Psychopharmacology 60, 1–11 (1978)

Psychopharmacology

Original Investigations

Dopaminergic Supersensitivity After Neuroleptics: Time-Course and Specificity

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Abstract. It is known that a single dose of a neuroleptic can elicit dopaminergic supersensitivity in animals. On the other hand, the clinical syndrome of tardive dyskinesia takes many months or years to develop. To resolve this apparent discrepancy, it is possible that subclinical or latent tardive dyskinesia is fully compensated in most patients taking neuroleptics. In others, where the tardive dyskinesia is full-blown and grossly apparent, the dopaminergic supersensitivity may be decompensated. Such compensatory and decompensatory phases have been proposed earlier by Hornykiewicz (1974), in the case of Parkinson's Disease.

Dopaminergic supersensitivity persists for a period proportional to the length of the neuroleptic treatment. It is not yet clear whether the relation between the length of treatment and the persistence of supersensitivity holds for very long treatments, but in principle the relationship might account for the persistence of tardive dyskinesia after years of neuroleptic pretreatment.

Key words: Tardive dyskinesia – Dopamine receptors – Stereotypy

Time-Course of Development of Dopaminergic Supersensitivity

There appears to be a correlation between the time-course of development of tolerance to a neuroleptic with the rate of development of dopaminergic supersensitivity. For example, according to Ezrin-Waters and Seeman (1977), tolerance of catalepsy to haloperidol develops rapidly over the first five days and then develops more slowly. While the development of this tolerance may to some extent be accounted for by learning from test to test, it correlates well with the rate of development (Lerner and Nosé, 1977; Asper et al., 1973) of dopaminergic supersensitivity.

Although the time-course of development of dopaminergic supersensitivity has received some attention, there is little or no information on the rate of development of dopamine/neuroleptic receptors in the first days of neuroleptic treatment. For example, Christensen et al. (1976) reported an increase in sensitivity to apomorphine-induced stereotypies within a day or two after single injection of chlorpromazine or haloperidol; similar results were reported on climbing behavior by Costentin et al. (1977) and Martres et al. (1977). However, detailed information on the time-course of development of the receptor alterations after repeated neuroleptic administration has not yet been reported. The shortest treatment schedule hitherto reported was by Burt et al. (1977), who treated rats with haloperidol for 7 days and then withdrew them for five days. By that time it was found that the ^{3}H-haloperidol receptors had already achieved their maximum increase (Table 1).

This rapid development of dopaminergic supersensitivity in animals (albeit at massive doses) is faster than the rate of development of tardive dyskinetic symptoms in patients. This is one of the main reasons why Tarsy and Baldessarini (1977) feel that neuroleptic-induced dopaminergic supersensitivity (in animals) may not be an appropriate model for tardive dyskinesia.

According to Crane (1973), the development of tardive dyskinesia within the first 6 months of treatment is unusual and most of the patients with tardive dyskinesia developed their symptoms after neuroleptic treatment for one year or more. Tarsy and Baldessarini (1977) suggest, therefore, that the dopaminergic supersensitivity seen after repeated neuroleptic treatment of animals is a better model for acute dyskinesia. This dyskinesia appears within 2–5 days after the initiation of the neuroleptic treatment (Fig. 1).

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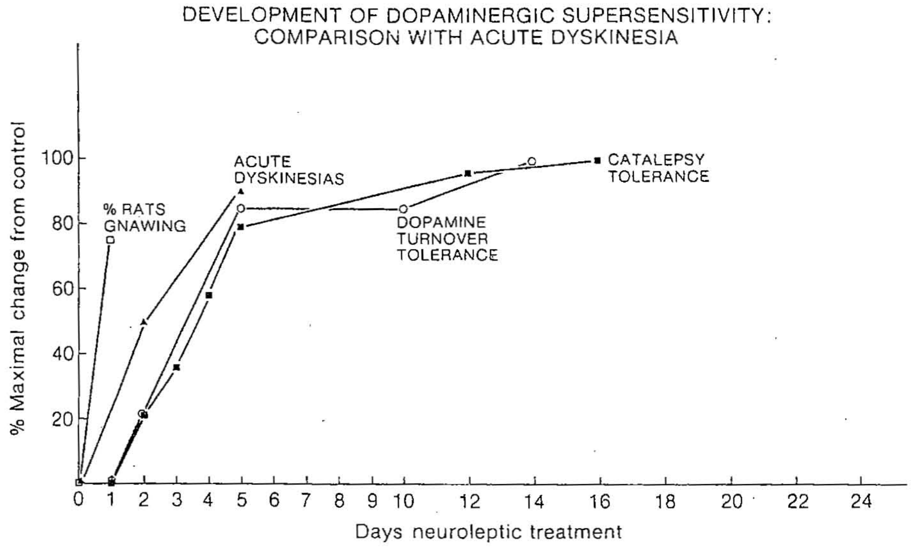

Fig. 1. Time-course of dopaminergic supersensitivity. Maximal observed change from the control was taken as 100%. Rat gnawing: Christensen et al. (1976). Acute dyskinesias: Marsden et al. (1975). Turnover tolerance: Lerner and Nosé (1977). Catalepsy tolerance: Ezrin-Waters and Seeman (1977)

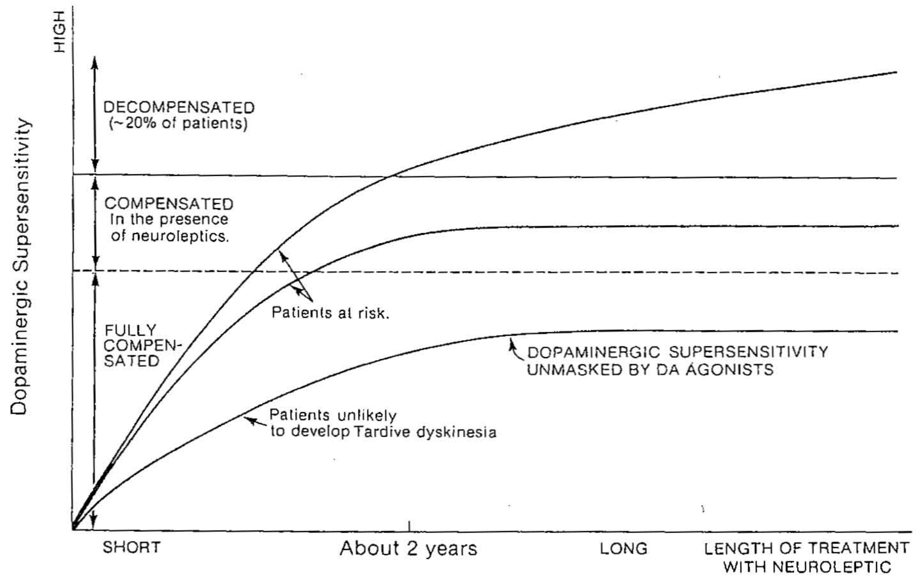

Fig. 2. Compensation of dopaminergic supersensitivity in tardive dyskinesia – a model. Decompensated dopaminergic supersensitivity leads to spontaneous appearance of dyskinetic symptoms. Dopaminergic supersensitivity compensated in the presence of neuroleptics will be clinically dormant until neuroleptics are discontinued or dose is lowered. Fully compensated dopaminergic supersensitivity could be precipitated by dopamine agonists or anticholinergic drugs

In order to demonstrate behavioural dopaminergic supersensitivity in rats which have received long-term neuroleptics, it is necessary to challenge them with either dopamine-mimetic drugs or anticholinergic drugs (Tarsy and Baldessarini, 1974; Gianutsos and Lal, 1976). This is because such rats do not spontaneously show stereotypy. Similarly, many patients on long-term neuroleptics may not spontaneously exhibit any obvious dyskinetic signs in the early stages. Such patients may have a latent or subclinical dyskinesia which is fully compensated by certain adaptations in the brain (see Fig. 2).

This suggestion of a *latent compensated form* of tardive dyskinesia is analogous to the early compensated phase of Parkinson's Disease, as proposed by Hornkiewicz (1974). In this early stage of Parkinson's Disease, it is thought that the dopaminergic cell loss is counterbalanced by several compensatory changes in

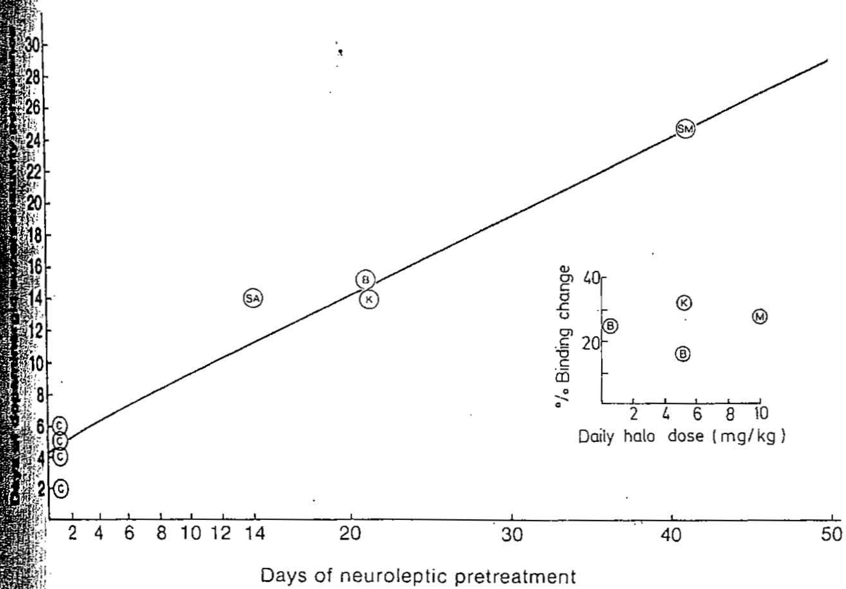

Fig. 3. Correlation of the persistence of dopaminergic supersensitivity with length of neuroleptic pretreatment. *C.*: Christensen et al. (1976), stereotypy. *S.A.*: Sayers et al. (1975), turning. *B.*: Burt et al. (1977), neuroleptic binding. *K.*: Kobayashi et al. (1978), neuroleptic binding. *S.M.*: Smith et al. (1976), stereotypy. *Inset:* correlation of the daily dose with maximal neuroleptic binding increase over controls, Muller and Seeman (1977)

neurotransmitter function. Thus, in order to unmask the latent dyskinesia, it is necessary to challenge acutely with L-Dopa or to block any cholinergic compensations by anticholinergic drugs. It seems reasonable to think that such compensatory mechanisms would effectively mask the latent tardive dyskinetic state for many months or years. Thus, the apparent discrepancy in time-course between the onset of dopaminergic supersensitivity, which is a matter of days or weeks, and the onset of frank dyskinesia, which is a matter of months or years, may be accounted for by these compensatory mechanisms.

Dissipation of Neuroleptic-Induced Dopaminergic Supersensitivity and of Tardive Dyskinesia

It has been stated that tardive dyskinesia may be irreversible or poorly reversible (Crane, 1973), although others report dissipation of the dyskinesia within several months (Quitkin et al., 1977). On the other hand, dopaminergic supersensitivity (in rats) induced by about a month's treatment with neuroleptics disappears within 2–4 weeks after withdrawal (Fig. 3).

According to Crane (1973), tardive dyskinesia symptoms are either irreversible or very poorly reversible. Early withdrawal after the dyskinetic symptoms are first observed improves the prognosis (Crane, 1973; Quitkin et al., 1977). When patients are under continuous or frequent medical observation (Quitkin et al., 1977) and withdrawn within a median time of 1 month,

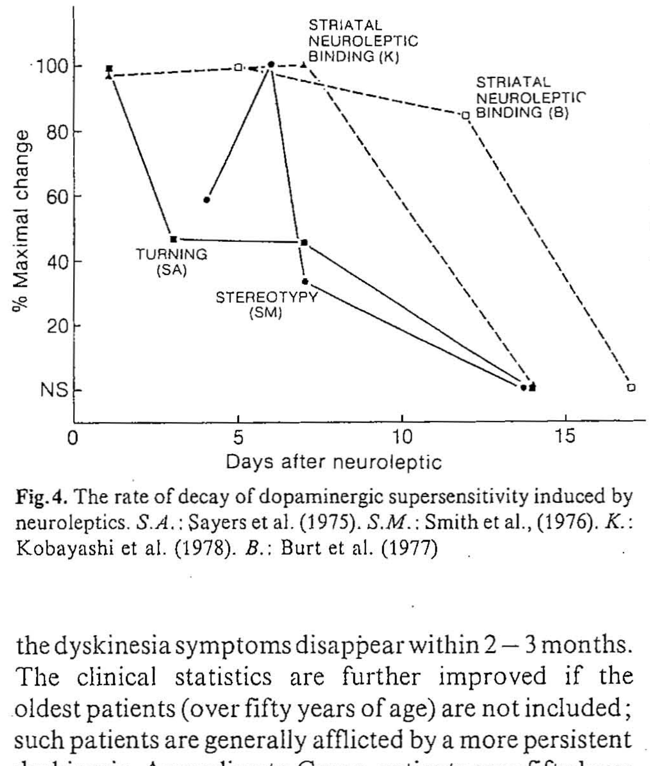

Fig. 4. The rate of decay of dopaminergic supersensitivity induced by neuroleptics. *S.A.*: Sayers et al. (1975). *S.M.*: Smith et al., (1976). *K.*: Kobayashi et al. (1978). *B.*: Burt et al. (1977)

the dyskinesia symptoms disappear within 2–3 months. The clinical statistics are further improved if the oldest patients (over fifty years of age) are not included; such patients are generally afflicted by a more persistent dyskinesia. According to Crane, patients over fifty have poorer prognosis in the reversal of tardive dyskinesia.

These observations suggest that tardive dyskinesia is considerably reversible, particularly in young patients. Similar observations on a different time scale are observed in the neuroleptic-treated rodents (Fig. 4). The result in Fig. 4 shows that the length of time needed for reversal of dopaminergic supersensitivity appears to correlate with the duration of neuroleptic administration, regardless of the type and dose of neuroleptic employed, and regardless of the type of supersensitive property monitored.

Dose-Dependency in Long-Term Neuroleptic Treatment

The experiments with chronic neuroleptic showed little dose-dependency (Fig. 3, inset). It is probable that the effect could be dose-dependent at lower neuroleptic concentrations. Interestingly, according to Crane (1973), no consistent dose-dependency can be demonstrated for the incidence of tardive dyskinesia.

Effects of Long-Term Neuroleptic Treatment on Dopamine Receptors (Table 1)

Soon after the development of the ^{3}H-haloperidol assay method for neuroleptic/dopamine receptors (Seeman et al., 1975; Burt et al., 1975), Muller and Seeman reported that these receptors increased after long-term neuroleptic treatment (Muller and Seeman, 1976; Burt et al., 1977). This has been recently more fully examined (Kobayashi et al., 1978; Muller and Seeman, 1977; Burt et al., 1977; Friedhoff et al., 1977). The maximum increase appears to be around 30% for the ^{3}H-neuroleptic receptor (striatum) and about 65% for the ^{3}H-apomorphine sites. This increase is characteristic for all neuroleptics studied, except for clozapine in the study by Kobayashi et al. (1978). Clozapine has generally yielded conflicting results. Chronic treatment with this drug resulted in stimulated locomotion (Smith and Davis, 1976; Gianutsos and Moore, 1977) and stereotypy in the hands of Smith and Davis (1976) but not of Gnegy et al. (1977). Chronic clozapine pretreatment had no effect on dopamine turnover (von Stralendorff et al., 1976; Gianutsos and Moore, 1977) in different brain areas, but large decreases of dopamine turnover after long-term clozapine was observed in the striatum and the olfactory tubercle (Gianutsos and Moore, 1977). There was also no effect on the adenylate cyclase (Gnegy et al., 1977).

The increase in locomotor behaviour after repeated neuroleptics suggests that dopaminergic supersensitivity occurs in the mesolimbic areas. Locomotion has been shown to be associated primarily with the mesolimbic rather than striatal dopaminergic system (Jackson et al., 1975a, b; Costall and Naylor, 1975; Pijnenburg et al., 1976; Creese and Iversen, 1974). Jackson et al. (1975a) have shown that long-term penfluridol potentiates the locomotor response to dopamine administered to the nucleus accumbens but not to the striatum. These results are supported by our findings (Fig. 5) of dopaminergic supersensitivity in the mesolimbic areas. Klawans et al. (1977) did not show a

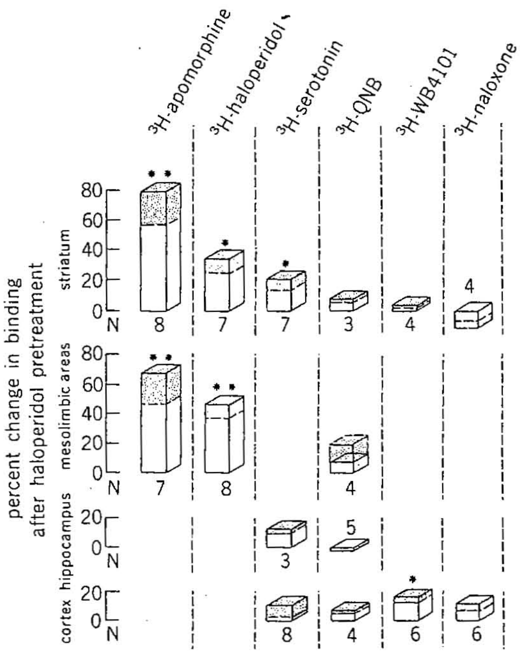

Fig. 5. Percentage changes in neurotransmitter receptors (rat brain regions) following long-term haloperidol treatment (10 mg/kg/day for at least 3 weeks). *Height of the bars:* mean percentage change. *Shaded portion:* SEM. The number of completely independently-assayed membrane preparations (from 2 to 15 rats per preparation) used in each experiment (N) is indicated below each bar (* $P < 0.05$; ** $P < 0.02$, using Wilcoxon's rank test). Long-term haloperidol treatment selectively increased the dopamine/neuroleptic binding without significant effects on acetylcholine receptors (^{3}H-QNB), alpha-adrenergic receptors (^{3}H-WB-4101), or opiate receptors (^{3}H-naloxone)

significant increase in ^{3}H-dopamine binding to the limbic areas, even though the results show a large trend towards such increase. Tolerance to catalepsy after repeated neuroleptic administration was demonstrated by some, but not others (Table 1).

Effects of Long-Term Nonneuroleptic Drugs on Dopamine Transmission

From the drugs summarized in Table 2, opiates are the drugs closest to neuroleptics in terms of their effect on the dopaminergic system after repeated administration. Tolerance to the cataleptic effects as well as to dopamine turnover occurs with both opiates and neuroleptics (Gessa and Tagliamonte, 1975).

Reports of cross tolerance between neuroleptics and opiates have been published (Puri and Lal, 1974; Ezrin-Waters and Seeman, 1977), even though the two studies do not agree whether the cross tolerance is one-way or two-way. Acutely, both opiates and neuroleptics induce catalepsy, even though there are differences in appearance of the animal, as well as different pathways involved (Costall and Naylor, 1973); furthermore,

Table 3. The effect of chronic administration of neuroleptics on non-dopaminergic neurotransmission

% Δ	Drug/dose/day	R_x	W	Assay conditions	References
Noradrenaline:					
NS	Chlorpromazine 5 mg/kg i.p.	7 d	3 d	adenylate cyclase limbic	Dolphin et al. (1977)
60%	Chlorpromazine 5 mg/kg i.p.	7 d	3 d	adenylate cyclase limbic; 100 μM NA	Dolphin et al. (1977)
NS	Chlorpromazine 5 mg/kg i.p.	7 d	3 d	clonidine-locomotion	Dolphin et al. (1977)
167%	Haloperidol 3 mg/kg i.p	3 wks	4 d	clonidine-locomotion	Dustan and Jackson (1978)
113%	Haloperidol 10 mg/kg p.o.	3 wks	2 d	cx 1 nM WB-4101 ± 1 μM phenox.	Muller and Seeman (1977)
NS	Haloperidol 10 mg/kg p.o.	3 wks	2 d	st 1 nM WB-4101 ± 1 μM phenox.	Muller and Seeman (1977)
Serotonin:					
100%	Chlorpromazine 30 mg/kg i.p.	4 d	18 h	locomotion with L-tryptophan	Heal et al. (1976)
NS	Haloperidol 10 mg/kg i.p.	5 d	3 d	locomotion with L-trypophan	Heal et al. (1976)
NS	Spiroperidol 1 mg/kg i.p.	4 d	18 h	locomotion with L-trypophan	Heal et al. (1976)
120%	Haloperidol 10 mg/kg p.o.	3 wks	2 d	st 3 nM 5-HT ± 100 nM	Muller and Seeman (1977)
NS	Haloperidol 10 mg/kg p.o.	3 wks	2 d	hippo 3 nM 5-HT ± 100 nM 5-HT	Muller and Seeman (1977)
NS	Haloperidol 10 mg/kg p.o.	3 wks	2 d	cx 3 nM 5-HT ± 100 nM 5-HT	Muller and Seeman (1977)
Acetylcholine:					
NS	Haloperidol 3 mg/kg i.p.	3 wks	4 d	benztropine-locomotion	Dustan and Jackson (1976)
−17%	Haloperidol 3 mg/kg in water	3 wks	4 d	reserpine-blocked locomotion	Dustan and Jackson (1977)
266%	Haloperidol 3 mg/kg in water	2 wks	4 d	atropine-locomotion	Dustan and Jackson (1977)
58%	Haloperidol 2.5–10 mg/kg i.p.	24 d	3–5 d	pilocarp-blocked locomotion	Gianutsos and Lal (1976)
73%	Haloperidol 2.5–10 mg/kg i.p.	3 wks	3–5 d	dexetimide-locomotion	Gianutsos and Lal (1976)
NS	Haloperidol 5 mg/kg i.p.	3 wks	14 d	st 1 nM QNB ± 1 μM atrop.	Kobayashi et al. (1978)
NS	Haloperidol 10 mg/kg p.o.	3 wks	2 d	st 1 nM QNB ± 100 nM scop.	Muller and Seeman (1977)
−31%	Haloperidol 5 mg/kg i. p.	3 wks	14 d	hippo 1 nM QNB ± 1 μM atrop.	Kobayashi et al. (1978)
NS	Haloperidol 5 mg/kg i.p.	3 wks	1–7 d	hippo 1 nM QNB ± 1 μM atrop.	Kobayashi et al. (1978)
NS	Haloperidol 10 mg/kg p.o.	3 wks	2 d	hippo 1 nM QNB ± 0.1 μM scop.	Muller and Seeman (1977)
NS	Haloperidol 10 mg/kg p.o.	3 wks	2 d	mli 1 nM QNB ± 0.1 μM scop.	Muller and Seeman (1977)
NS	Haloperidol 10 mg/kg p.o.	3 wks	2 d	cx 1 nM QNB ± 0.1 μM scop.	Muller and Seeman (1977)
GABA:					
NS	Haloperidol 5 mg/kg i.p.	3 wks	1–14 d	st 10 nM GABA ± 0.5 nM GABA	Kobayashi et al. (1978)
NS	Haloperidol 5 mg/kg i.p.	24 d	3–5 d	hippo 10 nM GABA ± 0.5 μM GABA	Kobayashi et al. (1978)

there are biochemical differences (Kuschinsky and Hornykiewicz, 1972; Leysen et al., 1977) as well as pharmacological differences (Ezrin-Waters et al., 1976). Both groups of drugs block amphetamine-induced stereotypy (Sasame et al., 1972) as well as increase dopamine turnover (Ahtee and Kaariainen, 1973). Chronic neuroleptic treatment does not produce any significant change in the striatal or cortical naloxone binding (Fig. 5). The morphine pretreatment profile also differs from the neuroleptic profile in that morphine does not produce supersensitivity to apomorphine (Table 2).

Long-term neuroleptic treatment consistently elevates ^{3}H-neuroleptic receptors (Table 1); dopamine-sensitive adenylate cyclase, however, is inconsistently altered (Table 1; Burkard and Bartholini, 1974).

Of the other drugs reviewed, the only drug showing some similarity to neuroleptics is ethanol. It causes stimulation of locomotion (Table 2), but there is no evidence of ethanol-induced dopaminergic supersensitivity. Phenobarbital, diazepam, promethazine, and (-)-butaclamol also do not produce dopaminergic supersensitivity.

The tolerance in dopamine turnover (striatum) after neuroleptics has been noted by several labs with one exception (Puri and Lal, 1974); there is no agreement on whether such tolerance occurs in the limbic areas. Moreover, the degree of tolerance in turnover is of comparable magnitude to the increase in ^{3}H-neuroleptic receptors.

Chronic administration of dopamine agonists (amphetamine, L-Dopa or bromocryptine) induce apparent dopaminergic 'behavioural-facilitation', as monitored by stereotypy (Klawans and Margolin, 1975; Klawans et al., 1977; Fuxe et al., 1973). Chronic treatment with these agonists produces tolerance to their acute dopamine-turnover-reducing effect. This agrees with our proposal that chronic agonist pretreatment produces dopaminergic subsensitivity of dopaminergic autoreceptors and thus produces apparent behavioural dopaminergic facilitation (Muller and Seeman, in preparation).

We have found that the binding of ^{3}H-apomorphine in the striatum is reduced in the chronically apomorphine- or amphetamine-treated rat, while the ^{3}H-haloperidol sites (displaceable by a low concentration of pimozide) is not altered by the same pretreatment. Apomorphine is thought to have some predilection for presynaptic sites (Carlsson, 1975) and pimozide prefers postsynaptic receptors (Gianutsos et al., 1976; Walters and Roth, 1976). We thus interpret the drop in ^{3}H-apomorphine sites as a reduction in autoreceptors after repeated administration of amphetamine and apomorphine. The findings of Burt et al. (1977) and Friedhoff et al. (1977) did not detect changes after chronic agonist pretreatment, possibly because their methods did not distinguish between pre- and postsynaptic binding.

Effects of Long-Term Neuroleptics on Nondopaminergic Transmission

Several studies indicate that there may be a possible noradrenergic supersensitivity following repeated neuroleptic administration (Table 3). Dolphin et al. (1977) report supersensitivity of the limbic adenylate cyclase to 10 μM noradrenaline while the baseline adenylate cyclase activity was unchanged by the treatment. Stimulation of locomotion with clonidine was more pronounced in the study of Dustan and Jackson (1976), but not in that of Dolphin et al. (1977). We have reported an increase in alpha-adrenergic receptors in the rat cortex but not in the striatum (Muller and Seeman, 1977; Fig. 5). Such a possible noradrenergic supersensitivity might be due to blockade of noradrenergic receptors by neuroleptics (U'Prichard et al., 1977; Andén et al., 1970; Keller et al., 1973).

Chronic neuroleptic treatment does not potentiate the locomotor response to L-tryptophan. Of the neuroleptics studied by Heal et al. (1976), chlorpromazine was the only one which caused apparent behavioural supersensitivity to L-tryptophan. In our binding studies, ^{3}H-serotonin binding was increased in the striatum but not in the cortex or hippocampus after repeated haloperidol treatment. Since we saw the same effect in the striatum of rats treated chronically with ethanol, we think that the neuroleptic-induced increase in the striatal binding might not be a specific effect (Muller and Seeman, 1977).

Table 3 shows no consistent changes in the cholinergic or GABA sites after repeated haloperidol administration. The apparent cholinergic hyposensitivity of the cholinergic system reported by Gianutsos and Lal (1976) could be accounted for by an increase in tonic dopaminergic action, thus swinging the cholinergic-dopaminergic balance towards dopamine even if the sensitivity of the cholinergic system remained unchanged.

Acknowledgements. Supported by the Ontario Mental Health Foundation and the Medical Research Council of Canada.

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Received February 24, 1978