Tardive Dyskinesia, Dopamine Receptors, and Neuroleptic Damage to Cell Membranes

PHILIP SEEMAN, MD, PhD, FRSC

Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada

The long-term treatment of schizophrenic patients with neuroleptics is associated with neuroleptic accumulation in neuromelanin-containing cells with ensuing nigral cell damage. Thus, in addition to early or short-term up-regulation of D₂ dopamine receptors, the late stage denervation supersensitivity may result in a further proliferation of D₂ dopamine receptors in those parts of the human striatum controlling mouth-lips-tongue motion. Young individuals, upon reduction or removal of the neuroleptic, may have neural sprouting with subsequent D₂ down-regulation and reversal of their dyskinesia. Older individuals may not readily exhibit sprouting and D₂ down-regulation, possibly accounting for a more persistent form of dyskinesia. (J Clin Psychopharmacol 1988;3S–9S)

The antipsychotic action of neuroleptic drugs appears to be mediated by their selective action on D₂ dopamine receptors. Although some neuroleptics also block D₁ dopamine receptors, this D₁-blocking action is not related to the clinical antipsychotic dose. Positron tomography indicates that the antipsychotic action is accompanied by D₂ blockade but not by D₁ blockade.

Elevated D₂ in Psychosis

The density of D₂ receptors is elevated in the postmortem brains from schizophrenics, although it has been suggested that this elevation may be a result of medication. The density of D₂ receptors is also seen to be elevated threefold in living schizophrenics never treated with neuroleptics, as measured by positron tomography, using N-[¹¹C] methylspiperone and using the haloperidol-blocked region as baseline. Using [¹¹C]raclopride and using cerebellum as baseline, however, in schizophrenics never treated with neuroleptics, Farde and coauthors found no difference in the putamen D₂ densities between control subjects (23.9 pmol/g) and schizophrenics (24.4 pmol/g). The high control density of 23.9 pmol/g, however, is well outside the normal putamen D₂ range of 13.5 ± 0.3 pmol/g as measured in vitro for 188 different putamens. It is important to note that the in vitro and in vivo D₂ densities are the same for rat striatum.

All studies agree, however, that D₂ receptors are elevated in the striata of neuroleptic-medicating patients or animals. Long-term neuroleptics generally raise D₂ receptors by 35% (range, 10% to 65%) in animals and about 35% in patients with Alzheimer’s and Huntington’s diseases. Thus, although there is evidence that psychotic (both schizophrenic and manic-depressive) patients never treated with neuroleptics have more D₂ receptors, possibly accounting for their positive psychotic features (hallucinations or delusions), it is important to consider the possible pathological mechanisms that may result in the neuroleptic-induced component of the extra D₂ receptors.

Neuroleptic Affinity for Melanin

It has long been known that neuroleptics have a considerable avidity for binding to all of the various forms of melanin, including neuromelanin. The dissociation constants of the neuroleptics for melanin are within an order of magnitude of those that block D₂ receptors, as indicated in Table 1.

Although it is known that neuromelanin synthesis in the pigmented substantia nigral neurones is different from melanin synthesis elsewhere (e.g., albinos have normal pigmented nigral cells), the high content of neuromelanin in nigral neurones would retain considerable neuroleptic during long-term neuroleptic treatment. The neuroleptic-neuromelanin complex would...
TABLE 1. Dissociation constants of neuroleptics for D₂ dopamine receptors and melanin

<table>
<thead>
<tr>
<th></th>
<th>K (nM) at D₂ (Ref. 21)</th>
<th>K (nM) for melanin (Refs. 22, 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluphenazine</td>
<td>0.2</td>
<td>77</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1.2</td>
<td>65</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>3</td>
<td>2.6</td>
</tr>
<tr>
<td>Clozapine</td>
<td>86</td>
<td>65</td>
</tr>
</tbody>
</table>

eventually become a "depot" source of neuroleptic, which would be released at a high molarity within the cell or near the cell membrane. It would be reasonable to expect neuroleptic concentrations on the order of 100 to 1000 nM within the cell, as discussed elsewhere.²⁵

**Neuroleptic Damage to Cell Membranes**

Because neuroleptics are highly surface-active²⁶ and readily accumulate in cell membranes,²⁵, ²⁷ they expand and invaginate cell membranes.²⁷, ²⁸ This action may be seen not only in simple erythrocytes,²⁸ but also in corneal cells,²⁹ where the invagination ultimately leads to a myelin-like figure composed of a neuroleptic-membrane complex. Such myelin-like figures are also seen in the caudate nucleus in postmortem tissue from patients who had received long-term neuroleptics.³⁰

Thus, it appears that prolonged administration of neuroleptics may result in the accumulation of neuroleptics within two types of cell organelles—neuromelanin granules (or deposits) and neuroleptic-myelin figures. This process is depicted in Figure 1.

The long-term accumulation of neuroleptics may result in local concentrations high enough to damage cell membranes with the possible ensuing death of the entire nigral cell. It is known that such neuroleptic-induced nigral cell damage occurs in rat striata,³¹ as well as in postmortem human tissues from patients who had tardive dyskinesia (TD).³² Reduced size of the basal ganglia has also been measured in tardive dyskinetic patients.³³ This type of cellular pathology may also occur in the skin.³⁴ The skin, however, has regenerative abilities that nigral cells do not.

Although non-neuroleptics such as imipramine also bind to neuromelanin,³⁵ the membrane-binding³⁶ and membrane-lytic properties of imipramine are much weaker than those of neuroleptics.²⁶

**Dopaminergic Supersensitivity after Long-Term Neuroleptics**

TD is most simply explained by dopaminergic supersensitivity resulting from nigral cell damage by long-term neuroleptics with various degrees of ensuing denervation supersensitivity in the striatal regions controlling oral and other motions. Although this dopaminergic basis for TD has been questioned³⁷-³⁹ and defended,⁴⁰ the majority of evidence is consistent with such a hypothesis, as follows.

**Neuroleptic-induced behavioral dopaminergic supersensitivity**

It has long been known that prolonged treatment of animals with neuroleptics elicits behavioral supersensitivity to dopamine agonists.⁴¹ ⁴² Further work needs to be done to determine whether those animals demonstrating nigral damage have prolonged behavioral supersensitivity.
Neuroleptic- and lesion-induced elevation of dopamine receptors

Virtually all neuroleptics given in high doses for long periods of weeks, months, or years will induce elevated densities of D₂ receptors. Randall and associates found that mice of all ages, when treated with long-term neuroleptics, subsequently exhibited behavioral dopaminergic supersensitivity in direct relation to the striatal density of D₂ receptors.

As mentioned previously, the postmortem striata from schizophrenic patients have elevated densities of D₂ receptors. However, striata from six schizophrenic patients who died with a movement disorder revealed the same elevated densities of D₂ receptors as did tissue from six patients who did not have a movement disorder. It is important to emphasize that not all striatal regions containing D₂ receptors are able to proliferate D₂ receptors after dopaminergic denervation. Denervation-induced elevation of D₂ receptors is restricted to the ventral and dorsolateral regions of the striatum. Because the human striatum is not homogeneous but undoubtedly contains “mouth-motion” regions, “neck-motion” regions, and so forth, it will be essential to examine the D₂ densities in large slices of postmortem human striata.

In the human striatum, long-term neuroleptics elevate the D₂ density by about 25%. Such striata from neuroleptic-treated schizophrenic patients exhibit significantly more D₂ receptors in the right striatum, consistent with the observation that such patients exhibit more TD on the left side of the face. Furthermore, schizophrenics whose neuroleptic medication has been discontinued for over 26 weeks also rotate to the left, consistent with extra D₂ receptors in the right striatum.

Such additional detailed anatomical resolution will also be essential in measuring D₂ receptors by means of positron tomography. For example, Barrio and coauthors did not find any elevation in D₂ receptors in nigral-lesioned (by 1-methyl-4-phenyl-tetrahydropyridine [MPTP]) monkeys using positron tomography, although in vitro studies in such MPTP-lesioned monkeys show a 25% elevation in D₂ density.

Factors determining starting time of TD: species, dose, and age

It has been argued that there is a discrepancy between the time course of neuroleptic-induced elevation of D₂ receptors in animals (about 1 to 2 weeks) and the time course of development of human TD (generally 6 months to 2 years before onset). However, there appear to be two types or stages of neuroleptic-induced elevations of D₂ receptors.

The early stage would occur in the first few weeks of neuroleptic administration when little nigral damage occurs. Extra D₂ receptors synthesized during this time would be expected to disappear upon withdrawal of the neuroleptic. The late stage of neuroleptic administration would be when the neuroleptic dose had sufficiently accumulated to cause nigral damage with ensuing denervation supersensitivity. Such stages of D₂ elevation are consistent with the work of Staunton and associates, who found that the extra D₂ receptors induced by neuroleptics and by lesions were additive.

Thus, TD may be considered as the late stage, because it is associated with cell damage. However, a few weeks of neuroleptic administration to rats may be considered as being that of the early stage with little if any cell damage.

The total dose is an important risk factor. Thus, patients typically receiving 0.25 mg/kg of haloperidol daily for their psychosis would be expected to take longer to accumulate toxic levels of neuroleptic in their nigral neuromelanin compared with rats taking 5 mg/kg/day.

Rat nigral neuromelanin may have substantively different properties than human nigral melanin in accumulating high levels of neuroleptics. There is little if any information on this topic.

Age is a very important risk factor in the development of TD, as well as in its reversibility. Thus, it is difficult to compare the human age and neural plasticity with the rat age and plasticity.

Reversibility of TD in the young

The majority (76% to 87% or more) of patients with TD, particularly the younger ones, improve or lose their dyskinesia upon reduction or removal of neuroleptics. As mentioned above, younger individuals would have more neural plasticity and neuronal sprouting such as to result in down-regulation of D₂ receptors.

Prevalence of TD in relation to D₂ receptors

Although the prevalence of TD may range from 25% to 45% in the schizophrenic population, some groups of schizophrenics may have a prevalence of 68% or more. In addition to total neuroleptic dose and age (see previous sections above), an important factor determining prevalence is whether the patient is taking neuroleptics at the time of neurological assessment. Latent dyskinesia becomes overtly manifest upon removal of the D₂ blockade by the neuroleptic.

Thus, although all rats may exhibit elevated D₂ densities after long-term neuroleptics, not all patients may...
have had sufficient nigral damage to their mouth-motion regions to yield 100% prevalence of TD.

Estrogen and dopamine receptors

It is known that women, particularly postmenopausal women, are at greater risk for TD than are men.70–74 This is consistent with the neuroleptic-like features of estrogens.71, 75 It is possible that the combined neuroleptic-estrogen action in the premenopausal phase may result in somewhat more nigral damage, but this has not been investigated.

TD blocked by D2-selective neuroleptics

Although weak in absolute potency, sulpiride and the related benzamides are known to be selective in blocking D2 receptors.13, 76 Thus, the effective blockade of dyskinesia in both animals and patients by sulpiride,77–81 by oxipermid,81, 82 or by tiapride83, 84 strongly supports the key role of D2 in mediating the dyskinesia. Compared with all other neuroleptics, sulpiride has the highest selectivity for D2. This selectivity is illustrated by its low dissociation constant of 18 nM for D2,85 and its high dissociation constants for other receptors (between 7000 and 54,000 nM for alpha-adrenoceptors, and over 100,000 nM for beta-adrenoceptors).76 Objections have been previously raised39 that neuroleptics may block TD by blocking both dopamine receptors and adrenoceptors. The D2-selective action of these benzamides, however, largely overcomes these objections.

TD improves upon dopamine depletion

The alleviation of TD by dopamine-depleting drugs further suggests a supersensitive dopamine system in this syndrome.86–88

Down-regulation of dopamine receptors

Dopamine agonists down-regulate D2 receptors and appear to reduce TD in about 24% to 50% of patients.89–92 Although this is consistent with dopaminergic supersensitivity as a basis for TD, other workers93 found little effect of such agonist therapy (using L-dopa).

Improvement of TD via down-regulation of beta-adrenoceptors

A significant number of patients with TD improve on antidepressant drugs or other forms of antidepressant treatment.94–102 Because virtually all modes of antidepressant treatment are known to down-regulate beta-adrenoceptors, and because the beta-adrenoceptors enhance the release of dopamine, such beta-adrenoceptor down-regulation would be expected to reduce the spontaneous or impulse-triggered release of dopamine, alleviating the dyskinetic state (Fig. 2).

Role of dopamine autoreceptors

TD and related disorders are slightly to moderately improved by low doses of dopamine agonists that act on dopamine autoreceptors to reduce the release of dopamine.103–105

In conclusion, although dopaminergic supersensitivity appears to be a consistent component in TD, other neurotransmitters, such as noradrenaline94–102 or GABA,106–114 may well contribute to the overall syndrome. The general features of neuroleptic accumulation, cell membrane damage, and dopaminergic supersensitivity have been previously outlined.115
References


4. Seeman P. Dopamine receptors and the dopamine hypothesis of schizophrenia. Synaphe 1987;1:133–52.


16. Lindquist NG, Ullberg S. The melanin affinity of chloroquine and chlorpromazine studied by whole body autoradiography. Acta Pharmacol Toxicol 1972;31(suppl 1)1:1–32.


