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Dyskinesias in Monkeys: Interaction of Methamphetamine with Prior Methadone Treatment[1]

ROBERT D. EIBERGEN[2] AND KRISTIN R. CARLSON

Department of Pharmacology, University of Pittsburgh School of Medicine
Pittsburgh, PA 15261, USA

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EIBERGEN, R. D. AND K. R. CARLSON. *Dyskinesias in monkeys: interaction of methamphetamine with prior methadone treatment.* PHARMAC. BIOCHEM. BEHAV. 5(2) 175–187, 1976. – Rhesus monkeys with a history of drinking methadone, but presently drug-free, were injected with low doses of methamphetamine (MA). They immediately developed oral dyskinesias resembling the symptoms of tardive dyskinesia in humans, a condition resulting from chronic blockade of striatal dopamine receptors by neuroleptics. Nine of 11 control monkeys failed to develop dyskinesias during prolonged MA administration. A stressful stimulus intensified the MA-elicited oral dyskinesias, an effect analogous to exacerbation of tardive dyskinesias by emotional stress. Control monkeys were then injected with methadone, chlorpromazine, haloperidol, or saline for 45 days. Ten days following this chronic treatment, MA immediately elicited oral dyskinesias in the methadone and chlorpromazine monkeys. Acute administration of the dopaminergic blocking agents chlorpromazine, spiroperidol, and clozapine eliminated MA-elicited dyskinesias, whereas the α-adrenergic blocker phentolamine was ineffective. Physostigmine blocked the dyskinesias in 1 of 2 cases. Sedative doses of phenobarbital and diazepam had no effect on oral dyskinesias. These data indicate that chronic treatment with methadone or other dopamine receptor blocking agents leads to receptor supersensitivity to the actions of MA.

Methadone Neuroleptics Dopamine Receptor supersensitivity Methamphetamine Tardive dyskinesia
Oral dyskinesias Stress Dopaminergic blockers Monkey Narcotics Chlorpromazine Haloperidol

CHRONIC administration of increasing doses of methamphetamine to the rhesus monkey induces a developing pattern of stereotyped behaviors [21,22]. Low and moderate doses (2 10 mg/kg, IM) produce stereotyped searching, grooming and picking at the skin, and jerking of the body. After several months of intoxication, higher doses elicit another more intense form of stereotyped behavior, oral dyskinesias. These consist of involuntary repetitive movements of the face and mouth, such as tongue rolling and protrusion, wide opening of the mouth, and lateral jaw displacement. The movements are virtually identical to symptoms of tardive dyskinesia in humans, a condition arising in conjunction with long-term use of neuroleptic agents [12, 13, 14, 15, 17, 32, 33, 60, 68].

Tardive dyskinesia is thought to result from the chronic blockade of dopamine receptors in the striatum produced by neuroleptics [3, 35, 36]. During blockade the receptors become supersensitive, such that after the blockade is reduced or lifted endogenous dopamine produces exaggerated oral behaviors [35,36]. It is well-established that such supersensitivity develops in experimental animals during prolonged neuroleptic administration; after discontinuation of such agents as chlorpromazine or haloperidol, lower doses of dopaminergic agonists are able to elicit stereotyped behaviors [38, 55, 57, 67]. Further, ongoing stereotyped behaviors can be eliminated by acute administration of the neuroleptic blocking drug [11, 26, 46, 52, 57, 64].

These findings are consistent with clinical observations. The symptoms of tardive dyskinesia characteristically appear when neuroleptic therapy is halted or the drug dosage is reduced [7, 13, 14, 15], and symptoms can be alleviated by reinstitution of neuroleptic administration [24, 28, 40, 65]. The striatal dopaminergic system is further implicated by the fact that administration of dopamine agonists exacerbates present symptoms [23, 28, 40] and can precipitate them in symptom-free patients [28]. Anticholinergic drugs, which potentiate striatal dopamine activity [4], can also exacerbate and precipitate oral symptoms [12, 28, 37]. Drugs having the opposite effect in the cholinergic system ameliorate the symptoms [7, 24, 28].

Thus, it appears that supersensitivity of the striatal dopamine system results from its chronic blockade by

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[2] Present address: Dept. of Psychiatry, Box 3838, Duke University Medical Center, Durham, NC 27710.

neuroleptic agents. There is considerable evidence that methadone also blocks striatal dopamine receptors. Several studies have revealed biochemical changes in rat striatum indicative of dopaminergic receptor blockade [1, 2, 42, 47, 52, 56], and stereotyped behaviors elicited by dopamine agonists can be blocked by narcotics [25, 52, 56]. It is reasonable to hypothesize, therefore, that chronic administration of narcotics might lead to the development of dopaminergic supersensitivity. A few studies have shown heightened sensitivity to dopamine agonists in rodents during the acute withdrawal stage from morphine [20, 43, 51], as well as 30 days thereafter [29]. There is one report [41] of a failure to find potentiation of stereotyped behaviors after 7 days of chronic morphine pretreatment, possibly too brief a blockade. We have recently found that guinea pigs subjected to a 5-week treatment with methadone or chlorpromazine showed more intense oral stereotyped behaviors in response to methamphetamine administered up to 3 weeks following termination of chronic drug treatment [19].

The present experiments were undertaken to examine the effects of chronic methadone administration on the development of supersensitivity in the rhesus monkey. We first tested the efficacy of low doses of methamphetamine in eliciting oral dyskinesias in former methadone-consuming and control monkeys (a preliminary report appears in [18]). Our second experiment evolved from clinical reports that symptoms of tardive dyskinesia are exacerbated by emotionally stressful events [12, 13, 17, 33, 40]; thus, we evaluated the effects of stress on monkeys exhibiting oral dyskinesias. Third, control monkeys which had not responded to methamphetamine with oral dyskinesias previously received parenteral methadone, chlorpromazine or haloperidol for 45 days, in an attempt to convert them to the subsequent elicitation of oral dyskinesias by methamphetamine. Finally, we studied the effects of acute administration of dopaminergic antagonists and other agents on methamphetamine-elicited stereotyped behaviors.

METHOD

Animals

The animals were nineteen adolescent and adult male rhesus monkeys (*Macaca mulatta*). They were housed individually, had ad lib access to water from an automatic dispensing system, and were fed Purina monkey chow each morning.

The 8 monkeys in the M group had formerly drunk methadone hydrochloride (Dolophine; 10.0 mg/ml; Lilly), available for 1 hr daily in 100 ml Tang orange drink, for 10–22 months while some of them participated in other behavioral experiments [6]. The doses available (1.0–3.0 mg/kg) were well below those required to produce physical dependence in the monkey, and the animals had subsequently been drug-free for 2–17 months prior to methamphetamine treatment (see [18] for the drug histories of M1–M7). An additional monkey, M8, had consumed an average of 1.8 mg/kg methadone for 11 months and had been drug-free for the following 10 months.

The C group consisted of 11 monkeys which had no experience with narcotics or amphetamines.

Procedure

On all test days monkeys were transported to a cage in a separate room. This cage was identical to the home cages, 80 × 90 × 75 cm high, except that it had a squeeze back which was used to immobilize the monkeys for drug injections. On some test days monkeys were then returned to their home cages, where they were observed regularly for a minimum of 6 hr following injection. On other days, a monkey remained in the test cage for 4–6 hr where he was continuously observed, videotapes were made, and other manipulations appropriate to the various experiments were performed.

Experiment 1. All monkeys received IM injections of freshly prepared methamphetamine hydrochloride (Sigma) dissolved in sterile physiological saline (50 mg/ml as the salt). One injection per day was administered on a schedule of 4 consecutive injection days followed by 3 rest days. This weekly cycle, which mimicks human "spree" abuse [21,22], was repeated for up to 19 weeks. Methamphetamine (MA) doses began at 1.0 or 2.0 mg/kg and were gradually increased, usually to 5.0 mg/kg but in one case (M7) to 7.5 mg/kg.

The nature, frequency, and duration of each monkey's MA-elicited stereotyped behavior were recorded. The behaviors of major interest in this study, oral dyskinesias, were considered present if a monkey exhibited one or more of the following criterion behaviors for at least 4 hr post-injection: (a) tongue protrusion; (b) widely open mouth with lateral displacement of the jaw; (c) widely open mouth with rotation of the tongue inside cheek; (d) sucking the inside of the cheek; (e) copious salivation, probably resulting from these motions; (f) expulsion of air from mouth with a loud grunt. Lip-smacking and rapid teeth chattering movements, which are characteristic of non-drugged rhesus monkeys and are frequently elicited by low doses of amphetamines [21,22], were not considered evidence of oral dyskinesias.

Experiment 2. Since the symptoms of tardive dyskinesia are exacerbated by emotional stress [12, 13, 17, 33, 40], we examined the effect of a stressful stimulus on the monkeys' oral dyskinesias. Tongue protrusion was the most common and easily quantified dyskinesia, and therefore we used 4 monkeys which responded to low doses of MA with this behavior. For each monkey, a dose of MA was chosen which was just subthreshold for the elicitation of strong tongue protrusions. Thus, M1 received 1.5 mg/kg, M2 received 2.0 mg/kg, M6 received 0.5 mg/kg, and C8 received 1.0 mg/kg.

A Gra-Lab Universal Timer, whose loud alarm buzzer served as the stressful stimulus, was placed in the experimental cage. The buzzer was controlled by the experimenter through a remote switch. An automatic timer signalled the beginning and end of a 20-sec sampling interval during every min of the test sessions. The number of tongue protrusions occurring during each sampling interval was recorded.

The monkey was adapted to the test cage for 30 min, and a subsequent 30 min control period preceded MA injection. Spontaneous tongue protrusions were recorded during each of the sampling intervals in the first 15 min of the control period. During the second 15 min, the buzzer was sounded during approximately half of the sampling intervals.

MA was injected at the end of the control period. Tongue protrusions were recorded during the 90 min immediately following MA and for 30 min beginning at 2 and 4 hr post-MA. The buzzer was not sounded during the

first 45 min following MA. During approximately half of the sampling intervals from 46–60 and 76–90 min, the buzzer was activated. In the 30 min observation periods at 2 and 4 hr, the buzzer was sounded during approximately half the sampling intervals in the last 15 min of each period (135–150 and 256–270 min). In all these periods the order of buzzer and no buzzer intervals was determined by a pseudorandom schedule.

Experiment 3. Control monkeys which had not exhibited MA-elicited oral dyskinesias in Experiment 1 were placed on a chronic parenteral drug regimen, to determine whether this treatment would convert them to oral dyskinesias in response to MA administered after the chronic treatment was terminated. Thus, 7 C monkeys received the following drugs twice daily, the injections separated by approximately 12 hr.

Methadone (MD): C2 and C7 received increasing doses (1.0–10.0 mg/kg/day) SC for 45 days.

Chlorpromazine (CPZ): C9 and C10 received IM injections of Thorazine (25 mg/ml; Smith, Kline & French). C9 was begun at 2.0 and increased to 10.0 mg/kg/day, and C10 began at 1.0 and was increased to 5.0 mg/kg/day. CPZ produced moderate sedation and pronounced anorexia in C10. He refused laboratory chow from the first injection day, progressively refused even highly palatable foods, and died from apparent starvation on the 28th injection day. C9 began refusing food after 30 injection days, forcing termination of CPZ administration after Day 31.

Haloperidol (HPD): C1 and C4 received 0.2 mg/kg/day IM Haldol (5.0 mg/ml; McNeil) for 45 days. Because HPD produced persistent, though not as severe, anorexia, the dose was not increased.

Saline (SAL): C11 received sterile physiological saline SC for 45 days, in a volume adjusted to that given the MD monkeys.

A narcotic antagonist challenge was used to assess the degree of physical dependence in MD monkeys C2 and C7, and for control purposes in C1, C4, and C11 (the remaining monkey, C9, had terminated chronic drug treatment before this test was administered). The monkeys received a SC injection of naloxone hydrochloride (Narcan; 0.4 mg/ml; Endo) 1 hr following the first daily injection of their respective chronic drug. On Day 42 of the chronic drug regimen they received 0.10 mg/kg naloxone, and on Day 44 they received 0.15 mg/kg. These doses precipitate abstinence symptoms of moderate intensity in morphine-dependent rhesus monkeys [5].

A 10-day drug-free period followed the chronic drug administration phase. Each monkey was observed periodically for at least 8 hr on every chronic drug injection and drug-free day. On the 11th day following termination of chronic drug treatment, a 4-day cycle of 2.0 mg/kg MA injections was begun. The monkeys were examined for oral dyskinesias in the same fashion as in Experiment 1.

Experiment 4. Since dopaminergic blockers and cholinergic agonists reduce both the symptoms of tardive dyskinesia [7, 24, 28, 40, 65] and amphetamine-induced stereotyped behaviors in animals [4, 11, 26, 39, 46, 52, 57, 58, 64], we administered acutely these and other drugs to determine their effects on oral dyskinesias and other stereotyped behaviors. The drugs were tested in 2 ways: in some tests the drug was administered 60 min before MA, to determine if the drug could prevent the occurrence of MA-induced stereotyped behaviors, and in other tests the potential blocker was administered 45 min after MA, to determine if it could antagonize ongoing MA-induced stereotyped behavior.

The following drugs were used: dopamine blockers were chlorpromazine hydrochloride, haloperidol, spiroperidol (0.2 mg/ml), and clozapine (2.0 mg/ml). The cholinergic drug was physostigmine salicylate (Antilirium; 1.0 mg/ml; O'Neil, Jones & Feldman). To assess possible chlorpromazine effects mediated via noradrenergic receptor blockade, the α-receptor blocking agent phentolamine mesylate (Regitine; 5.0 mg/ml; Ciba) was used. Finally, to control for any nonspecific depressant effects produced by the neuroleptics, sodium phenobarbital (Luminal; 130.0 mg/ml; Winthrop) and diazepam (Valium; 5.0 mg/ml; Roche) tests were conducted. Drugs were administered by IM injection, except for several tests with PO clozapine.

The effect of these drugs on stereotyped behaviors was evaluated with reference to control sessions in which sterile saline was injected before or after the same MA dose. In approximately half the cases the control session was held one week prior to the drug test, and in the other half one week following it. These tests were conducted at various times before and during the cyclic MA schedule in Experiment 1.

The monkey was adapted to the experimental cage for 30 min. As in Experiment 2, the frequency of stereotyped behaviors was recorded during a 20-sec sampling interval in each min. Behaviors were counted in this fashion during a 30 min control period prior to MA administration, during the 90 min immediately following MA, and for 30 min beginning at 2 hr, 4 hr, and occasionally 6 hr post-MA. The mean rate/min was computed for successive 15-min periods of the session.

RESULTS

Experiment 1

Table 1 presents the results, expanded over our preliminary report [18] by the addition of monkeys M8 and C8-C11, and by data from additional MA injections administered to M7, C6, and C7. Pronounced oral dyskinesias were elicited almost immediately in 7 of the 8 former methadone monkeys by only 2.0 mg/kg MA. The dyskinesias typically began 5–10 min after injection and occurred at rates of 25–60 events/min.

Once MA elicited a dyskinesia, it continued to elicit it on each subsequent occasion. M1 and M4 received MA on more than 30 subsequent days, and each time MA produced the dyskinesia; this was also true of M monkeys tested less often.

A dose-effect relationship was obtained with respect to the duration of the oral dyskinesias. In M1 and M4, for example, after 2.0 mg/kg MA the dyskinesias persisted for 36 hr, whereas after 5.0 mg/kg they were apparent for 72 hr, i.e. throughout the 3 rest days of the MA cycle.

Concerning the form of the oral dyskinesias, tongue protrusion was the most common. It was particularly severe in M1 and M2, who showed pronounced extensions of the tongue repeated at a rapid rate and accompanied by profuse salivation which they appeared to disregard (Fig. 1). Other M monkeys' oral behaviors consisted of a wide opening of the mouth, in some cases followed by maximal lateral displacement of the mandible and expulsion of air from the lungs with a loud grunt. This cycle was repeated at a relatively slow rate. Even in the case of wide mouth opening alone, the behavior did not resemble rhesus

TABLE 1

RESULTS OF METHAMPHETAMINE (MA) ADMINISTRATION TO MONKEYS WHICH HAD FORMERLY CONSUMED METHADONE (M GROUP) AND CONTROLS (C GROUP)

Monkey	DYS*	DAY†	MA Dose (mg/kg)	Principal Behaviors
M1	+	1	2.0	Tongue protrusion
M2	+	1	2.0	Tongue protrusion
M3	+	1	2.0	Jaw displacement
M4	+	1	2.0	Sucking and blowing out cheek
M5	+	4	2.0	Wide mouth opening
M6	+	4	2.0	Tongue protrusion
M7	+	59	6.0	Lip grooming, mild chewing: tongue protrusion
M8	+	2	2.0	Tongue protrusion
C1	0	8	1.0 → 2.0	Mild chewing
C2	0	8	1.0 → 2.0	Body jerk
C3	0	31	2.0 → 5.0	Shuffling movements
C4	0	45	2.0 → 5.0	Body jerk
C5	0	40	2.0 → 5.0	Facial grimace‡, writhing
C6	+	47	5.0	Biting finger, vocalization: tongue protrusion
C7	0	48	2.0 → 5.0	Body jerk
C8	+	2	1.0	Tongue protrusion
C9	0	8	1.0 → 2.0	Mild chewing
C10	0	8	1.0 → 2.0	No response
C11	0	8	1.0 → 2.0	Circling, mild chewing

*DYS indicates the presence (+) or absence (0) of oral dyskinesias.

†DAY indicates the injection day on which oral dyskinesias were first observed using the dose specified, or the total number of injection days covering the dosage range specified for monkeys not exhibiting dyskinesias.

‡Although this behavior is seen in cases of tardive dyskinesia in humans, it was not considered a dyskinesia for this monkey since he exhibited it prior to MA administration.

monkey threat behavior, in that the mouth was not held fully open and the teeth were not bared. Finally, M4's oral dyskinesia consisted of repeatedly pushing out his cheek with his tongue, pushing it in with a knuckle, and then sucking and biting it; bleeding from inside his mouth was often observed.

In addition to oral dyskinesias, 3 monkeys (M1, M3, and M5) exhibited choreiform limb movements after 1 or 2 days at 2.0 mg/kg MA. These behaviors resembled the abnormal movements of the extremities seen in tardive dyskinesia [28,35], consisting of rhythmic flailing of the upper and lower limbs when the monkey was in a sitting or reclining position.

The monkeys did not appear distressed after MA. Typically there was a small increase in locomotion during the first 15 min after injection, but this behavior tended to subside after a number of injections. In fact, MA seemed to induce what has been termed "paradoxical taming" [10] in M1 and M4. These monkeys were oblivious to environmental events while engaging in their oral dyskinesias. It was possible to handle them, and the experimenter's fingers could be safely placed in their mouths. Needles lightly applied to their lips and noses did not produce a withdrawal response.

Regarding the C monkeys, only C8 displayed oral dyskinesias early in the course of MA administration. Not only had this monkey exhibited small tongue protrusions in response to stressful stimuli prior to testing with MA, but there were definite differences between his MA-elicited oral dyskinesias and those of the M group. In C8 the dyskinesia was very sporadic, appearing shortly after MA, disappearing for several hr and then returning. When present, the tongue protrusions occurred erratically and not in the highly rhythmic and predictable fashion of the M monkeys. In addition, the dyskinesia was not observed on all injection days: at 1.0 mg/kg it occurred only on the second and third days of the 4-day cycle, and at 2.0 mg/kg only on the third day. This pattern was in marked contrast to the oral dyskinesias in the M monkeys which were seen on each injection day following their initial appearance, and occurred with consistent regularity through at least four hr and often for much longer periods.

After prolonged MA administration, C6 developed tongue protrusions similar in quality and frequency to those of the M monkeys. They continued to be elicited by each subsequent MA injection, and were seen at reduced frequency up to 48 hr following MA.

The stereotyped behaviors elicited by MA in the remaining C monkeys consisted of mild chewing movements, rhythmic jerking, writhing or shuffling movements of the body, and in one animal vocalization and biting of the fingers. With the exception of C6, these behaviors did not change throughout the course of MA administration, nor did the behaviors increase in frequency, intensity, or duration as the doses of MA were increased. It is possible that at least some of these monkeys would have progressed to oral dyskinesias had we continued to administer MA and incremented the dosage to the levels (10.0 - 20.0 mg/kg) found necessary in normal monkeys by other experimenters [21,22].

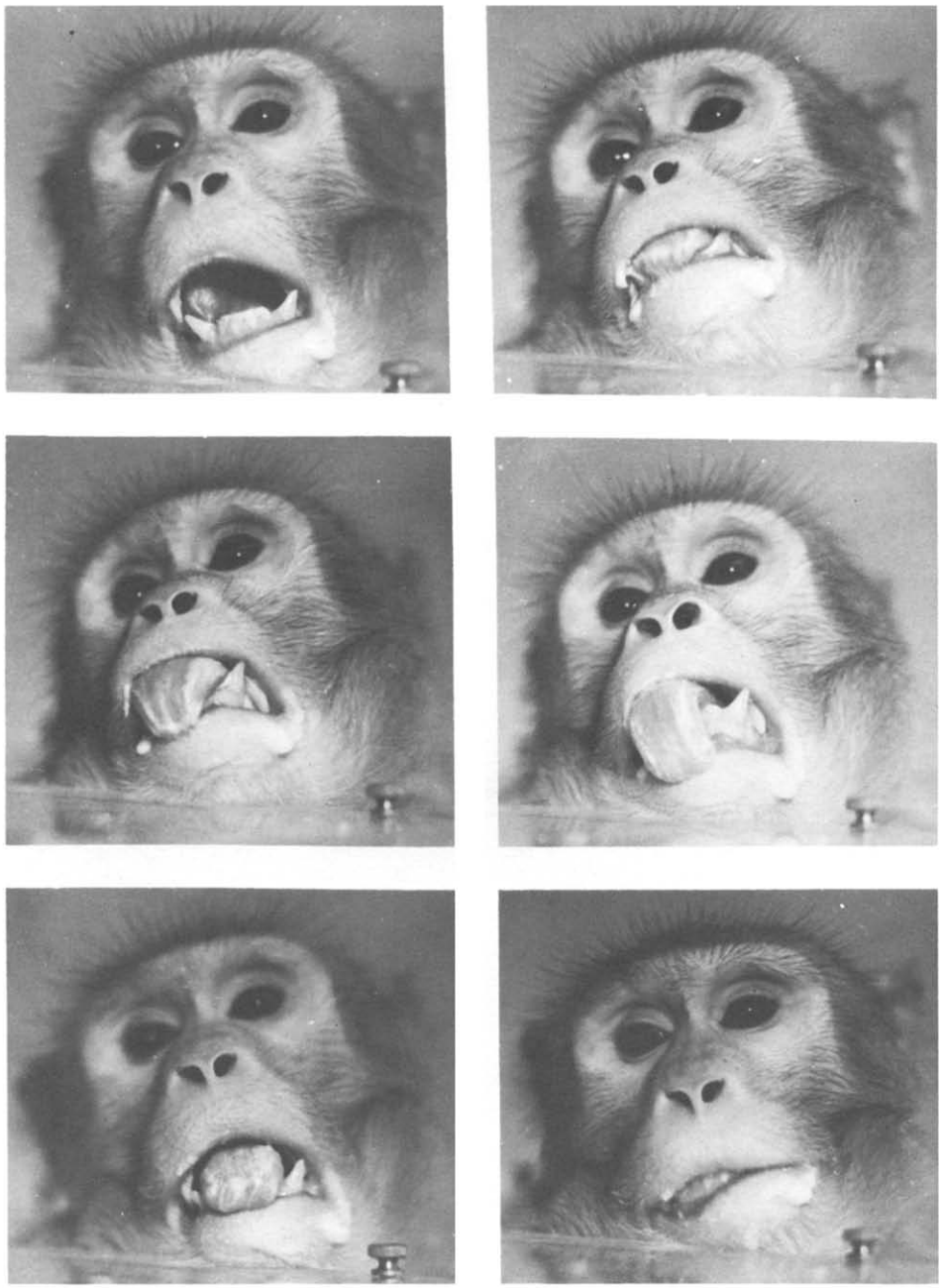

FIG. 1. Sequence illustrating a typical tongue protrusion in M1 following 4.0 mg/kg MA.

A noteworthy aspect of these results is that the methadone doses previously consumed were very low. The M monkeys had not been physically dependent, since they had not responded to a naloxone challenge nor to abrupt drug withdrawal. These doses, however, were certainly sufficient to sensitize them to MA administration as long as 17 months after methadone was terminated.

Experiment 2

The effect of stress on the rate of oral dyskinesias is shown in Fig. 2. Tongue protrusions were minimal or nonexistent during periods in which there were not any buzzer intervals, whether before or after MA. Thus, we present data only from periods in which buzzer and no buzzer intervals were alternated, which provides a direct comparison between these two conditions.

During the control period prior to MA administration, the buzzer had no effect on tongue protrusions. However, following MA the buzzer markedly increased the rate of tongue protrusions in the M monkeys. When the buzzer was sounded, these animals immediately began to extend their tongues at a high rate (more than 1/sec for M6). The increase was limited to the buzzer intervals, and tongue

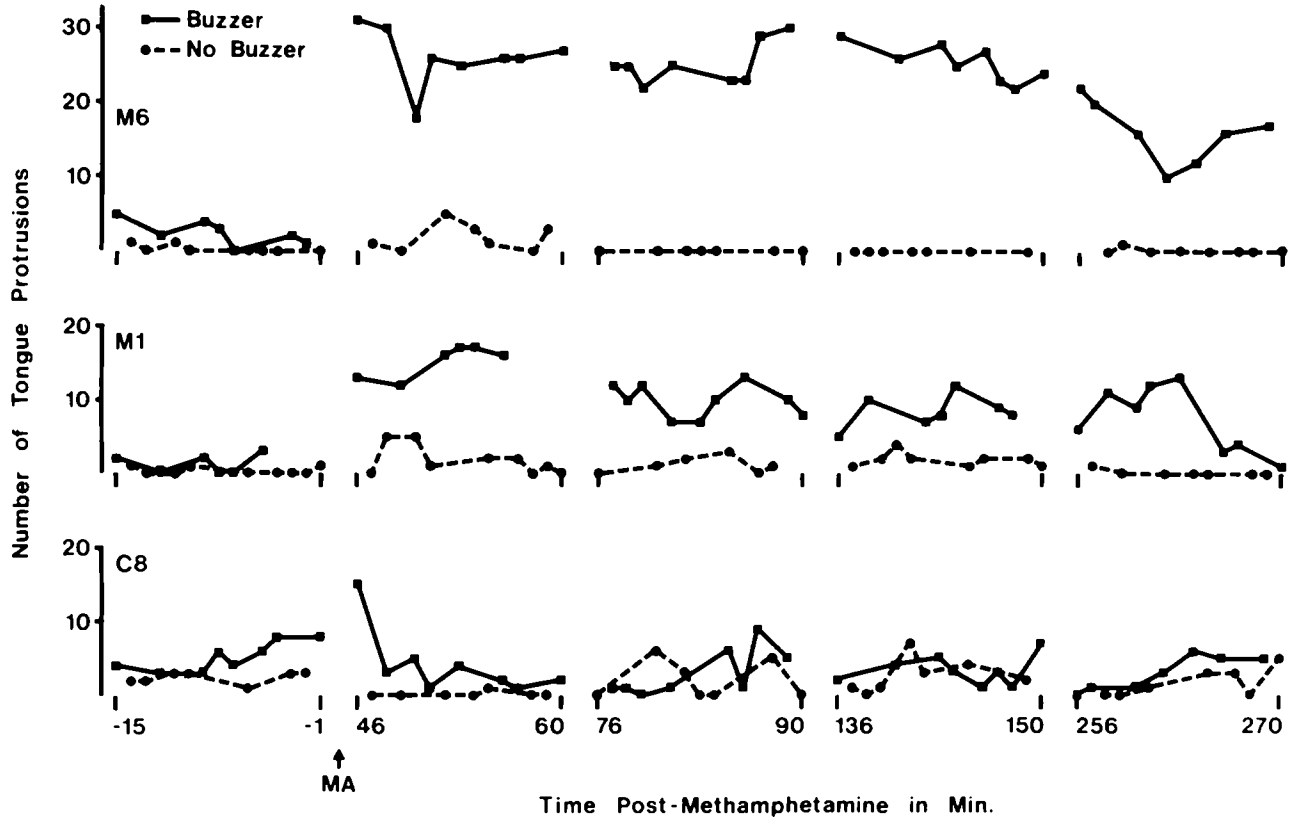

FIG. 2. Effect of stress on the rate of oral dyskinesias in 3 monkeys. Number of tongue protrusions in the 20-sec observation period during each min are plotted as a function of time before and after MA administration (at arrow). Stress periods are those in which a loud buzzer was sounded (Buzzer), non-stress periods were quiet (No Buzzer). Animal M6 illustrates the largest effect and M1 the smallest effect observed in former methadone monkeys. C8 illustrates the lack of effect in a control monkey.

protrusions quickly returned to low levels when the buzzer was turned off. The monkeys did not appear to be greatly agitated, in that they did not engage in frantic escape attempts nor in attacks on the buzzer. Typically, they would simply huddle in a far corner of the cage and engage in the tongue protrusions.

Figure 2 contains data from only the first test session; however, the exacerbation of oral dyskinesias was again demonstrated in the M monkeys during a subsequent session. By the third session, the buzzer had become ineffective with M2 and M6. It is possible that they had adapted to the buzzer's stressful effects by this time, since the presentation of feared stimuli such as a handler's glove continued to exacerbate the dyskinetic symptoms after the buzzer had failed to do so.

The buzzer did not increase the rate of tongue protrusions in C8. This is probably due to the underlying differences between this monkey's pattern of MA-elicited tongue protrusions and those of the M monkeys, as noted in Experiment 1.

Moreover, in identical test sessions conducted with other C monkeys, we found that the buzzer did not increase the rate of other MA-induced stereotyped behaviors such as body jerks or mild chewing. Invariably, the buzzer produced either freezing, i.e., huddling in a corner with cessation of the stereotyped behavior, or led to other motor activity competitive with the stereotyped behavior such as running and banging against the cage walls. Therefore, the results with the M monkeys were not due to general augmentation of stereotyped behaviors, but to a stress-induced exacerbation of one particular type, oral dyskinesias.

Experiment 3

The naloxone challenges on Days 42 and 44 of the chronic parenteral drug regimen had no effect on the SAL and HPD monkeys. In the MD monkeys, however, both doses of naloxone produced symptoms indicative of mild to moderate physical dependence [62,63]. These monkeys stretched out on their sides and assumed other abnormal postures, retched, yawned, and were extremely apprehensive of feared objects such as a handler's glove. Further, naloxone antagonized the mydriasis which is a characteristic response to narcotic analgesics in the rhesus monkey. These symptoms lasted for several hr, and were more intense with the higher dose of naloxone.

In addition, both MD monkeys exhibited brief episodes of oral dyskinesias approximately 5 min after naloxone injection. In C2, 0.10 mg/kg produced a single pronounced tongue protrusion, in which the tongue was extended maximally, twisted at a 90 degree angle, and held in that position for approximately 30 sec. The higher dose of naloxone produced retching in which the tongue was considerably extended; however, such protrusions could not be dissociated from the retching itself. In C7, 0.15

TABLE 2

CONVERSION TO METHAMPHETAMINE (MA)-ELICITED ORAL DYSKINESIAS BY CHRONIC PARENTERAL DRUG ADMINISTRATION

Chronic Drug mg/kg day Duration	Monkey	Response to MA DYS*	DAY†	Principal Behaviors
Methadone	C2	+	3	Tongue protrusion
1.0 → 10.0	C7	+	1	Tongue protrusion, jaw displacement
45 Days				
Chlorpromazine	C9	+	2	Jaw displacement
2.0 → 10.0				
31 Days				
Haloperidol	C1	0		Vacant facial expression
0.2	C4	0		Body jerk
45 Days				
Saline	C11	0		Circling
45 Days				

*DYS indicates the presence (+) or absence (0) of oral dyskinesias.
†DAY indicates the injection day of the 4-day cycle on which oral dyskinesias were first observed.

mg/kg elicited an intense burst of rapid tongue protrusions and licking of the cage bars which lasted for approximately 30 sec.

With the exception of the above responses to naloxone, no monkey displayed oral dyskinesias during chronic drug treatment or the subsequent 10-day drug-free period.

The major results of this experiment concern the conversion to oral dyskinesias elicited by MA. As shown in Table 2, both MD monkeys exhibited oral dyskinesias in response to 2.0 mg/kg MA. The case of C7 is particularly striking in that he responded to this low dose on the first injection day, whereas he had not shown any oral dyskinesias over 48 days at doses up to 5.0 mg/kg in Experiment 1. It is unlikely, however, that his extensive prior experience with MA in some fashion predisposed this monkey to the subsequent production of dyskinesias, since the other MD monkey, C2, had received only 8 previous injections at doses up to 2.0 mg/kg and also exhibited oral dyskinesias in the present experiment.

There were some differences between the tongue protrusions elicited by MA in these monkeys as compared to those of the M group in Experiment 1. First, they occurred less frequently (5–10/min) and the tongue was not protruded as far. Second, they were somewhat delayed in onset, appearing 1–2 hr after MA injection, and increased in intensity over time. In fact, 48 hr following the Day 4 injection the dyskinesias occurred at a more rapid rate than they had 2 hr post-injection. This stands in contrast to the M monkeys, whose oral dyskinesias emerged immediately following MA injection and persisted for an equivalent amount of time but with diminishing frequency.

Chronic CPZ administration was also effective in converting C9 to MA-elicited oral dyskinesias. This is particularly interesting in view of the shorter course of chronic drug administration which he underwent, and his limited experience with MA prior to CPZ treatment. Typically, this monkey was very quiet during the first hr after MA injection, and then began to exhibit jaw displacements which persisted for up to 8 hr.

The dopamine receptor blocker [34] HPD, however, failed to convert either monkey to MA-elicited oral dyskinesias. C1 displayed very minor chewing movements after MA, but more consistently the same vacant, detached behavior which he had shown during HPD administration and which persisted for many months following this experiment. C4 exhibited the same response to MA which he had shown in Experiment 1. HPD administration appeared to produce persistent disturbed behavior in this monkey as well. For several months after the experiment he continued to alternately cower in the rear of his cage and strike out wildly toward the front when being observed.

As expected, the SAL monkey exhibited the same stereotyped behavior in response to MA as he had previously.

Experiment 4

The protocols and complete results are enumerated in Table 3; Figs. 3–6 present representative examples of the stength and duration of effect upon acute administration of each potential blocking drug.

The dopamine blocking agents chlorpromazine (CPZ) and spiroperidol (SPD) completely prevented the development of stereotyped behaviors when administered prior to MA (Fig. 3, top). Further, once MA had elicited stereotyped behaviors, subsequent acute administration of either drug strongly and rapidly antagonized the ongoing behavior (Fig. 3, bottom), including oral dyskinesias which were completely eliminated by SPD in M1. In all cases these effects persisted throughout the 4–6 hr formal observation period. Further, the effects of CPZ and SPD outlasted those of MA; periodic observations after the test session revealed no reappearance of an initially suppressed dyskinesia. Both drugs produced mild sedation, but clearly did not incapacitate the monkeys; they were quiet but alert and responsive to strange noises, gave full-blown threat displays when challenged by the observer, and ate raisins and orange juice when offered. The dopamine blocking agent haloperidol (HDP), however, did not reduce the frequency of tongue protrusions in C6 when administered after MA (Fig. 4, left).

The specific α-adrenergic blocker phentolamine (PTA) had no effect on stereotyped body jerks, whether admin-

TABLE 3

DRUG ADMINISTRATION PROTOCOLS AND RESULTS OF EXPERIMENT 4

Blocking Drug And Dose (mg/kg)	Before or After MA dose (mg/kg)	Monkey	MA-Elicited Behavior	Effect of Blocking Drug on Behavior
Chlorpromazine				
0.5	After 3.5	M7	Searching behind	Completely eliminated
1.0	After 2.0	M8	Body jerk	Completely eliminated
1.0	After 2.0	M8	Body jerk	Completely eliminated (Fig 3)
1.0	Before 2.0	C4	Body jerk	Completely blocked (Fig 3)
Spiroperidol				
0.025	After 5.0	M1	Tongue protrusion	Completely eliminated
0.05	After 5.0	M7	Lip grooming	Completely eliminated
0.025	After 2.0	C7	Body jerk	Completely eliminated (Fig 3)
0.025	Before 5.0	M7	Lip grooming	Completely blocked (Fig 3)
0.1	Before 2.0	C7	Body jerk	Completely blocked
Haloperidol				
0.05	After 6.0	C6	Tongue protrusion	No effect (Fig 4)
Phentolamine				
0.5	Before 2.5	C4	Body jerk	No effect (Fig 4)
0.5	After 2.5	C7	Body jerk	No effect
Clozapine				
P.O. 0.1	Before 5.0	M2	Tongue protrusion	Cut number in half (Fig 5)
0.5	Before 6.0	M2	Tongue protrusion	Cut number in half
1.0	Before 5.0	M7	Lip grooming	Delayed onset 1 hr., no effect on number
I.M. 2.5	After 5.0	M4	Sucking cheek	Completely eliminated (Fig 5)
Physostigmine				
0.1	Before 6.0	M7	Jaw displacement	Delayed onset 4 hr (Fig 5)
0.1	After 6.0	C6	Tongue protrusion	No effect (Fig 5)
Phenobarbital				
30.0	Before 6.0	M7	Jaw displacement	No effect
10.0	Before 2.5	M8	Body jerk	No effect
10.0	After 2.5	C4	Body jerk	No effect (Fig 6)
20.0	After 5.0	C6	Tongue protrusion	No effect
Diazepam				
1.0	After 4.0	M4	Sucking cheek	No effect (Fig 6)

istered before or after (Fig. 4, right) MA.

The results with the final dopamine blocking agent, clozapine (CLO), were particularly interesting. In terms of its effects on the oral dyskinesias of the M monkeys, it reduced by 50% the peak number of tongue protrusions when administered before MA, and rapidly eliminated cheek sucking when injected after MA (Fig. 5, left). However, it delayed but did not suppress non-oral stereotyped grooming in M7; SPD had completely blocked the appearance of this behavior in the same monkey (Fig. 3, right).

The cholinergic agent physostigmine (PHY) gave equivocable results. As shown in Fig. 5 (right), it considerably delayed the onset of oral dyskinesias in M7 when administered before MA, but the same dose administered after MA had no effect on tongue protrusions in C6.

Finally, neither phenobarbital (PBT) nor diazepam (DIA) had any effect on oral dyskinesias or other stereotyped behaviors (Fig. 6), even though at the higher doses of PBT the monkeys were ataxic and obviously sedated.

DISCUSSION

The present study has shown that prior experience with MD greatly enhances the rhesus monkey's sensitivity to MA. The stereotyped behaviors elicited by MA, oral dyskinesias, bear a striking qualitative resemblance to the symptoms of tardive dyskinesia in humans [12, 13, 14, 15, 17, 32, 33, 60, 68]. Further, the influence of a stressful stimulus on oral dyskinesias is in complete agreement with the frequently reported exacerbation by stress of symptoms in tardive dyskinesia patients [12, 13, 17, 33, 40].

The most obvious difference between the monkey's oral dyskinesias and those of tardive dyskinesia is that in the latter condition they often arise spontaneously when neuroleptic therapy is halted or the dosage reduced, whereas it was necessary to elicit the monkeys' dyskinesias by administering MA. Thus, it appears that in the monkeys a state of "latent sensitivity" was present, dependent on exogenous stimulation for expression.

The currently accepted theory concerning the develop-

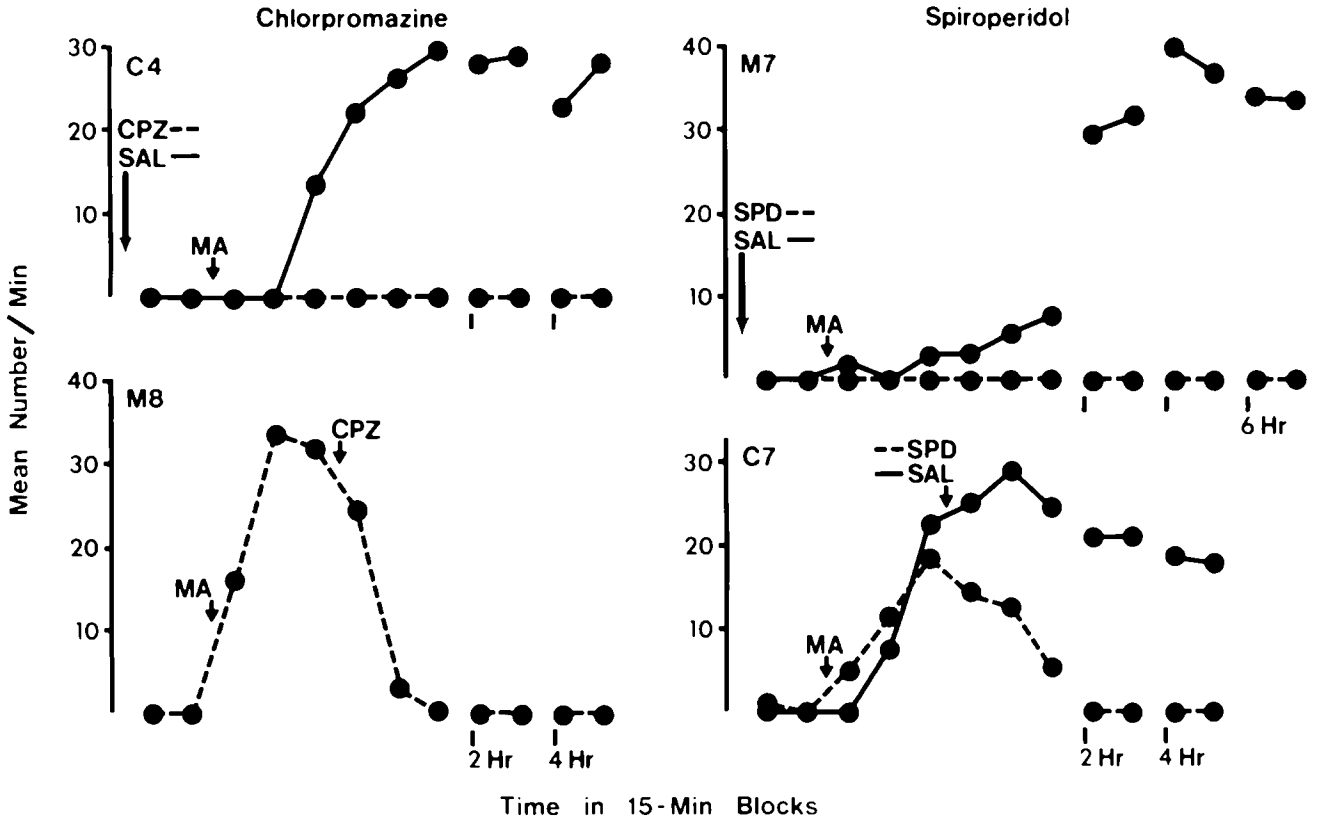

FIG. 3. Representative examples of the effect on MA-elicited stereotyped behavior of chlorpromazine (CPZ) and spiroperidol (SPD). Each panel depicts the mean number/min of a monkey's characteristic behavior over time. The monkey is identified in the upper left corner of each panel. The solid line represents data from the session in which saline (SAL) was administered, and the dashed line data from the session in which the monkey received the potential blocking drug. Arrows indicate the times at which the blocking drug or SAL, and MA, were injected. Drug doses are specified in Table 3. (No SAL control session was run with M8).

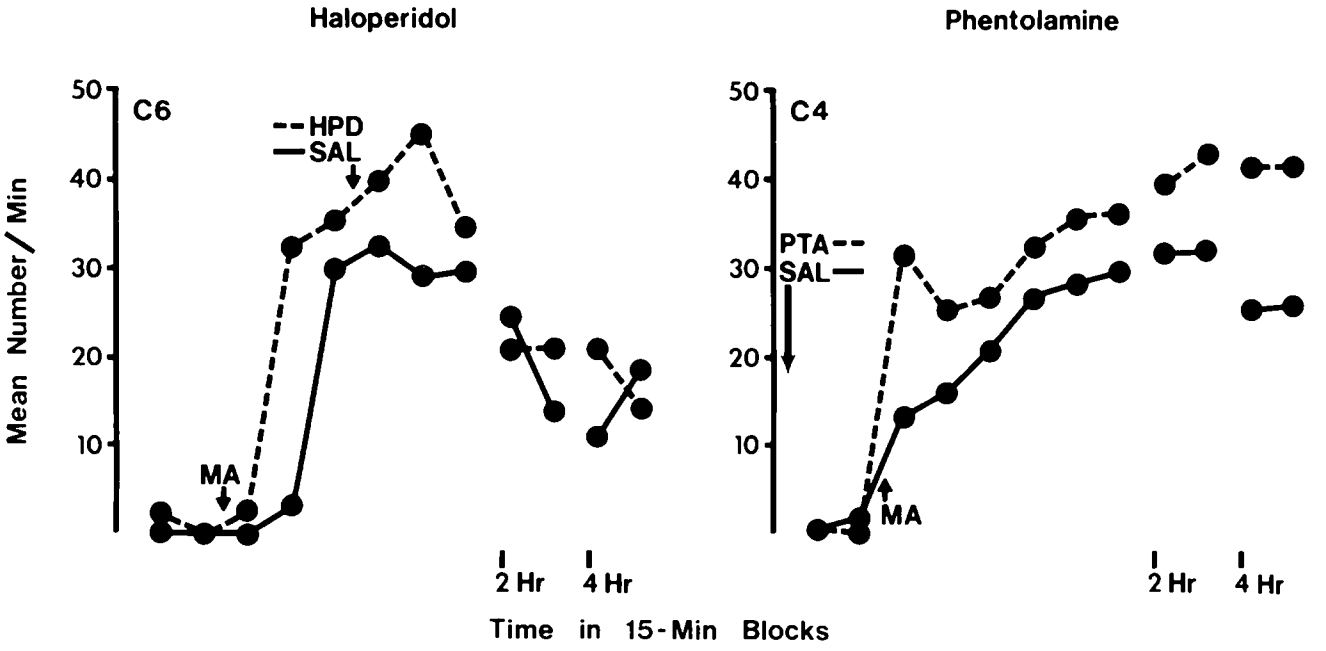

FIG. 4. Representative examples of the effect on MA-elicited stereotyped behavior of haloperidol (HPD) and phentolamine (PTA). For further explanation of symbols, see legend to Fig. 3.

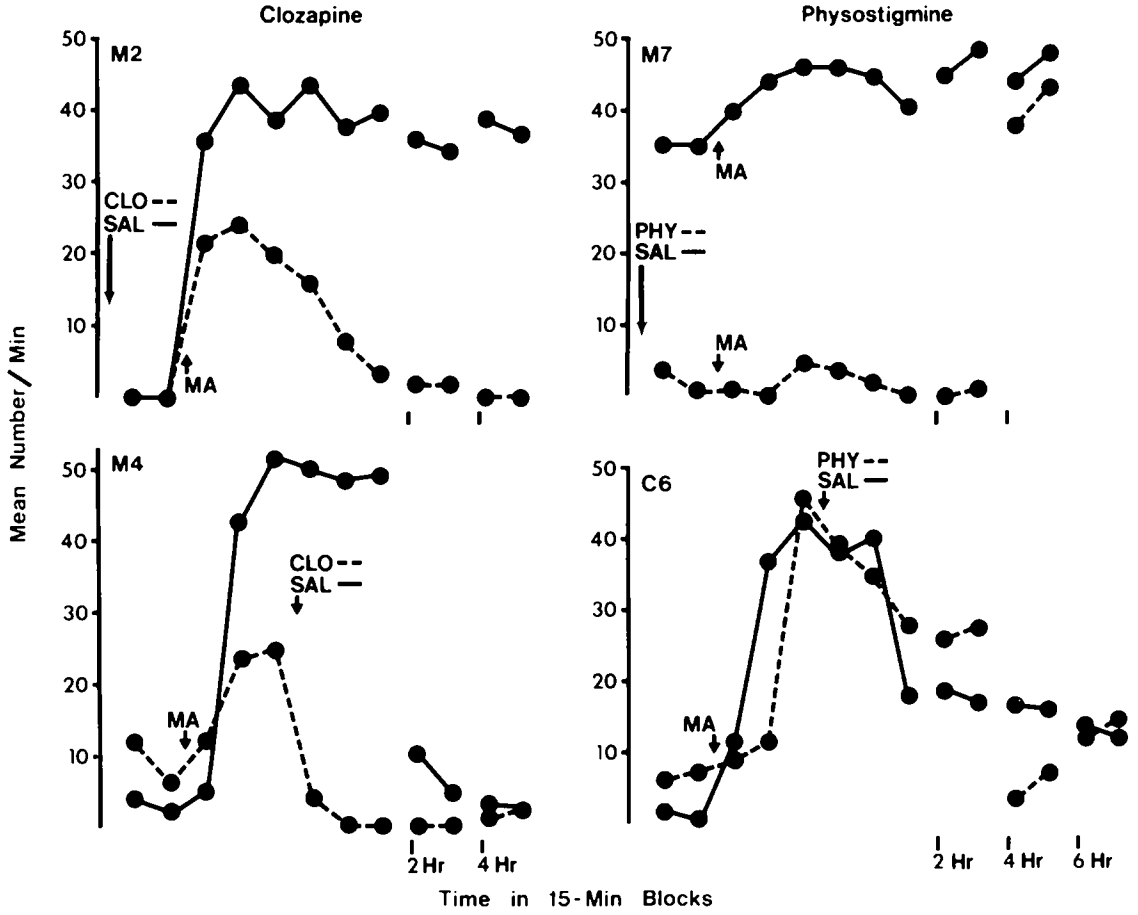

FIG. 5 Representative examples of the effect on MA-elicited stereotyped behavior of clozapine (CLO) and physostigmine (PHY). For further explanation of symbols, see legend to Fig. 3. Concerning the results with M7 (upper right panel), the initial high rate of stereotyped behavior in the SAL session, before MA was administered, represents a continuation of that behavior from MA administration on the previous day.

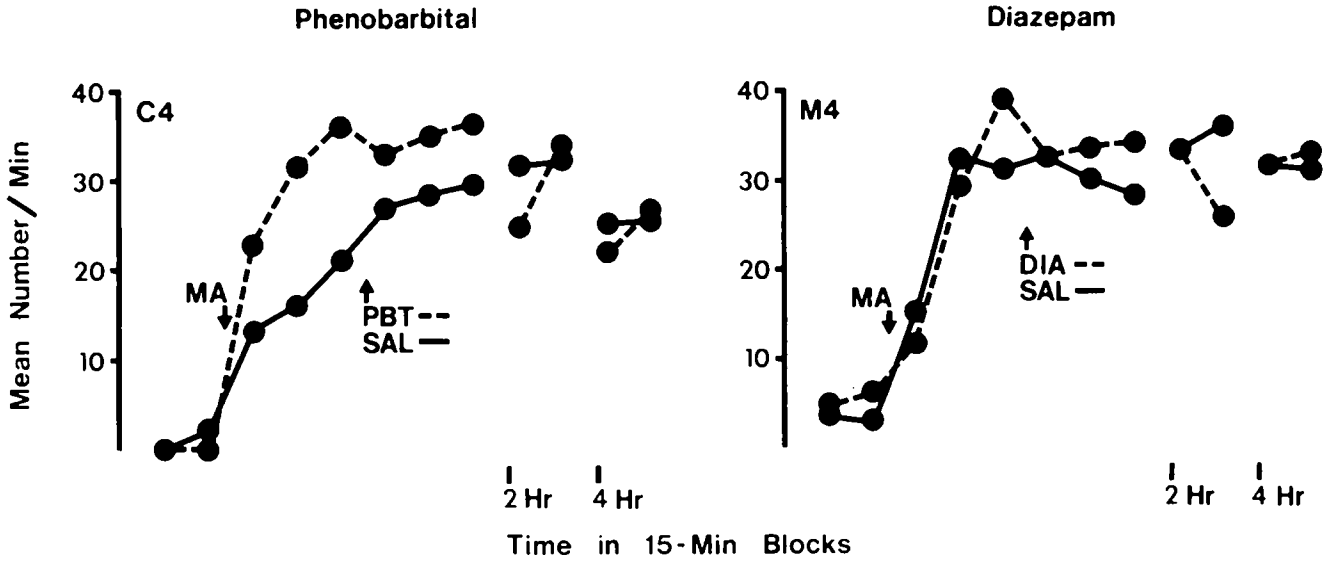

FIG. 6. Representative examples of the effect on MA-elicited stereotyped behavior of phenobarbital (PBT) and diazepam (DIA). For further explanation of symbols, see legend to Fig. 3.

ment of tardive dyskinesia is that chronic neuroleptic administration creates a dopaminergic receptor blockade, rendering the receptors supersensitive to the dopamine reaching them when the blockade is lifted [35,36]. We suggest that sensitivity to MA, subsequent to chronic MD treatment, may be explained by the same mechanism. There is considerable biochemical evidence that MD blocks dopamine receptors in the striatum [1, 2, 42, 47, 52, 56], and several behavioral studies have shown enhanced responses to dopamine agonists shortly after termination of chronic narcotic administration [20, 43, 51]. In addition, it has been shown that rats formerly dependent on morphine are more sensitive to the dopamine agonist apomorphine for 30 days after withdrawal [29], and we have demonstrated enhanced sensitivity to methamphetamine in the guinea pig for 3 weeks after chronic MD or CPZ treatment was terminated [19].

In further support of this hypothesis, we showed in Experiment 3 that even a relatively short period of parenteral administration of MD or CPZ was effective in sensitizing monkeys to the effects of MA administered 10 days subsequently. The failure of HPD to induce supersensitivity, even though superficially contradicting the theory, was not unexpected. Experiments in rhesus monkeys having close parallels with the present study have shown that long-term administration of CPZ results in the appearance of oral dyskinesias [48,50] whereas HPD, even in much higher doses than we used, is ineffective in this regard [50]. In addition, HPD and other butyrophenones seem to produce very few incidences of tardive dyskinesia in humans. In a recent article concerning four such cases, it was noted that "... reports of its (HPD) association with late or tardive dyskinesias are nearly nonexistent in the English language medical literature." [33].

The results of acute drug administration on MA-elicited behaviors (Experiment 4) are also consistent with a dopaminergic supersensitivity theory. The dopamine receptor blockers CPZ and SPD antagonized dyskinesias, confirming studies in other species [11, 26, 46, 52, 57, 64]. We attribute the failure of HPD to block stereotyped behaviors to the dose employed, since it has subsequently been shown that in primates much higher doses are necessary, i.e. 0.57 mg/kg for 3 days [27] and 1.25 mg/kg acutely [64].

The final dopaminergic antagonist, CLO, blocked oral dyskinesias but did not affect non-oral stereotypies. This differential effectiveness agrees with other evidence involving this drug. While CLO has only a weak antagonistic action on amphetamine- or apomorphine-induced stereotyped behaviors [45,65], it can suppress behaviors thought to be mediated by supersensitive dopamine receptors. For example, CLO is effective in alleviating symptoms of tardive dyskinesia [65], and reduces to control levels chronic haloperidol- or loxapine-induced supersensitive responses to apomorphine [57].

We were somewhat surprised that PHY was not consistently effective in suppressing oral dyskinesias, since cholinergic drugs antagonize stereotypies in rodents [4, 39, 58] and alleviate the symptoms of tardive dyskinesia [24,28]. We are currently pursuing this question. PTA's lack of effect on oral dyskinesias substantiates other evidence that α-adrenergic systems play no role in stereotyped behaviors [31, 53, 54, 59]. Finally, to attribute the effectiveness of the dopaminergic blockers to nonspecific depression of activity is clearly unwarranted, since sedative doses of PBT and DIA had no effect on dyskinesias.

Thus, we conclude that chronic MD administration induces a relatively permanent state of dopaminergic supersensitivity. Concerning the underlying neurochemical mechanism, the weight of evidence points to postsynaptic receptor blockade by MD [1, 2, 42, 47, 52, 56]. It is unlikely that presynaptic inhibition of dopamine release is responsible; although neuroleptics do have this action, MD does not [61].

The results of the present study raise several points of clinical significance involving the risk of developing extrapyramidal disorders due to long-term MD administration. First, the data indicate that methadone maintenance patients might be highly sensitive to amphetamines for an extended period of time after they terminate treatment. Although the use of amphetamines by these patients during and following treatment is well-documented [8, 9, 30, 49, 66], we are unaware of any clinical reports of unusual motor effects consequent to amphetamine self-administration. This may indicate that humans are for some reason not subject to this phenomenon; on the other hand, it may derive from inadequate medical follow-up reporting, particularly on program drop-outs, and from other factors discussed below.

The second conceivable risk which such patients might run is the spontaneous appearance of dyskinesias following termination of treatment. We raise this point even though our monkeys did not exhibit dyskinesias in the absence of stimulation by MA, because we consider that our data have demonstrated the presence of dopaminergic supersensitivity. In addition, the absence of clinical reports of spontaneous dyskinesias in former methadone maintenance patients may be explicable in terms of the populations receiving MD as opposed to neuroleptic drugs. By 1968, it was estimated that 100 million people had been treated with neuroleptics [40], while as recently as 1973 only 85,000 people had participated in methadone maintenance programs [44]. Since tardive dyskinesia seems to occur at maximum in only 12-14% of patients receiving neuroleptics [13], the number of methadone maintenance patients displaying symptoms would, on the basis of probability, be quite small and therefore possibly have escaped detection. Moreover, tardive dyskinesia was not recognized as a clinical problem until 10-12 years following the introduction of neuroleptics into widespread use [13]; the first methadone maintenance program was established only 11 years ago [16]. Finally, tardive dyskinesia is thought to be most prevalent in elderly female patients [13]; thus, the predominantly young male population of methadone maintenance programs might be less susceptible to the development of supersensitivity.

Whatever the reasons for the failure to date to observe symptoms of dopaminergic supersensitivity following MD treatment in humans, on the basis of the present report as well as other evidence in experimental animals we strongly suggest that further work should be undertaken to assess the degree to which such patients are at risk of developing extrapyramidal dyskinesias.

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