes of focused stereotypy. Furthermore, long-term treatment with higher doses (2.5–7.5 mg/kg) results in a progressively earlier onset of the stereotypy phase which is followed, in turn, by an enhanced period of locomotor activity.

A number of different mechanisms may account for the enhanced responsiveness, including an increase in catecholamine receptor sensitivity. Since post-junctional supersensitivity has been reported to occur in the central nervous system following a prolonged disruption of catecholaminergic neurotransmission (e.g. [3, 25, 38]), it is conceivable that a similar change occurs as a consequence of long-term amphetamine administration. Such treatment, for example, has been reported to deplete central catecholamine levels and to cause chromatolysis of catecholaminergic neurons [13, 23, 37]. The notion of a chronic amphetamine-induced supersensitivity has been supported by evidence that guinea pigs, pretreated with d-amphetamine for several weeks, exhibited stereotypy when challenged with a subthreshold dose of apomorphine, a dopamine (DA) receptor agonist [21]. Similar results were obtained in mice and, in this case, the enhanced response to apomorphine persisted for as long as 8 days after the last amphetamine injection [2]. In fact, chronic apomorphine treatment also increased the response to an apomorphine challenge 8 days later. These results suggest that long-term treatment with either d-amphetamine or apomorphine increases the sensitivity of central DA receptors.

Other studies bearing on this hypothesis, however, have

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produced conflicting findings. Kilbey and Ellinwood [20], for example, provided only partial support for an amphetamine-induced increase in DA receptor sensitivity when they reported that apomorphine elicited stereotypy sooner in amphetamine pretreated rats than in control animals but that there was no significant difference in the intensity of the apomorphine response. In contrast, other investigators found no significant change in either the onset latency or the intensity of the apomorphine response in rats pretreated for up to several weeks with d-amphetamine [16, 33, 42].

In an effort to clarify the possible involvement of DA receptor sensitivity in the behavioral alterations associated with long-term amphetamine treatment, we performed a detailed, dose analysis of the changes in stereotypy produced by amphetamine or apomorphine in rats following long-term amphetamine administration. The results of the present study are inconsistent with the hypothesis that receptor supersensitivity is the sole mechanism responsible for the altered amphetamine response.

GENERAL METHOD

Animals and Drugs

Following at least one week of housing under standard laboratory conditions, male Wistar rats (Hilltop Laboratories), weighing from 300–350 g, were individually placed in sound-attenuating behavioral chambers at least 24 hours prior to the first injection. The animals remained in the behavioral chambers for the duration of the experiment and received single daily injections of isotonic saline or different doses of either d-amphetamine sulfate (Smith, Kline and French) or apomorphine hydrochloride (Merck). All drugs were administered subcutaneously (SC) in a volume of 1 ml/kg (free base).

Apparatus and Procedure

The behavioral chambers and data recording system have been described in detail elsewhere [36]. Briefly, food and water were available on a continuous basis and lighting was maintained according to a 12-hour bright-light (6 a.m.–6 p.m.) and 12-hour dim-light cycle. The rats were injected at about 10 a.m. each day during which time the chambers were cleaned and serviced. This entire process required about 2 minutes per chamber and represented the only time during the day that the animals were disturbed. Movements from one quadrant to another (crossovers) were automatically counted by means of contacts in the floor of each chamber. Rearings were recorded by touchplates set approximately 13 cm above the floor. Both measures of locomotion were monitored continuously by a NOVA 1200 computer. Focused stereotypy was monitored by independent observers through a viewing lens mounted in the door of each chamber. The observers were unaware of the treatment conditions for individual animals. Each rat was observed for 1-minute periods beginning at 5 minutes after the injection and at successive 10-minute intervals thereafter for the duration of the drug response. Individual components of stereotypy, including sniffing, repetitive movements of the head and limbs, and oral behaviors (licking and biting), were rated according to their duration (i.e., 1 = discontinuous, 2 = continuous) and intensity (1 = mild, 2 = moderate, 3 = intense) during each 1-minute observation period. For analysis of results, the duration and intensity scores for each interval were multiplied to yield a single value. Thus, a score of 6 (continuous × intense) is the maximum possible score for a given behavior at each interval. A total stereotypy score was obtained for each animal by summing individual interval values across the entire drug response. For example, 54 is the total maximum score for a given behavior summed over a 90-minute period (9 intervals). The locomotion and stereotypy data were analyzed by *t*-tests.

EXPERIMENT 1

If long-term amphetamine treatment primarily increases DA receptor sensitivity, then the behavior that emerges with repeated injections should reflect a shift to the left in the dose-response curve. This prediction, however, is only partially supported by the available evidence. Thus, although repeated amphetamine administration results in an increasingly rapid onset of stereotypy, the duration of this response is not correspondingly increased as occurs with increasing doses administered acutely [31,35]. In fact, the duration of the stereotypy phase appears to be reduced with long-term treatment, suggesting that the behavioral changes produced by repeated amphetamine injections are inconsistent with the supersensitivity hypothesis.

In order to accurately characterize the behavioral alterations that occur with multiple amphetamine injections, more detailed studies are required. In the present experiment, we examined how individual components of stereotypy change with repeated administration. Whereas the supersensitivity hypothesis predicts a shift toward intense forms of stereotypy, we found that the licking and biting responses (oral stereotypies) produced by d-amphetamine actually diminish with long-term treatment.

Procedure

Different groups of rats, consisting of at least 10 animals per group, received single daily injections of saline, 2.5 or 5.5 mg/kg d-amphetamine for 4 consecutive days. On Day 5, all animals received either 2.5 or 5.5 mg/kg d-amphetamine, and drug-induced changes in locomotion and stereotypy were recorded as described above.

Results and Discussion

Repeated daily administration of 2.5 or 5.5 mg/kg d-amphetamine produced the characteristic pattern of behavioral augmentation. In accord with our previous findings [36], an acute injection produced a dose-dependent multiphasic response pattern, consisting of early and late phases of locomotor activity and an intermediate phase of focused stereotypy, during which ambulation and rearing were absent. With multiple injections, the behavioral augmentation, which is characterized primarily by a progressively more rapid onset of focused stereotypy, was manifested as a significant reduction in the number of crossovers during the first 30 minutes of the response to 2.5 mg/kg (2.2 ± 0.7 for Day 5 vs 14.0 ± 2.8 for Day 1, $p<0.01$) and to 5.5 mg/kg (1.4 ± 0.05 for Day 5 vs 6.6 ± 1.5 for Day 1, $p<0.01$) d-amphetamine. Direct observations of the animals confirmed the earlier onset of stereotypy for both doses; however, whereas repetitive head and limb movements were significantly increased with multiple injections of 2.5 mg/kg d-amphetamine, the oral stereotypies, which were present following a single injection of 5.5 mg/kg d-amphetamine, were markedly reduced with repeated administration of this dose (Table 1).

The reduction in oral stereotypy with multiple injections

TABLE 1

ALTERATIONS IN STEREOTYPY WITH REPEATED ADMINISTRATION OF D-AMPHETAMINE

Dose (mg/kg)	Components of Stereotypy*					
	Sniffing		Repetitive Movements		Oral Stereotypy	
	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
2.5	62.5 ± 2.3	58.3 ± 2.0	6.6 ± 2.8	33.1 ± 2.5†	0.3 ± 0.2	0.8 ± 0.4
5.5	18.1 ± 3.3	27.5 ± 7.5	37.5 ± 9.0	38.1 ± 6.1	27.3 ± 5.2	8.6 ± 2.6†

*Total stereotypy ratings for 4 hours (24 intervals); values are mean ± S.E.M.
†Significant differences from Day 1 are indicated: $p<0.01$.

TABLE 2

ALTERATIONS IN APOMORPHINE-INDUCED ORAL STEREOTYPY FOLLOWING REPEATED AMPHETAMINE

Pretreatment	N	Treatment	Oral Stereotypy*	
			Licking	Biting
Saline (4 days)	11	Apomorphine, 0.5 mg/kg	20.7 ± 1.2	3.3 ± 2.1
d-Amph., 5.0 mg/kg (4 days)	12	Apomorphine, 0.5 mg/kg	4.8 ± 1.5†	1.2 ± 0.6
Saline (4 days)	10	Apomorphine, 2.0 mg/kg	7.5 ± 0.7	20.5 ± 1.5
d-Amph., 5.0 mg/kg (4 days)	10	Apomorphine, 2.0 mg/kg	8.1 ± 1.3	1.0 ± 0.3†

*Total oral stereotypy score for 90 minutes (9 intervals); values are mean ± S.E.M.
†Significant differences from corresponding saline controls are indicated: $p<0.01$.

of 5.5 mg/kg d-amphetamine argues against the suggestion that DA receptor supersensitivity is the sole mechanism underlying the behavioral alterations following long-term amphetamine treatment. In fact, the apparent tolerance that develops to amphetamine-induced oral stereotypy is consistent with a decrease in receptor sensitivity.

EXPERIMENT 2

Considerable evidence suggests that the licking and biting behaviors produced by high doses of amphetamine are mediated, in large part, by a facilitation of DA transmission in the neostriatum [6,15]. Apomorphine, on the other hand, has been reported to elicit these behaviors by directly stimulating neostriatal DA receptors [7,18]. Thus, if the reduction of oral stereotypy with chronic amphetamine administration is due to a decrease in receptor sensitivity, then the licking and biting behaviors produced by apomorphine should also be reduced in amphetamine pretreated animals. To test this hypothesis, we monitored the behavioral response to apomorphine following repeated injections of an amphetamine dose that when administered acutely produces episodes of oral stereotypy.

Procedure

Rats were pretreated with saline or 5.0 mg/kg d-amphetamine for 4 consecutive days and then challenged 24 hours later with 0.5 or 2.0 mg/kg apomorphine. Observers, unaware of the pretreatment conditions, monitored the apomorphine response according to the procedures described above. At least 10 animals comprised each treatment group.

Results and Discussion

In saline pretreated rats, 0.5 mg/kg apomorphine produced oral stereotypy that was characterized primarily by vigorous licking, whereas that produced by the high dose of the drug was manifested as intense biting. As shown in Table 2, repeated administration of 5.0 mg/kg d-amphetamine reduced both these components of oral stereotypy. Thus, amphetamine treatment significantly attenuated the licking produced by 0.5 mg/kg apomorphine and the biting response to 2.0 mg/kg apomorphine. The peak stereotypy scores for other components of the apomorphine response, including sniffing, repetitive head and limb movements and forward locomotion, were not significantly altered by prior exposure to amphetamine.

These results indicate that the apparent tolerance to amphetamine-induced oral stereotypy cannot be explained by metabolic or dispositional factors unique to amphetamine since the licking and biting response to apomorphine is also reduced in amphetamine pretreated animals. Rather, our results suggest, at least to the extent that apomorphine can be

used as a test for DA receptor sensitivity, that the decrease in oral behaviors with chronic amphetamine administration is mediated, in part, by a hyposensitivity of DA receptors. Such a mechanism, however, cannot explain the full range of behavioral alterations associated with long-term amphetamine treatment since, apart from oral stereotypy, the behavioral response to apomorphine did not appear to be altered by repeated amphetamine injections.

GENERAL DISCUSSION

An accumulating body of evidence suggests that the focused stereotyped behavior produced by amphetamine and related stimulants does not represent a single phenomenon but rather consists of at least two distinct components. At relatively low doses, for example, amphetamine stereotypy is manifested primarily as sniffing and repetitive head and limb movements, but as the dose is increased episodes of licking and biting predominate. This shift in behavior does not appear to be due to a dose-dependent activation of a single neuronal system since a number of drugs have been reported to elicit only one or the other of these behaviors. For example, whereas phenethylamine and amantadine produce sniffing and head bobbing but little or no oral stereotypy even at relatively high doses [4, 24, 27], some aporphine derivatives elicit licking and biting behaviors almost exclusively [10,19]. That different brain mechanisms are involved in the expression of various components of stereotypy has been supported by a series of lesion studies. Thus, selective destruction of DA nerve terminals in the neostriatum has been reported to abolish amphetamine-induced oral behaviors [15], but not repetitive sniffing or head bobbing [1,8]. Similar damage in the nucleus accumbens, on the other hand, appears to eliminate bouts of sniffing and repetitive head and limb movements [9]. A regional differentiation in the behavioral response to amphetamine is also consistent with evidence that the nucleus accumbens, but not the neostriatum, is involved in the augmentation of amphetamine-induced sniffing following chronic exposure to a stressful stimulus [12]. Thus, the stereotyped behaviors produced by amphetamine appear to be mediated by different neuronal systems. Our results, which suggest that tolerance develops to licking and biting but not other aspects of amphetamine stereotypy, support this view.

If DA receptors in the neostriatum mediate amphetamine-induced oral stereotypies, then the apparent tolerance to these behaviors may reflect a decreased sensitivity of neostriatal DA receptors. Although our results with apomorphine are consistent with this hypothesis, DA receptor binding assays, which have been used as an index of receptor sensitivity, do not reveal a corresponding decrease in DA binding with long-term amphetamine treatment. In fact, only relatively high doses of amphetamine administered for several weeks have been reported to decrease DA binding, whereas treatments approximating our chronic schedule produce no measurable change in receptor sensitivity [5,17]. It is interesting to note, however, that long-term treatment with 2.5 mg/kg d-amphetamine, which results in a progressive augmentation of sniffing and head bobbing, increases the responsiveness of neostriatal neurons to a challenge injection of apomorphine [29]. Thus, it is possible that the dose-dependent changes in behavior associated with multiple amphetamine injections reflect, in part, a differential sensitivity of neostriatal DA receptors.

Alternatively, the various components of the stereotypy produced by amphetamine may be mediated by the same dopaminergic mechanism, but tolerance may develop to licking and biting behaviors because the relatively high doses required to elicit these behaviors deplete another neurotransmitter that normally modulates some aspects of the behavioral response to amphetamine. This hypothesis is strengthened by evidence that serotonin, which appears to regulate DA transmission in the forebrain [11, 14, 26], is reduced following chronic treatment with high amphetamine doses [40]. Furthermore, the stereotyped behaviors produced by both amphetamine and apomorphine are attenuated in rats following a reduction of brain serotonin levels [22, 34, 39].

We have previously reported that although neurons in the neostriatum are inhibited by low doses of d-amphetamine (0.5–2.5 mg/kg) that do not elicit intense stereotypy, increasing the dose (5.0–7.5 mg/kg) shifts the firing pattern to a prolonged increase in unit activity [30,32]. This shift in firing rate, which may be an important correlate of the behavioral transition to intense stereotypy, appears to be mediated, at least in part, by serotonin. Stimulation of the dorsal raphe nucleus, for example, which provides serotonergic input to the neostriatum, accelerates the activity of neostriatal neurons [41], whereas a depletion of brain serotonin levels attenuates the amphetamine-induced increase in neostriatal unit activity [28]. Thus, the behavioral alterations that emerge with long-term amphetamine treatment may reflect a changing dopaminergic-serotonergic balance in the neostriatum.

In summary, our results show that certain aspects of amphetamine-induced stereotypy are enhanced with repeated administration. As the dose is increased, however, the licking and biting behaviors produced by this drug are attenuated, suggesting that tolerance develops to some components of the behavioral response to amphetamine. A similar reduction in oral stereotypies was observed in response to apomorphine following repeated amphetamine treatment. Thus, the changes in stimulant-induced stereotyped behaviors that accompany long-term administration cannot be simply explained by a shift in receptor sensitivity.

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