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Long-Term Chlorpromazine in Rhesus Monkeys: Production of Dyskinesias and Changes in Social Behavior

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Abstract. The daily administration of chlorpromazine (CPZ) in doses of 8–40 mg/kg over 113 weeks to four rhesus monkeys produced dyskinesias and alterations in social behavior. General activity and social interactions were reduced by CPZ treatment but social aggression was elevated during initial drug administration. These behaviors returned to normal when treatment was discontinued. Dyskinesias appeared during CPZ treatment, and two striking ones, gravel mouth and hand gesture, persisted for 12 weeks after drug withdrawal.

These results indicate that dyskinesias which share major features of human tardive dyskinesia can be produced in nonhuman primates by long-term CPZ treatment.

Key words: Tardive dyskinesia – Chlorpromazine – Animal models – Rhesus monkeys – Social behavior

The clinical literature on tardive dyskinesia (TD) is extensive with regard to the nature and rate of occurrence of the syndrome as well as clinical trials of treatment agents. Baldessarini and Tarsy (1978) have recently reviewed this area.

The development of animal models for TD and basic research into the mechanisms of this syndrome have been difficult. Notwithstanding, the following animal models have been proposed:

Rubovits et al. (1973) found that prolonged chlorpromazine (CPZ) treatment lowered the threshold for amphetamine-induced stereotypy in rats and felt that these data supported this as a model of TD. Other investigators have used apomorphine-induced stereotypies in similar models of TD (Davis et al. 1979; Tye et al. 1979).

Behavioral-biochemical hypotheses have provided a basis for testing the effects of dopamine (DA) agonists, cholinergic, anticholinergic, and a variety of other drug classes of potential use in the treatment of human patients with TD (Christensen and Nielsen 1979; Clow et al. 1978; Sayers et al. 1977). This overall strategy places rats on chronic neuroleptic treatment and then studies the effects of various drugs on such dependent measures as stereotyped behavior. There is usually little attention to the ongoing social or behavioral effects of the chronic neuroleptics themselves. There have been a number of studies of experimental dyskinesias in nonhuman primates (Mones 1978; Paulson 1973; Ng et al. 1973; Messiha 1974; Eibergen and Carlson 1975; Gunne and Barany 1976; Bedard et al. 1977; Weiss et al. 1977; Weiss and Santelli 1978). These studies have used an assortment of drugs in various species of monkeys to produce a variety of movement disorders.

In a review of drug-induced dyskinesias, Sassin (1975) stated that easily definable dyskinetic syndromes had been produced by injections of L-Dopa, apomorphine, trivastal carbachol, sodium azide, tetrahydrocannabinol, phenothiazines, and amphetamines into three species of monkeys. He felt that there was adequate evidence that the production of dyskinesias in monkeys was biochemically related to the status of dopaminergic systems.

While nonhuman primate studies referenced earlier are extensive, they share important limitations with the previously mentioned rodent studies. In many experimental models, signs of TD in animals are not elicited by neuroleptic treatment alone but depend on challenges with other drugs. Dose-effect relationships of the second drug are used as indicators of neurochemical mechanisms which mediate the effects of neuroleptics. Additionally, rodent models may elucidate some of the

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chemical mechanisms but present the problem of determining which movements can serve as analogues of human TD. Therefore, nonhuman primate models have been advocated because of the similarities of facial and limb movements and the comparability of many neurobiological systems. However, previously reported pharmacologically-induced TD-like syndromes in monkeys occur over time periods of hours or days. Human TD, by comparison, is a chronic disorder which occurs in the context of long-term neuroleptic administration.

In summary, neuroleptics are often the drugs of choice in treating psychotic disorders in humans even though these drugs are frequently associated with development of dyskinesias. Current animal models of dyskinesias, including TD, have significant problems, solution of which could lead to advances in the understanding and treatment of the disease.

In the present paper, we report the occurrence of oral-facial and limb movement dyskinesias in rhesus monkeys which were observed during and after long-term treatment with CPZ. Unique to our study is careful social testing over a prolonged period of time so that we have data relevant to the long-term dyskinesia producing effects of neuroleptics as well as their social effects.

Material and Methods

Subjects. Four 3.5 year old rhesus macaques which had received CPZ (kindly supplied by Smith, Kline and French Ltd., Philadelphia, PA, USA) for 12 weeks in a rehabilitative study 1 year prior to this study (McKinney et al. 1973) were used. Assessments at the start of the present study did not reveal any dyskinesia symptoms.

Drug Administration. The subjects were given the liquid concentrate form of CPZ once a day at 11:00 AM, 7 days a week, in peanut butter sandwiches for 113 weeks. The animals were monitored closely to ensure that they had actually eaten the entire sandwich. Treatment periods were divided into baseline (6 weeks), low dose (54 weeks with drug increasing from 8 mg/kg to 20 mg/kg), no treatment (8 weeks of no drug administration), high dose (49 weeks with drug increasing from 20 mg/kg to 40 mg/kg with the last 35 weeks at 40 mg/kg) and no treatment (12 weeks of no drug administration).

Behavioral Assessments. Two forms of behavioral data were taken. The first form was a social behavior check list of 27 operationally defined categories, which have been described in detail elsewhere (Moran and McKinney 1975). These categories were recorded as modified frequencies, i.e., the number of 15 s intervals in which the behavior occurred during a 5-min rating period for each animal in each testing session. Behavior testing done by experienced observers previously shown to have an inter-rater reliability of $P > 0.90$ by Pearson product correlation. Because of limited personnel, it was not possible to have all observers "blind". However, the operational behavior categories in use were not susceptible to subtle interpretation. Data were collected twice a day at 9:00 AM, approximately 22 h after drug administration and at 1:30 PM, approximately 2.5 h after drug administration. The animals were tested as a group of four in a playroom situation (Sackett 1968).

The second form was a symptom check list. These categories (Table 1) are indicative of movement disorders, and were recorded as to whether they were observed at least once whenever the monkeys were tested. We selected them by our best estimation of the kinds of TD symptoms that rhesus monkeys would be physically able and likely to duplicate. These data were gathered on the same schedule as the social behavior check list; however, since these behaviors were not present before CPZ administration, no quantitative data could be taken in the first baseline period.

Statistics. The social behavior check list categories were analyzed utilizing two-way within-subjects analyses of variance with time of day and drug blocks as repeated measures. The symptom check list percentage data were analyzed utilizing two-way within subjects analyses of variance with time blocks and time of day as factors (Kirk 1968). The Fisher LSD test was used for post-hoc contrasts.

Results

The data from the social behavior check list showed that similar responses occurred in both the AM and PM sessions. However, the AM sessions, as might be expected since they were much further from maximum drug effect (22 h as opposed to 2.5 h) showed the response to a lesser degree. For that reason, only changes in behavior which were found to be statistically significant as main effects or interactions of time blocks with CPZ treatment at the $P < 0.05$ level during the PM sessions will be discussed. These changes are summarized in Table 2.

Passive and huddle, which are indicative of withdrawal from or indifference to both the social and nonsocial environment, were elevated during both low and high drug treatment periods. During no treatment phases, these behaviors occurred at lower levels.

Table 1. Definitions for symptom check-list categories

Fly catcher: Consists of flipping the tongue out of the side of the mouth with a scooping motion
Gravel mouth: A rolling, sometimes slightly protruding motion of the tongue. This mouthing appears to simulate the action which might occur if the animal had a dry mouth
Tremors: A continuous, seemingly involuntary "quivering" involving any part of the body
Drooling: Foaming of saliva around the mouth or chin
Rigidity: A state similar to the passive position, but with tense, tightly contracted muscles. The toes may also be tightly curled
Posturing: Animal freezes in "midstep" and holds this often awkward position. Frequently the eyes close as this posture is maintained
Ptosis: Drooping eyelids
Trancelike: Animal sits or stands in a relaxed state and frequently stares vacantly into space, or seems to be tracking an invisible object
Hand gesturing: Holding and maintaining the hand or foot and limb in an atypical position. Many times the fingers or toes are held in an unflexed, somewhat rigid and unnatural position
Sedation: General drowsy and slow behavior indicated by lack of movement, or very slow movement, and little or no interest in the environment

Table 2. Behaviors of four rhesus monkeys treated with chlorpromazine (CPZ)

Categories	Mean modified frequency ± SEM (20 maximum)				
	Baseline 6 weeks	Low CPZ 64 weeks	Off drug-1 8 weeks	High CPZ 49 weeks	Off drug-2 12 weeks
Social behaviors					
Passive	5.1 ± 2.6	10.5 ± 1.0	8.4 ± 1.6	13.6 ± 1.4*	9.8 ± 2.1
Huddle	2.7 ± 2.7	3.7 ± 1.8*	0.2 ± 0.2	2.8 ± 0.9*	0.4 ± 0.3
Locomotion	14.4 ± 2.1	8.3 ± 1.7*	12.9 ± 0.9	7.2 ± 1.2*	11.4 ± 1.5
Environment exploration	7.2 ± 1.5	5.0 ± 0.8*	9.7 ± 1.9	4.9 ± 1.2*	6.8 ± 2.3
Proximity	0.03 ± 0.03	0.04 ± 0.02*	0.32 ± 0.20	0.04 ± 0.02*	0.39 ± 0.21
Social exploration	0.13 ± 0.13	0.01 ± 0.01*	0.28 ± 0.14	0.01 ± 0*	0.18 ± 0.13
Aggression[a]	None	0.26 ± 0.07	None	None	None
Fear grimace[b]	0.32 ± 0.03	0.79 ± 0.16	0.17 ± 0.02	0.30 ± 0.21	0.33 ± 0.29
	Mean percent of maximum frequency ± SEM				
Symptom behaviors					
Ptosis[c]	None	37.1 ± 14.9*	3.2 ± 3.2	32.8 ± 10.3*	None
Sedation[c]	None	76.8 ± 5.1*	4.7 ± 1.6	37.6 ± 7.1*	None
Tremor[c]	None	28.7 ± 10.4*	1.6 ± 1.6	31.3 ± 14.8*	14.9 ± 14.9
Hand gesture[d]	None	24.8 ± 5.7*	56.3 ± 9.9	52.3 ± 15.0	50.7 ± 12.5
Rigidity[e]	None	8.0 ± 3.1*	None	0.8 ± 0.3	1.0 ± 0.9
Gravel mouth[e]	None	16.7 ± 10.1	3.1 ± 3.1	21.9 ± 11.5*	21.3 ± 10.6*

[a] Means of AM and PM sessions for two most dominant animals
[b] Means of AM and PM sessions for two most subordinate animals
[c] Means of PM sessions
[d] Means of AM sessions
[e] Means of AM and PM sessions
* $P < 0.05$ compared to off drug-1 condition

The categories of locomotion and environment exploration, which have the opposite connotation of passive and huddle and indicate active interaction with the environment, occurred at uniformly lower rates during the low and high drug treatment periods and at higher rates during the no-treatment periods.

Categories of proximity and social exploration showed low levels during initial baseline periods and remained low during drug administration blocks. Both behaviors showed significant increases during times off CPZ. These changes, while quantitatively of low mean frequency, represent reliable alterations in social behavior over 139 weeks.

The categories of fear grimace and aggression showed a marked elevation during the first few weeks of drug administration and then returned to baseline. The frequency of these behaviors was not increased during subsequent off-drug periods or when the drug was reintroduced at a higher dose level in the second drug period.

Only those categories from the symptom check list that occurred with enough frequency to be analyzed are presented.

The categories of ptosis, sedation, and tremor were drug dependent and occurred at increased levels during both low and high drug treatment periods and then were either eliminated or dropped to lower levels during both of the no-treatment phases. Rigidity showed an initial upsurge at the onset of drug administration and then dropped to lower levels which were maintained through both the no-treatment periods and the high dose period.

The categories of gravel mouth and hand gesture were drug-induced and sustained over both low and high drug treatment periods as well as the last no-treatment period. In other words, these categories persisted even after drug discontinuation and during the drug treatment periods were more prominent in the morning (the testing sessions furthest removed from drug administration).

Discussion

There were discernible social behavioral effects associated with extended CPZ administration. Some could have been predicted; others were unexpected and suggest the creation of tardive symptoms in rhesus monkeys. In general, quiescent behaviors from the social check list, both disturbed and nondisturbed, constituted much of the behavioral repertoire of the animals during drug treatment periods. Physical activity and social interactions, which were considerably reduced during treatment periods, accounted for a much higher percentage of the animals' behavior during periods of no drug treatment.

Drug-related dyskinesias, as defined in the symptom check list, did occur with long-term administration of CPZ, although many did not persist after drug termination. This might be interpreted to mean that drug-induced movement disorders occurred but that they are not analogous to human TD. However, the significant exceptions to this are the categories of gravel mouth and hand gesture. These behaviors were drug-induced and with the exception of the first no treatment period persisted throughout the study, including the last 12 weeks off drug.

Did we produce TD in the monkeys? Certainly the category of gravel mouth closely resembling TD in humans, was drug-induced, and persisted after drug administration stopped. This is similar to many instances of TD in humans where stopping the neuroleptic does not interrupt the TD syndrome. Not all TD features were produced, nor were all pharmacological responses examined, but these data suggest lines of future research and ways in which nonhuman primate models could provide a means of studying the effects of neuroleptics in a social context.

Clear social effects were observed early in the first treatment period and during the no-treatment periods. Specifically, behaviors associated with social aggression were elevated in the initial drug treatment period and social interactions occurred most frequently during no-treatment periods. This strongly suggests that there are different initial social effects from CPZ administration versus the effects that occur with chronic or intermittent administration. It is difficult to completely interpret the social results; however, it seems clear that long-term social effects of neuroleptics cannot be ignored in humans or monkeys.

The fact that the monkeys in this study had prior experience with CPZ for 12 weeks 1 year earlier poses the question of whether they may have been predisposed to the development of dyskinesia. The research of Weiss et al. (1977) found that haloperidol sensitized the monkeys some 508 days later to its dyskinesia-inducing effects. This occurred at challenge doses considerably lower than those used in the original treatment. Data from the present within-subjects study does not address itself to this problem.

In summary, the present study indicates that a syndrome with features similar to human TD can be produced in rhesus monkeys following long-term treatment with CPZ. It is important to continue to pursue the development of this and a variety of other animal models to better understand this important and devastating syndrome.

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