Pharmacology Biochemistry & Behavior, Vol. 30, pp. 899–904. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Opioid Influence on Some Aspects of Stereotyped Behavior Induced by Repeated Amphetamine Treatment

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Received 17 March 1987

CANCELA, L. M., J. ARTINIÁN AND S. FULGINITI. *Opioid influence on some aspects of stereotyped behavior induced by repeated amphetamine treatment.* PHARMACOL BIOCHEM BEHAV **30**(4) 899–904, 1988.—Rats were administered repeated IP injections of dl-amphetamine (AMPH) according to a chronic escalating dose schedule (three doses per 24 hr, for four days, two days or one day). Animals treated for four days exhibited a diminished oral stereotypy in response to a challenge of 12 mg/kg AMPH or 2 mg/kg SC apomorphine (APO), 72 hr after withdrawal. Pretreatment with 2 mg/kg IP naloxone (NAL) during the period of chronic AMPH administration prevented the reduction in oral stereotypy induced by AMPH or APO. No differences were detected among the mean of stereotypy scores from the different treatments in response to a challenge dose of 6 mg/kg AMPH. Neurochemical data showed that NAL pretreatment reversed the depletion of striatal dopamine content induced by chronic AMPH. When repeated injections of AMPH were given only one day, the diminished stereotypy response to AMPH or APO was not observed. Animals treated simultaneously with 1 mg/kg IP morphine or 5 μg/kg IP β-endorphin and repeated AMPH injections for one day, showed a reduced stereotyped response to AMPH or APO. These results suggest that opioid peptides are involved in the mechanisms underlying the decrease in oral behaviors following AMPH treatment.

Chronic amphetamine Naloxone Opioids Stereotypy Dopamine

REPEATED administration of amphetamine (AMPH) results in the development of both sensitization and tolerance to its behavioral effects depending on the behavior being monitored. Thus, tolerance develops to some effects of the drug, such as anorexia [28,29], facilitation of self-stimulation behavior [23,24], and reinforcing effects of the drug [27] while sensitization to locomotion occurs with long-term administration of AMPH [22, 39, 42]. As regards AMPH-induced stereotypy, some authors found that chronic treatment with the drug develops an enhancement when stereotypy was analyzed as a unitary phenomenon [33,42] while others, considering its different components, described an opposite effect of oral stereotypies [40].

It is known that AMPH causes striatal dopamine (DA) release [31] and that the nigrostriatal DA system is regarded as primarily, if not exclusively, in the mediation of AMPH-induced stereotypy [7, 21, 37]. On the other hand, there is strong evidence suggesting an interaction between opiates and dopaminergic neuronal systems. Anatomical [17,45], biochemical [9,44], electrophysiological [10] and behavioral [12, 18, 30] studies support this interaction. Furthermore, opioid receptors are present on dopaminergic neurons [35,36] and it has been shown that the opiate receptor activation can modify central DA release [2, 3, 25, 26].

In this paper we have tried to determine whether endogenous opioids are involved in the AMPH-induced changes in stereotyped behavior after chronic AMPH. We administered the opiate antagonist naloxone (NAL) or the opiate agonists β-endorphin (BE) or morphine (MORPH) combined with repeated daily injections of AMPH, and the effects of challenges with AMPH or apomorphine (APO), a DA receptor agonist, on stereotypy were tested 72 hr later. In an attempt to correlate behavioral and neurochemical changes, we determined the influence of NAL pretreatment on the effects of chronic AMPH on endogenous levels of DA and it deaminated metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in striatum and accumbens nucleus.

METHOD

Subjects

Male Wistar rats (300–350 g) were obtained from our own breeding stock and housed four per cage with ad lib access to food and water. They were maintained at 22±2°C in a 12-hr light-dark cycle (light beginning at 7:00 a.m.).

Drugs and Treatments

dl-Amphetamine sulphate (Purest), naloxone hydrochloride (kindly supplied by laboratories Ducilo S.A., Buenos Aires), β-endorphin (Sigma Chemical Co.), morphine hydrochloride (Verardo) and apomorphine hydrochloride (Sigma Chemical Co.) were dissolved in saline (SAL). The volume of injections was 0.1 ml/100 g body weight for all drugs. Injections were IP except APO that was injected SC.

Repeated treatment with AMPH consisted of the adminis-

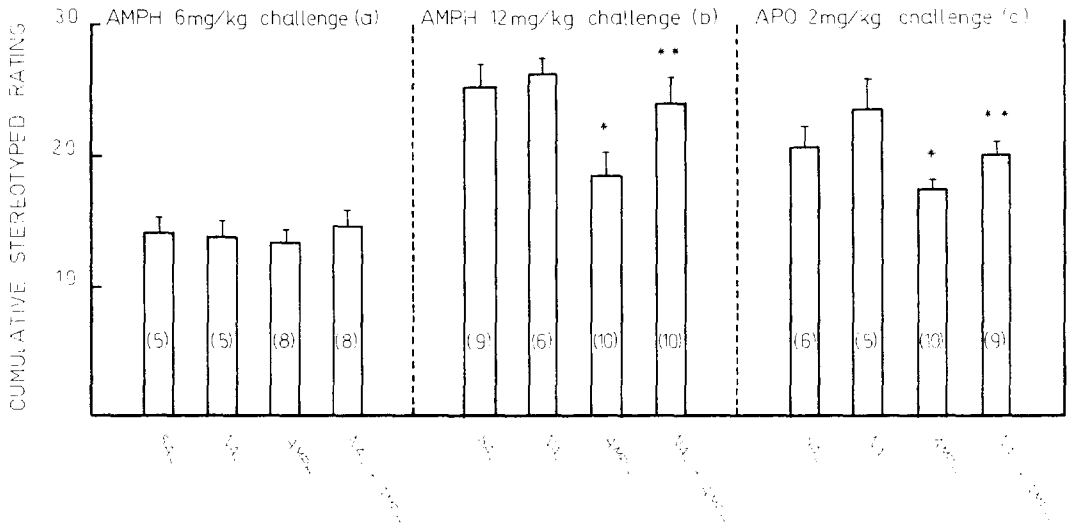

FIG. 1. Effects of NAL pretreatment on chronic AMPH-induced change in stereotyped response to challenges with AMPH or APO. Rats were treated with SAL or NAL (2 mg/kg) and 15 min later with SAL or increasing doses of AMPH for four days (AMPH 1–12). Seventy-two hours after the last injection, animals were administered AMPH (6 mg/kg or 12 mg/kg) or APO (2 mg/kg). The cumulative stereotyped rating for each animal was determined, 30 or 5 min after administration of AMPH or APO respectively, as the sum of each 5 min score for 30 min. Each bar represents the mean±SEM. Number of animals are noted in parentheses. Kruskal-Wallis one-way ANOVA: (b) and (c) $p<0.01$. *Significantly different from respective SAL group: $p<0.002$ (Mann-Whitney U-test). **Significantly different from respective AMPH group: $p<0.02$.

tration of escalating doses of the drug according to the chronic injection schedule used by Leith and Barret [23]. This treatment was employed because increasing multiple daily doses of the drug are taken by amphetamine users and it has been reported that this schedule develops tolerance to the facilitation of self-stimulation behavior provoked by this drug [23,24]. Animals were injected three times per 24 hr (8:00 a.m., 2:00 p.m. and 8:00 p.m.) for four days, beginning with a dose of 1 mg/kg and increasing by 1 mg/kg on each subsequent dose until a final injection of 12 mg/kg (AMPH 1–12). Animals were also injected with the same escalating doses for two days (AMPH 1–6) or for one day (AMPH 1–3). Control groups received SAL following the same schedule as AMPH groups. Doses and administration times of NAL, BE and MORPH used in each of the combined treatments studied are described in Fig. 1 and Fig. 2.

Behavioral Study

On the day of testing, animals were given a challenge dose of AMPH (12 mg/kg) or APO (2 mg/kg); rats from the groups treated with AMPH and/or NAL were also injected with a challenge dose of AMPH (6 mg/kg). These doses were used because in a preliminary study we observed, in agreement with other authors, that high doses of AMPH (12 mg/kg) or APO (2 mg/kg) induced predominantly licking, biting and gnawing (i.e., oral stereotypies) and lower doses of AMPH (6 mg/kg) led to continuous sniffing and small head movements, primarily. Thirty min after AMPH injection or 5 min after APO administration each rat was placed individually in a wire mesh cage (30×45×22 cm). Stereotyped behavior was assessed every 5 min for 30 min as described elsewhere [32] with minor modification. The original scoring scale consisted of: 0, animals same as saline-treated animals; 1, discontinuous sniffing, constant exploratory activity; 2, continuous sniffing and small head movements, periodic exploratory activity; 3, continuous sniffing and small head movements, discontinuous biting, gnawing and licking, brief periods of locomotor activity; and 4, continuous gnawing, biting and licking, no exploratory activity. According to stereotypy intensity, each score (0–4) was adjusted with an increase of 0.3=mild, 0.6 moderate or 0.9=intense. The cumulative stereotyped rating was expressed as the sum of the 5 min scores for a total of 30 min; thus, there was a maximum score of 29.4 per rat (6×4.9=29.4).

Neurochemical Study

Endogenous levels of DA and DOPAC were determined in striatum and accumbens nucleus, 30 min after the 12th AMPH injection or 72 hr after withdrawal. Rats were killed by decapitation between 2:30–3:00 p.m. to avoid any possible variations in the DA and DOPAC concentrations due to circadian rhythms; brains were quickly removed and striatum and accumbens nucleus were dissected according to Heffner *et al.* [11]. They were homogenized in 0.2 N perchloric acid. After centrifugation, the supernatant was passed through a 0.2 μm pore size cellulose filter and 20 μl sample analyzed by HPLC with electrochemical detection [46].

Statistical Analysis

Stereotyped behavior was analyzed by the nonparametric Kruskal-Wallis one-way analysis of variance followed by individual comparisons using the Mann-Whitney U-test. Statistical analysis of neurochemical data was made by using one-way ANOVA followed by Duncan's multiple range test.

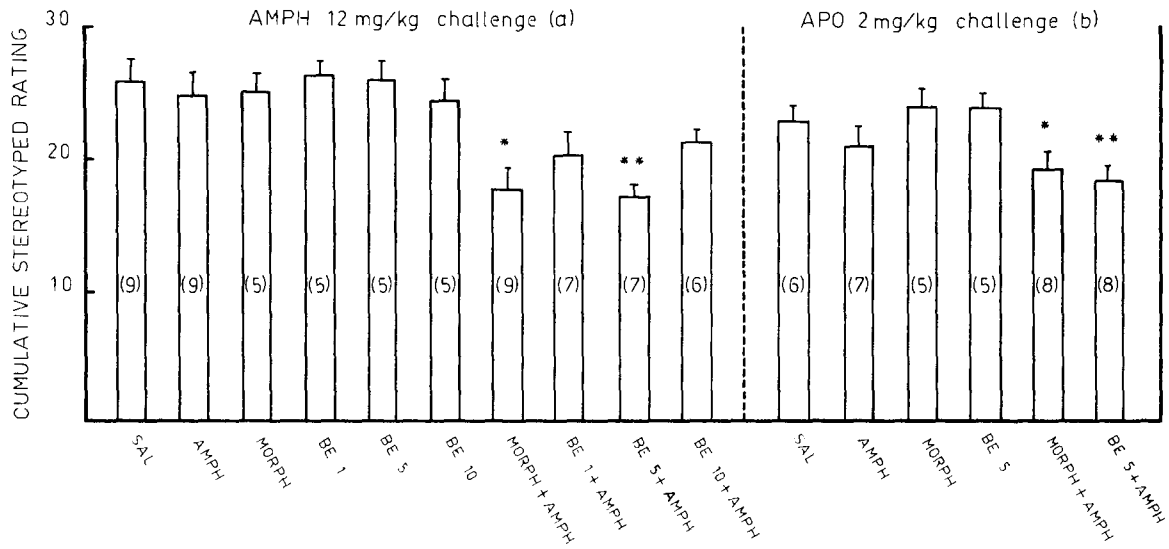

FIG. 2. Effects of the combined treatment with MORPH or BE and three increasing doses of AMPH (AMPH 1–3) on AMPH- or APO-induced stereotyped behavior. Rats were treated with SAL, MORPH (1 mg/kg) or BE (1, 5 or 10 μg/kg) simultaneously with SAL or three increasing doses of AMPH (AMPH 1–3) for one day. Seventy-two hours after the last injection, animals were administered AMPH (12 mg/kg) or APO (2 mg/kg). The cumulative stereotyped rating for each animal was determined as described in legend of Fig. 1. Kruskal-Wallis one-way ANOVA: (a) $p<0.01$ and (b) $p<0.05$. *Significantly different from SAL, MORPH and AMPH: (a) y (b) $p<0.05$. **Significantly different from SAL, BE_5 and AMPH: $p<0.02$.

RESULTS

Effects of NAL Pretreatment on Chronic AMPH-Induced Changes in Stereotyped Behavioral Response to Challenges With AMPH or APO

Repeated AMPH administration markedly reduced the stereotypy scores compared to those of SAL-, NAL- or NAL + AMPH-treated animals, in response to a challenge with 12 mg/kg AMPH or 2 mg/kg APO. No differences were detected among the mean of stereotypy scores from the different treatments in response to a challenge dose of 6 mg/kg AMPH (Fig. 1). Also, the stereotyped behavioral response to a challenge dose with 3 mg/kg AMPH was not modified; however, it was observed that a sensitization to locomotor stimulant effect of this challenge dose developed in AMPH- and NAL + AMPH-treated rats to an equal degree (data not shown).

At the end of chronic treatments body weight of rats receiving either only AMPH or NAL plus AMPH was 10% lower than controls.

Effects of Repeated Treatment With AMPH for One Day (1–3), Two Days (1–6) or Four Days (1–12) on AMPH- (12 mg/kg) or APO- (2 mg/kg) Induced Stereotyped Behavior

In order to determine the number of AMPH injections necessary for the onset of the reduced stereotyped behavioral response to AMPH and APO after repeated AMPH administration, we injected rats with AMPH for one day (AMPH 1–3), two days (AMPH 1–6) or four days (AMPH 1–12) and 72 hr after the last injection of each one of (AMPH 1–12) and 72 hr after the last injection of each one of the treatments, animals were tested with a challenge of AMPH or APO. Results are summarized in Table 1. They show that repeated AMPH treatment with increasing doses for four days as well as for two days, significantly attenuated the stereotypy induced by 12 mg/kg AMPH or 2 mg/kg APO. When AMPH treatment was only for one day, the stereotyped behavioral response to 12 mg/kg AMPH or 2 mg/kg APO was not modified.

TABLE 1

EFFECTS OF REPEATED TREATMENT WITH AMPH FOR ONE DAY (1-3), TWO DAYS (1-6) OR FOUR DAYS (1-12) ON STEREOTYPED BEHAVIORAL RESPONSE TO CHALLENGES WITH 12 mg/kg AMPH OR 2 mg/kg APO

	Cumulative Stereotyped Rating	
Treatment	AMPH 12 mg/kg*	APO 2 mg/kg†
SAL	25.2 ± 1.1 (9)	23.2 ± 1.9 (6)
AMPH 1–3	24.3 ± 1.8 (9)	22.9 ± 1.8 (7)
AMPH 1–6	19.7 ± 0.9[1] (9)	19.8 ± 0.9[3] (8)
AMPH 1–12	18.8 ± 0.8[2] (16)	17.1 ± 0.2[4] (7)

Seventy-two hours after the last treatment injection, animals were administered AMPH (12 mg/kg) or APO (2 mg/kg). The cumulative stereotyped rating for each animal was determined as noted in legend of Fig. 1. Data are the mean ± SEM. Kruskal-Wallis one-way ANOVA: *$p<0.01$ and †$p<0.001$.

Significantly different from SAL: [1]$p<0.02$, [2]$p<0.002$, [3]$p<0.03$; Significantly different from SAL and AMPH 1-6: [4]$p<0.001$.

TABLE 2

EFFECTS OF NAL PRETREATMENT ON CHRONIC AMPH-INDUCED CHANGES IN DA AND DOPAC LEVELS IN STRIATUM AND ACCUMBENS NUCLEUS

	30 Min After 12th Injection		72-hr Withdrawal	
Treatment	DA[a]	DOPAC[b]	DA	DOPAC
		Striatum		
SAL	10.9 ± 0.5 (10)	1.3 ± 0.2 (8)	10.2 ± 0.7 (8)	1.3 ± 0.1 (8)
NAL	10.6 ± 0.3 (7)	1.6 ± 0.1 (8)	10.5 ± 0.4 (4)	1.4 ± 0.2 (4)
AMPH	9.1 ± 0.2* (10)	0.7 ± 0.1* (10)	9.8 ± 0.2 (9)	1.3 ± 0.1 (9)
NAL + AMPH	10.3 ± 0.2 (10)	0.8 ± 0.1* (11)	9.6 ± 0.3 (9)	1.1 ± 0.1 (9)
		Accumbens Nucleus		
SAL	6.6 ± 0.4 (10)	1.3 ± 0.2 (7)	6.1 ± 0.6 (4)	1.5 ± 0.1 (4)
NAL	6.4 ± 0.3 (7)	1.4 ± 0.1 (6)	6.0 ± 0.4 (4)	1.5 ± 0.1 (4)
AMPH	6.3 ± 0.5 (9)	1.0 ± 0.2 (9)	5.4 ± 0.4 (7)	1.7 ± 0.2 (7)
NAL + AMPH	7.2 ± 0.6 (10)	0.9 ± 0.1 (7)	5.6 ± 0.1 (4)	1.6 ± 0.3 (4)

Animals received SAL or NAL and SAL or AMPH as described in legend of Table 1. Thirty min after 12th injection or 72 hr after withdrawal, rats were sacrificed. Values (expressed in μg/g wet weight tissue) are the mean ± SEM. Number of animals are noted in parentheses. Analysis of variance: [a]$F(3,33)=6.01$, $p<0.005$; [b]$F(3,31)=7.77$, $p<0.005$.

Significantly different from SAL: *$p<0.01$ (Duncan multiple range test).

Effects of the Combined Treatment With MORPH or BE and Three Increasing Doses of AMPH (AMPH 1–3) on AMPH- (12 mg/kg) or APO- (2 mg/kg) Induced Stereotyped Behavior

When three injections of MORPH (1 mg/kg) or BE (1, 5, 10 μg/kg) and three escalating doses of AMPH (1–3) were simultaneously administered, a significant effect of treatment on induced stereotyped behavior was obtained as revealed by Kruskall-Wallis one-way ANOVA (Fig. 2). Post hoc comparisons (Mann-Whitney U-test) indicated that combined treatment with MORPH (1 mg/kg) or BE (5 μg/kg) and AMPH (1–3) induced significantly lower scores of stereotypy induced by AMPH or APO than those obtained in the remaining treated groups. Thus, the combined treatment with MORPH or BE (5 μg/kg) and AMPH (1–3) produced an opposite effect to that observed with NAL and AMPH (1–12) treatment on stereotyped response to AMPH or APO.

Effects of NAL Pretreatment on Chronic AMPH-Induced Changes in DA and DOPAC Levels in Striatum and Accumbens Nucleus

Table 2 shows that 30 min after the 12th injection of AMPH repeated administration, striatum DA levels were significantly decreased and that pretreatment with NAL fully reversed this effect. DOPAC levels were significantly reduced 30 min after the last dose of AMPH. The previous administration of NAL did not modify the decrease in DOPAC content evoked by chronic AMPH treatment. Seventy-two hours after the 12th AMPH injection, DA and DOPAC returned to control values. In accumbens nucleus all treatments failed to modify DA and DOPAC levels. It should be noted that 30 min after an acute dose of 12 mg/kg AMPH, striatal DA levels were not modified whereas DOPAC content was significantly decreased (data not shown).

DISCUSSION

In agreement with previous findings [40] our results show that in animals withdrawn from chronic AMPH, the stereotyped behavioral response to a challenge dose of 12 mg/kg or 2 mg/kg APO, which induce predominantly oral stereotypies, was markedly reduced, whereas the sniffing primarily induced by a challenge dose of 6 mg/kg AMPH was not modified. Since the APO challenge dose used acts as a direct agonist on postsynaptic DA receptors, it is possible that the decrease in oral behaviors following chronic AMPH administration is mediated, in part, by a hyposensitivity of DA receptors. In support of this possibility, we might point out the studies of Kamata and Rebec [19] providing iontophoretic evidence for subsensitivity of postsynaptic DA receptors in striatum of rats pretreated chronically with AMPH, and those describing reduced binding DA sites in striatum following chronic AMPH [14,34]. However, other studies attempting to find a neural correlate of the behavioral changes induced by chronic AMPH disagree with the possibility mentioned above, since either no change or an increase in DA receptor binding have also been described (see [41]). The fact that some components of stereotyped behavior, i.e., sniffing and oral stereotypy, are modified by chronic AMPH in different ways suggests that brain mechanisms mediating the facilitation of the two types of behaviors must be different. While there is evidence that AMPH-induced sniffing is mediated by mesolimbic DA release [5], oral stereotypy is believed to be the result of AMPH-induced DA release in the striatum or the direct stimulating effect of APO on striatal postsynaptic DA receptors [16,21].

When NAL was administered during chronic AMPH administration the decrease in oral behaviors was prevented. It is possible that these behavioral findings correlate with our neurochemical data showing that NAL pretreatment reversed the chronic AMPH-induced decrease in striatal DA levels observed 30 min after the 12th AMPH injection. Other authors that also analyzed the attenuation of AMPH-induced behavior caused by NAL found that NAL diminished the enhancing effect of d-AMPH on DA release in striatum and accumbens nucleus [11]. Because there is evidence that opioids facilitate dopaminergic transmission in striatum through stimulation of opioid receptors [3, 4, 26, 44], NAL may block this opioid modulation and thereby decrease the DA release induced by AMPH and as a consequence, prevent the possible development of postsynaptic DA receptor hyposensitivity. However, even if this NAL effect could by reliably shown by DA binding studies, we cannot rule out an influence of NAL on other monoaminergic systems that modulate dopaminergic transmission primarily involved in the behavioral stereotyped response to AMPH. A depletion of striatal DA by chronic AMPH has been reported by others and presumably reflects a persisting release of DA by AMPH [6,43]. Since 72 hr after withdrawal DA and DOPAC concentrations were no longer significantly different from the control values, we can rule out destruction of DA nerve termi-

nals following chronic AMPH schedule. Because NAL pretreatment did not modify the chronic AMPH-induced decrease in DOPAC content observed 30 min after the last AMPH injection, it is unlikely that NAL influences MAO inhibition exerted by AMPH [8].

On the other hand, the experiments carried out with animals treated with AMPH for one day show that this schedule did not modify the stereotypic response to a challenge with a high dose of AMPH or APO and, as expected, when it was concomitantly administered with MORPH or BE (5 μg/kg) the response was less intense. The systemic administration of BE has been reported to enter brain regions of the rat [13,38]. Although this substance is inactivated very rapidly in the brain, BE from plasma is relatively resistant to enzymatic breakdown and penetrates rather slowly into the CSF [13]. It is conceivable, therefore, that our findings, like those reported from several laboratories, can be attributed to effects on opioid systems in the brain (see [15,20]). It should be addressed that Woo *et al.* [47] found that when opioids are injected directly into the caudate-putamen, the behavioral effects of acute AMPH are enhanced and reduced by NAL. However, we can't discard the participation of peripheral mechanisms in our experiments. The lack of facilitatory influence of the highest dose of BE (10 μg/kg) in the decrease of oral stereotyped behaviors, may be due to modulatory influence of BE on other neurotransmitter systems that in some way may affect the nigrostriatal dopaminergic pathway.

Taken together, the present findings suggest that endogenous opioids are potential activators of the mechanism underlying the development of apparent tolerance to oral behavior after chronic AMPH treatment.

ACKNOWLEDGEMENTS

This work was supported by grants from Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) and from CONICOR (Córdoba). We are grateful to Gabriel Cuadra and Nancy Córdoba for their help in HPLC determinations.

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