EXPERIMENTAL EVALUATION OF THE ANTIDEPRESSANT AND NEUROLEPTIC ACTIVITY OF MAPROTILINE

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Summary: Maprotiline, a tetracyclic antidepressant drug, was evaluated for antidepressant and neuroleptic activity. In antidepressant tests, maprotiline antagonized reserpine-induced ptosis in rats but, unlike the tricyclic antidepressants, was found to antagonize methamphetamine stereotypy in rats, to decrease the intensity of L–dopa induced behavioural syndrome in pargyline–pretreated mice and to be ineffective in intensifying the 5–HTP induced behavioural syndrome. In neuroleptic tests, maprotiline was found to, antagonize apomorphine–induced cage climbing behaviour, induce catalepsy, inhibit the CAR and traction response, decrease the spontaneous motor activity and exploratory behaviour, and to potentiate the hypnotic effect of pentobarbitone. Our results indicate that maprotiline exhibits a profile of activity which resembles the neuroleptics and most probably exerts post–synaptic striatal DA receptor blocking activity.

Key words: maprotiline, antidepressant activity, neuroleptic activity, traction response, methamphetamine stereotypy, reserpine–induced ptosis, apomorphine climbing behaviour, conditioned avoidance response

INTRODUCTION

Maprotiline hydrochloride (LUDIOMIL) is a new tetracyclic antidepressant drug which exerts antidepressant activity by blocking the neuronal reuptake of noradrenaline (19, 20, 24). Recently Delini-Stula and Vassout (10), on the basis of their observation that maprotiline antagonises apomorphine-induced contralateral turning in rats with unilateral 6-hydroxydopamine lesions of the substantia nigra, have suggested that maprotiline possesses postsynaptic dopamine (DA) receptor blocking activity. We therefore, decided to re-evaluate the antidepressant and neuroleptic activity of maprotiline.

MATERIALS AND METHODS

Male albino rats and mice, weighing between 100 to 200 *g* and 20 to 30 *g* respectively, were used for the study. They were allowed food and water *ad libitum* upto the time of experimentation. Each animal was used once only. All observations were made between 10.00 and 17.00 hr at 27 to 30°C in a noiseless, diffusely illuminated room.

The drugs used were maprotiline HCl (Ciba-Geigy), desipramine HCl (Ciba-Geigy), imipramine HCl (Ciba-Geigy), clomipramine HCl (Ciba-Geigy), chlorpromazine HCl (May and Baker), pentobarbitone Na (Abbott), pargyline HCl (Abbott), apomorphine HCl (Sigma), l-dihydroxyphenylalanine (Roche), 5-hydroxytryptophan (Sigma), haloperidol ('Serenace' injection, Searle), reserpine ('Serpasil' injection, Ciba) and methamphetamine HCl ('Methedrine' injection, Burroughs Wellcome). Maprotiline (MAP), desipramine (DMI), imipramine (IMI), clomipramine (CIMI), chlorpromazine (CPZ), pentobarbitone (PEN) and pargyline (PAR) were dissolved in distilled water while apomorphine (APO) was dissolved in distilled water containing 0.2 *mg/ml* ascorbic acid. Haloperidol (HAL), reserpine (RES) and methamphetamine (MAMP) injection solutions were diluted to required strength with distilled water, L-dihydroxyphenylalanine (L-DOPA) was dissolved in minimal quantity of 0.5 N HCl, neutralised to pH 5 with sodium bicarbonate and diluted to required strength with distilled water while 5-hydroxytryptophan (5-HTP) was dissolved in physiological saline. The doses refer to the forms mentioned. All drugs, except 5-HTP, were administered intraperitoneally while 5-HTP was injected intravenously through the tail vein. In rats, all drugs except MAP, were injected in a volume of 0.2 *ml*/100 *g* body weight while MAP was injected in a volume of 0.5 *ml*/100 *g* body weight. In mice, all drugs were injected in a volume of 0.1 *ml*/10 *g* body weight. Control animals received requisite volume of vehicle intraperitoneally. Unless otherwise stated groups of 10 animals per dose level of the drug were used.

The significance of differences between means was assessed by the Student's unpaired t-test while the ED_{50} was computed by the method of Miller and Tainter (21).

Reserpine-induced ptosis in rats :

The animals received either MAP, DMI, IMI or distilled water (control group) followed 1 hr later by RES. They were tested for ptosis 3 hr after RES injection. Ptosis in each eye was graded according to the method of Lapin (18) as follows : complete ptosis =4 points; more than half closed =3 points; half closed =2 points; less than half closed =1 point; absence of ptosis =0 point. The mean response of both eyes was noted. The maximal mean response for ptosis was 4 points.

Methamphetamine-induced stereotyped behaviour (SB) in rats :

The effect of MAP pretreatment on MAMP induced SB was studied by the method of Costall and Naylor (6). The animals received either MAP, IMI, DMI, HAL or distilled water (control group) followed 30 min later by MAMP. For observation

the animals were placed in individual cages made of wire netting, measuring 30 *cm* x 20 *cm* and 20 *cm* high. They were placed in the observation cages 30 min before drug treatment to allow adaptation to the environment. The intensity of SB was assessed over a 30 sec observation period at 10 min intervals for 4 hr according to the following scoring system : 0 : short lasting period of locomotor activity but no SB; 1 : discontinuous sniffing, constant exploratory activity, 2 : continuous sniffing and small head movements, periodic exploratory activity; 3 : continuous sniffing and small head movements, discontinuous gnawing, biting or licking and very brief periods of locomotor activity and 4 : continuous gnawing, biting or licking, no exploratory activity and occasional backward locomotion.

L–DOPA induced behavioural syndrome in mice :

The method similar to that of Ross *et al.* (28) was followed. The animals received PAR (20 *mg/kg*) followed 4 hr later by either MAP, DMI, IMI or distilled water (control group) and followed 1 hr later by L–DOPA injection. Following the injection of L–DOPA the animals were observed for 1 hr for the presence of following signs: 1) piloerection, 2) salivation, 3) exophthalmos, 4) Straub tail, 5) tremors, 6) excitation and increased motor activity and 7) abduction and extension of the hind limbs. The scoring method followed was similar to that of Rubin *et al.* (29). Each mouse was given one point for each sign and the maximum score for a mouse was 7 points.

5-HTP-induced behavioural syndrome in mice :

The method similar to that of Hyttel and Fjalland (16) was followed. The animals received either MAP, CIMI or distilled water (control group) followed 30 min later by 5–HTP. In the consecutive 15 min the animals were observed for the presence of the following signs: 1) head twitches, 2) excitation, 3) tremor and 4) abduction and extension of the hind limbs. Each animal was given one point for each sign and the maximum score for a mouse was 4 points.

Apomorphine–induced cage climbing behaviour in mice :

Effect of MAP pretreatment on APO–induced climbing behaviour was studied by the method of Costall *et al.* (7). The animals received either MAP, HAL or distilled water (control group) followed 30 min later by APO. For observation the animals were placed in individual Perspex cages measuring 27 *cm* x 20 *cm* and 15 *cm* high. One of the vertical faces was wire netted with 1 cm^2 wire mesh, made of wire 2 *mm* in diameter, for ventila-

tion and to allow climbing. Mice were placed in the observation cages 30 min before drug treatment to allow adaptation to the environment. The animals were individually tested for climbing bahaviour taking 'the percentage of time spent climbing during the 30 min period after the first climb' as a measure of climbing ('climbing index'). Further, the maximum time (in min) spent in a single climb throughout the duration of the apomorphine effect was also recorded.

Conditioned avoidance response (CAR) in rats :

The effect on CAR was studied in trained rats by the technique of Cook and Weidley (4). Both control and drug–treated groups were tested for CAR 30 min after the injection. The drug effect on CAR was expressed as the percentage of animals which failed to climb the pole on hearing the buzzer but did climb the pole in response to the electric shock.

Traction response in mice :

The control and drug–treated groups were tested for the traction response by the method of Courvoisier *et al.* (8) at 60 min time interval after the injection. The response was said to be inhibited when the animal was unable to draw itself up to touch the wire within 5 sec of placement.

Induction of catalepsy in mice:

The animals were tested for catalepsy 60 min after drug injection by placing both front paws on a wooden block 4 cm high and were considered cataleptic if they maintained this posture for atleast 30 sec (1).

Spontaneous motor activity (SMA) in rats:

The technique described by Vad *et al.* (32) was used for recording SMA. Only one animal was placed in the activity cage at a time. After waiting for 10 min to allow the initial excitement to pass away, the vertical movements of the animal were recorded by the lever of the Marey's tambour on a moving kymograph for the next 30 min. The animal was then injected drug or distilled water and was kept aside for 20 min. It was then placed in the activity cage and after 10 min interval, the record was again made for 30 min.

Exploratory behaviour of mice :

Effect on exploratory behaviour was studied by the method of Shillito (30). One control group was always used simultaneously with groups to which various doses of drugs had been adminisered. Mice were placed one at a time on the left hand corner of a wooden board measuring 61 x 61 cm onto which 12 tunnels 7.5 cm long and 4 cm in diameter were fixed arranged in a symmetrical pattern. The tunnels were numbered. Drugs were given 30 min before the observations, while the control group received distilled water. Each mouse was watched for 5 min after it was placed on the board. The number of different tunnels entered in the first minute, the total number of tunnels entered as well as the total number of different tunnels entered during the 5 min observation period by the animal was noted. The experiments were conducted at the same time each afternoon.

Pentobarbitone induced sleep in mice :

The animals received the hypnotic (40 *mg/kg*) or subhypnotic (20 *mg/kg*) dose of PEN 30 min after receiving distilled water (control group) or MAP. The time of loss and recovery of righting reflex was used to determine the duration of sleep. The mean sleeping time with standard error, was determined for each group.

RESULTS

The doses of antidepressants and neuroleptics used in the present study had no effect on the motor co-ordination, muscle tone or righting reflex of the animals.

1. *Effect on reserpine-induced ptosis in rats :*

MAP, DMI and IMI significantly ($P<0.001$) anagonized reserpine-induced ptosis (Table I). While DMI and IMI were equally effective, MAP was significantly ($P<0.01$) less effective than either DMI or IMI in antagonizing reserpine-induced potosis (Table I).

2. *Effect on methamphetamine-induced SB in rats :*

Pretreatment with 10 *mg/kg* dose of IMI and DMI significantly increased the intensity of MAMP stereotypy while MAP (10 and 20 *mg/kg*) like HAL (0.25 *mg/kg*) significantly decreased the intensity of MAMP stereotypy (Table II).

TABLE I : Effect of maprotiline, desipramine and imipramine on reserpine-induced ptosis in rats.

Group	*Treatment dose mg/kg*	*Ptosis score Mean±S.E.M.*	*Statistically compared groups*
1.	Vehicle + RES 5 (30)	3.72±0.04	—
2.	MAP 20 + RES 5 (10)	2.12±0.24	2 vs. 1* 2 vs. 3**
3.	DMI 20 + RES 5 (10)	0.90±0.16	3 vs. 1* 3 vs. 4***
4.	IMI 20 + RES 5 (10)	1.10±0.12	4 vs. 1* 4 vs. 2**

*P<0.001; **P<0.01; ***P>0.05.

Numerals following the drugs indicate their doses (*mg/kg*).

Figures in parenthesis indicate the number of animals.

TABLE II : Effect of maprotiline, imipramine, desipramine and haloperidol on methamphetamine-induced stereotyped behaviour in rats.

Study	*Treatment dose mg/kg*	*Intensity score Mean±S.E.M.*
I	1. MAMP 4	2.4±0.16
	2. IMI 10 + MAMP 4	3.4±0.16*
	3. DMI 10 + MAMP 4	3.2±0.13*
	4. MAP 10 + MAMP 4	1.5±0.16*
	5. MAP 20 + MAMP 4	0.7±0.15**
	6. HAL 0.25 + MAMP 4	0
II	1. MAMP 6	3.6±0.16
	2. MAP 10 + MAMP 6	2.7±0.15*
	3. MAP 20 + MAMP 6	1.6±0.16**
	4. HAL 0.25 + MAMP 6	0.7±0.15**

*P<0.01; **P<0.001. Numerals following the drugs indicate their doses (*mg/kg*).

3. *Effect on L-DOPA-induced behavioural syndrome in mice* :

IMI and DMI, in doses of 10 and 20 *mg/kg*, were equally effective in intensifying the L-DOPA induced behavioural syndrome while MAP in doses of 10 and 20 *mg/kg* decreased the intensity of L-DOPA induced behavioural syndrome in a dose-dependent manner (Table III).

TABLE III : Effect of maprotiline, imipramine and desipramine on L-DOPA induced behavioural syndrome in mice.

Study	Treatment dose mg/kg	Intensity score Mean ± S.E.M
I	1. L-DOPA 100	4.6±0.16
	2. MAP 10 + L-DOPA 100	3.0±0.00*
	3. MAP 20 + L-DOPA 100	2.7±0.15*
II	1. L-DOPA 100	4.5±0.16
	2. IMI 10 + L-DOPA 100	6.0±0.00*
	3. IMI 20 + L-DOPA 100	7.0±0.00*
III	1. L-DOPA 100	4.7±0.15
	2. DMI 10 + L-DOPA 100	6.2±0.13*
	3. DMI 20 + L-DOPA 100	7.0±0.00*

*$P<0.001$. Numerals following the drugs indicate their doses (*mg/kg*).

4. *Effect on 5-HTP induced behavioural syndrome in mice :*

MAP (5-20 *mg/kg*) was ineffective in intensifying the 5-HTP induced behavioural syndrome while CIMI (5-20 *mg/kg*) did intensify it (Table IV).

TABLE IV : Effect of maprotiline and clomipramine on 5-HTP induced behavioural syndrome in mice.

Study	Treatment dose mg/kg	Intensity score Mean ± S.E.M.
I	1. 5-HTP 100	1.5±0.16
	2. MAP 5 + 5-HTP 100	1.6±0.15
	3. MAP 10 + 5-HTP 100	1.7±0.15
	4. MAP 20 + 5-HTP 100	1.4±0.16
II	1. 5-HTP 100	1.6±0.16
	2. CIMI 5 + 5-HTP 100	2.7±0.15*
	3. CIMI 10 + 5-HTP 100	3.7±0.15**
	4. CIMI 20 + 5-HTP 100	4.0±0.00**

*$P<0.01$; **$P<0.001$. Numerals following the drugs indicate their doses (*mg/kg*).

5 *Effect on apomorphine-induced climbing behaviour in mice.*

Pretreatment with MAP (2.5-10 *mg/kg*) and HAL (0.05 and 0.1 *mg/kg*) antagonized APO (*1 mg/kg*)-induced climbing behaviour (Table V).

TABLE V : Effect of maprotiline and haloperidol on apomorphine-induced cage climbing behaviour in mice.

Study	Treatment dose mg/kg	Climbing index (%) Mean±S.E.M.	Maximum time (min) Mean±S.E.M.
I	1. APO 1	74.4±2.2	12.2±0.9
	2. MAP 1.25 + APO 1	72.7±2.9	11.9±0.7
	3. MAP 2.50 + APO 1	44.2±2.7*	6.4±0.6*
	4. MAP 5.00 + APO 1	20.4±3.2**	2.7±1.1**
	5. MAP 10.0 + APO 1	0.0±0.0	0.0±0.0
II	1. APO 1	72.9±2.7	12.1±0.7
	2. HAL 0.05 + APO 1	7.5±3.2**	1.1±0.9**
	3. HAL 0.10 + APO 1	0.0±0.0	0.0±010

*P<0.01. **P<0.001. Numerals following the drugs indicate their doses (*mg/kg*).

6. *Effect on CAR in rats :*

The ED_{50} of MAP for inhibiting the CAR was 14.13 *mg* ± 0.44 while those of CPZ and HAL were 4.07 *mg* ± 0.14 and 0.38 *mg* ± 0.02 respectively. DMI upto 40 *mg/kg* body weight was inactive in inhibiting the CAR.

7. *Influence on traction response in mice :*

The ED_{50} of MAP for inhibiting the traction response was 18.75 *mg* ± 0.64 while those of CPZ and HAL were 5.62 *mg* ± 0.31 and 0.69 *mg* ± 0.04 respectively. DMI and IMI upto 40 *mg/kg* body weight were inactive in inhibiting the traction response.

8. *Induction of catalepsy in mice :*

MAP at 2.5 *mg/kg* dose did not induce catalepsy while at doses of 5 and 10 *mg/kg* it induced catalepsy in 50% and 100% of the animals respectively. DMI and IMI upto 20 *mg/kg* dose did not induce catalepsy while HAL (0.25 *mg/kg*) induced catalepsy in 100% of the animals tested.

9. *Effect on spontaneous motor activity (SMA) in rats :*

MAP at a dose of 2.5 *mg/kg* did not affect the SMA. However, an increase in dose to 5 *mg/kg* slightly, reduced the SMA and a further increase in dose to 10 *mg/kg*

reduced the SMA markedly. DMI had no effect on SMA in the dose range (2.5-10 *mg/kg*) studied. CPZ at a dose of 2 *mg/kg* reduced the SMA markedly.

10. *Effect on exploratory behaviour of mice :*

MAP (2.5 *mg/kg*) and DMI (2.5 - 10 *mg/kg*) did not significantly affect the exploratory behaviour. However, MAP (5 and 10 *mg/kg*) and CPZ (2 *mg/kg*) did significantly decrease the exploratory behaviour of mice. The number of different tunnels entered during the first min and during the 5 min of observation period and the total number of tunnels entered during the 5 min period was significantly lower than that of their respective control group (Table VI).

TABLE VI : Effect of maprotiline, desipramine and chlorpromazine on the exploratory behaviour of mice.

Study	*Treatment dose mg/kg*	*Total number of different tunnels entered during the first min (mean±S.E.M.)*	*Total number of different tunnels entered during the 5 min period (mean±S.E.M.)*	*Total number of tunnels entered during the 5 min period (mean±S.E.M.)*
I	1. Control	2.1±0.10	7.2±0.44	16.2±0.89
	2. MAP 2.5	2.0±0.00	7.1±0.39	15.9±0.97
	1. Control	2.2±0.13	7.0±0.28	16.1±0.77
	2. DMI 2.5	2.2±0.13	7.2±0.42	16.0±0.74
II	1. Control	2.1±0.10	7.4±0.37	15.9±0.92
	2. MAP 5	1.2±0.13*	5.7±0.29*	12.4±0.72*
	1. Control	2.2±0.13	7.3±0.41	15.7±0.64
	2. DMI 5	2.0±0.00	7.1±0.37	15.8±0.75
III	1. Control	2.1±0.10	7.4±0.42	16.4±0.77
	2. MAP 10	0.9±0.10*	4.2±0.24*	10.7±0.69*
	1. Control	2.0±0.00	7.2±0.36	16.2±0.75
	2. DMI 10	1.8±0.13	7.3±0.38	16.1±0.64
IV	1. Control	2.2±0.13	7.2±0.43	16.2±0.77
	2. CPZ 2	0.7±0.15*	3.7±0.22*	10.2±0.65*

*Significant in relation to corresponding controls ($P < 0.05$ or less).

Numerals following the drugs indicate their doses (*mg/kg*).

11. *Effect on pentobarbitone sleep in mice :*

Pretreatment with MAP (10 and 20 *mg/kg*) not only significantly prolonged pentobarbitone (40 *mg/kg*) sleeping time but also induced sleep in mice treated with a subhypnotic (20 *mg/kg*) dose of pentobarbitone (Table VII).

TABLE VII : Effect of maprotiline pretreatment in mice treated with a hypnotic and subhypnotic dose of pentobarbitone.

Group	*Dose and route (mg/kg, ip)*	*n*	*Number of animals which slept*	*Sleeping time in min Mean±S.E.M.*
I	PEN 40	20	20	47.4±2.79
II	MAP 10+PEN 40	10	10	74.9±3.22*
	MAP 20+PEN 40	10	10	92.4±3.42*
III	PEN 20	40	0	0
IV	MAP 10+PEN 20	20	18**	9.2±0.74
	MAP 20+PEN 20	20	20**	12.7±0.52

n= Number of animals used. Numerals following the drugs indicate their doses *(mg/kg)*.

*The statistical significance of differences between means was calculated by Student's unpaired t–test. Group II is compared with Group I; $P<0.001$.

**Results analysed by Fisher's exact test. Group IV is compared with Group III; $P<0.001$.

DISCUSSION

The antidepressant activity of a drug is conventionally evaluated by testing its ability to antagonize or reverse reserpine-induced behavioural and autonomic effects, potentiate amphetamine responses, or the signs of excitation induced by L-DOPA in mice pretreated with a MAO inhibitor or the 5-HTP induced behavioural syndrome. A drug is evaluated for neuroleptic activity by testing its ability to antagonize methamphetamine or apomorphine stereotypy, inhibit the CAR and traction response, decrease the SMA and exploratory behaviour, induce the catalepsy and potentiate, the hypnotic effect of barbiturates (9, 14).

Our observation that maprotiline, though effective in anatagonizing reserpine–induced ptosis, was however, less effective than imipramine and desipramine, concurs with the findings reported by Baltzer *et al.* (2) and Benesova *et al.* (3).

Methamphetamine–induced SB results from activation of postsynaptic striatal and mesolimbic DA receptors by the released DA and is antagonized by postsynaptic DA receptor blockers like haloperidol (27, 33). Our observation that maprotiline, unlike imipramine

and desipramine but like haloperidol, decreased the intensity of methamphetamine stereotypy can be readily explained on the basis of the recent report of Delini–Stula and Vassout (10) that maprotiline possesses postsynaptic striatal DA receptor blocking activity. Further more, our observation that maprotiline like haloperidol antagonized apomorphine–induced climbing behaviour which occurs as a result of direct stimulation of postsynaptic striatal DA receptors by apomorphine and is antagonized by DA receptor blockers like haloperidol (7, 25), supports the contention of Delini–Stula and Vassout (10), that maprotiline possesses postsynaptic striatal DA receptor blocking activity, and helps to explain the anatagonism of methamphetamine stereotypy by maprotiline. Our finding that maprotiline antagonizes apomorphine–induced stereotyped climbing behaviour in mice confirms the observation of Olpe (23) Similarly our observation that imipramine and desipramine increase the intensity of methamphetamine stereotypy concurs with that of Simon and Lwoff (31).

In the past, potentiation of the L–dopa induced behavioural syndrome by the tricyclic antidepressants was related to their ability to block the neuronal reuptake of noradrenaline (11). However, recently it has been reported that administration of L–dopa predominantly increases the brain DA levels (13) and the potentiation of L–dopa induced behavioural syndrome by the anti–depressants is now co–related with their ability to inhibit the neuronal reuptake of DA (9, 22, 26). Though maprotiline in high doses inhibits the neuronal reuptake of DA (26), it is likely that at the doses used in the present study its postsynaptic DA receptor blocking activity might have manifested with resultant antagonism of the L–dopa–induced behavioural syndrome.

The potentiation of 5–HTP induced behavioural syndrome by clomipramine is attributed to its ability to inhibit the neuronal reuptake of 5–HT (16, 28). As reported (16, 28), clomipramine did potentiate the 5–HTP induced behavioural syndrome while maprotiline proved ineffective. Our finding with maprotiline confirms the report of Maitre *et al.* (20) that maprotiline is practically ineffective in inhibiting the neuronal reuptake of 5–HT.

CAR is a DA–mediated response (5) and the inhibition of CAR by neuroleptics like haloperidol, has been attributed to blockade of post–synaptic striatal DA receptors (17). Catalepsy is attributed to a lack of DA at postsynaptic striatal DA receptors and neuroleptics induce catalepsy by blocking postsynaptic striatal DA receptors (15). Our findings, on maprotiline antagonizing methamphetamine stereotypy and apomorphine–induced climbing behaviour, taken together with those of Olpe (23) and Delini–Stula and Vassout (10), suggest that maprotiline exerts postsynaptic DA receptor blocking activity. Thus it was expected to, and indeed was found to inhibit CAR in rats and to induce catalepsy in mice. Further, the traction response in mice and the SMA and exploratory behaviour of rodents, which is selectively inhibited by the DA receptor blockers (8, 14), was also inhibited by maprotiline.

The prolongation of pentobarbitone sleeping time by maprotiline is probably not mediated through interference with the metabolism of barbiturate as it was also found to induce sleep in mice treated with a subhypnotic dose of pentobarbitone. We suggest that maprotiline, by blocking the postsynaptic DA receptors (10), decreases the activity of the nigrostriatal and mesolimbic DA-ergic systems involved in cortical activation and behavioural arousal (12) and thus sensitizes the CNS to the depressant action of pentobarbitone with resultant potentiation of pentobarbitone hypnosis.

In conclusion, on the basis of our results, we suggest that maprotiline possesses postsynaptic striatal DA receptor blocking activity and exhibits activity profile resembling the neuroleptics.

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