

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 ³H-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 dyskinesic 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).

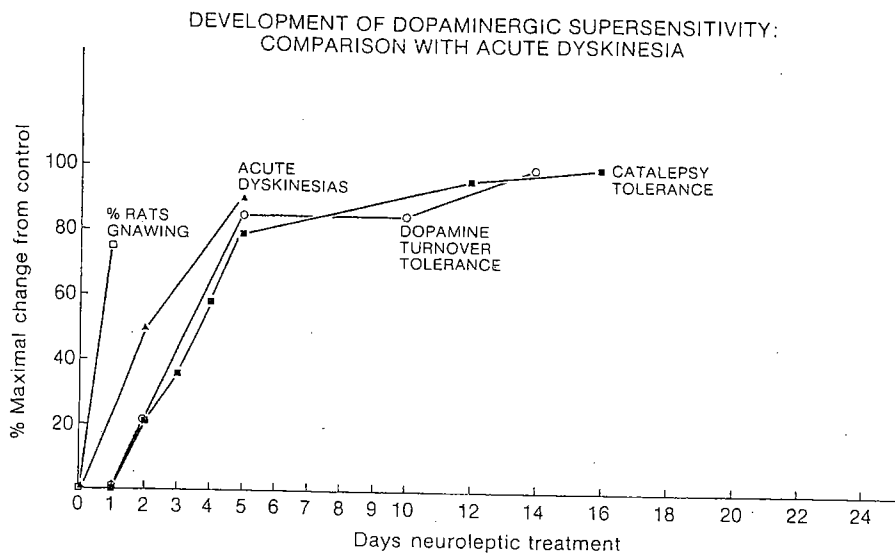


Fig. 1. Time-course of dopaminergic supersensitivity. Maximal observed change from the control was taken as 100%. Rat gnawing: Christensen et al. (1976). Acute dyskinesias: Marsden et al. (1975). Turnover tolerance: Lerner and Nosé (1977). Catalepsy tolerance: Ezrin-Waters and Seeman (1977)

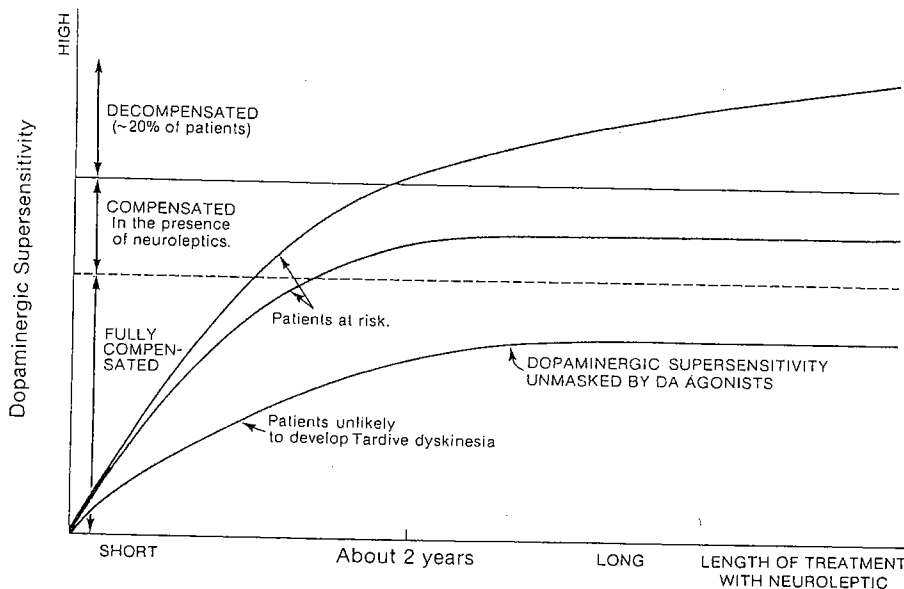


Fig. 2. Compensation of dopaminergic supersensitivity in tardive dyskinesia — a model. Decompensated dopaminergic supersensitivity leads to spontaneous appearance of dyskinetic symptoms. Dopaminergic supersensitivity compensated in the presence of neuroleptics will be clinically dormant until neuroleptics 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

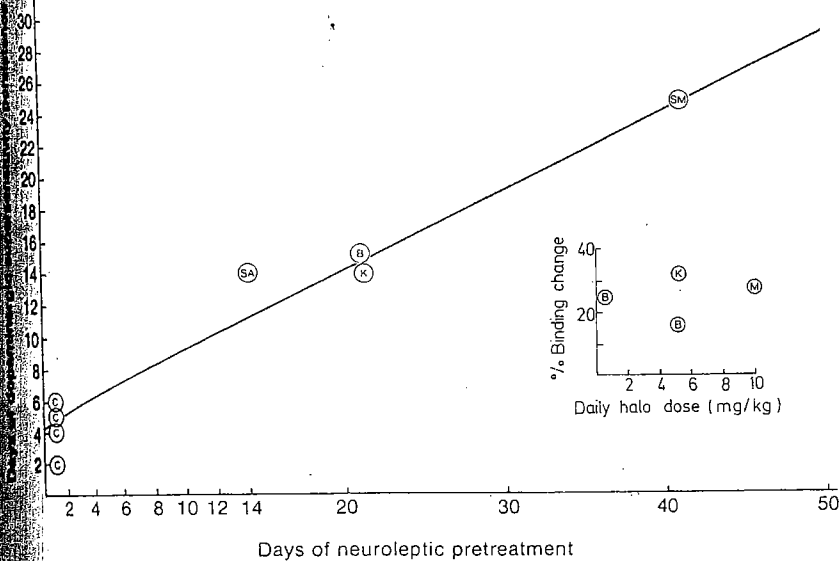


Fig. 3. Correlation of the persistence of dopaminergic supersensitivity with length of neuroleptic pretreatment. C.: Christensen et al. (1976), stereotypy. S.A.: Sayers et al. (1975), turning. B.: Burt et al. (1977), neuroleptic binding. K.: Kobayashi et al. (1978), neuroleptic binding. S.M.: Smith et 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,

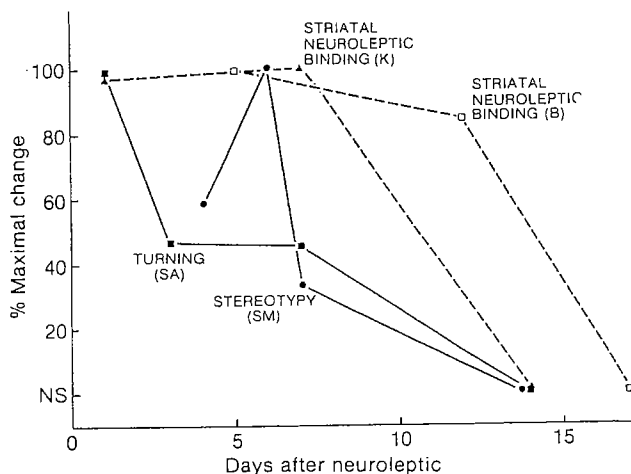


Fig. 4. The rate of decay of dopaminergic supersensitivity induced by neuroleptics. S.A.: Sayers et al. (1975). S.M.: Smith et al., (1976). K.: Kobayashi et al. (1978). B.: Burt et al. (1977)

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

