126

CLINICAL COURSE AND CELLULAR PATHOLOGY OF TARDIVE DYSKINESIA

CAROL A. TAMMINGA MARGARET G. WOERNER

Tardive dyskinesia (TD) is an iatrogenic human hyperkinetic movement disorder associated with chronic antipsychotic drug treatment. The cause of the syndrome, namely, chronic dopamine-receptor blockade, is specifically known and is straightforward to model. Thus, disease pathophysiology has been approached with surrogate preparations. Traditionally, factors mediating TD have been sought in striatal dopaminergic transmission. However, several incompatibilities have developed between the characteristics of the dopaminergic model and the presentation of the disorder (10). y-aminobutyric acid (GABA)-ergic transmission within the basal ganglia has also been targeted as the putative pathophysiologic agent in TD. Here, although biochemical characteristics between the model and the disease have appeared compatible, therapeutic implications have not been fully met, possibly because of inadequate pharmacologic tools (10).

Research has suggested that both these transmitter alterations, dopaminergic and GABAergic, may reflect an action of antipsychotic drugs on neuronal activity within the basal ganglia thalamocortical motor circuit. Clinically, antipsychotic drug action overall tends to normalize mental status in psychosis and produces symptom remission in diverse psychotic illnesses, including schizophrenia, bipolar disease, and dementia (8); parkinsonism characteristically occurs with traditional antipsychotics as a major side effect (42). On a cellular basis, gradual alterations produced by these drugs over time, within selected subcortical brain regions and at selected synapses of this circuit, likely result in TD. The mechanism of all these clinical actions is thought to begin with dopamine-receptor blockade, but thereafter it is critically mediated by altered neuronal activity (including GABAergic) in gray matter regions in the segregated, parallel frontal-subcortical modulatory motor circuits (35).

CLINICAL FEATURES AND COURSE OF TARDIVE DYSKINESIA

The presentation of TD is typical of a dyskinesia, with orofacial, axial, and extremity hyperkinetic movements. The movements worsen with stress and concomitant physical activity and diminish or disappear during sleep. TD onset is defining, in that all dyskinesias with their first onset within 6 months of ongoing antipsychotic treatment are diagnosed as TD (50). Consequently, it is expected that the diagnosis will be confounded by other categories of dyskinesia, including dyskinesias of schizophrenia and of the elderly. TD is distinguished from parkinsonism, the other major category of antipsychotic-induced movements, by being hyperkinetic, with delayed onset and delayed resolution after medication discontinuation, and by its contrasting pharmacology.

Movements in TD are typically suppressed by antipsychotic drugs, and they are suppressed or even show remission with potent GABA agonists; dopamine agonists exacerbate the movements, as can anticholinergic drugs (11). Although TD has a characteristic pharmacology, none of the drugs that suppress movements in probe studies are potent enough to be used as a treatment (36). Treatment approaches for TD are discussed later.

Although TD risk is inevitable with the traditional antipsychotics, the risk appears to have dropped significantly with the second-generation antipsychotic drugs, including clozapine, olanzapine, and risperidone, with which reduced risk has been demonstrated (38,63,66), and with quetiapine, with which reduced risk is probable. Therefore, even though TD may be diminishing as a significant clinical risk with modern antipsychotic treatment, its study has enabled

Carol A. Tamminga: Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, Maryland.

Margaret G. Woerner: Department of Psychiatry Research, Hillside Hospital, Long Island Jewish Health System, Glen Oaks, New York.

Neuroleptic Exposure (y)	Tardive Dyskinesia Cumulative Incidence, (95% CI)	Persistent Tardive Dyskinesia, (85% CI) Cumulative Incidence	Tardive Dyskinesia Hazard Rate ^a
1	.05 (.04–.07)	.03 (.02–.04)	_
5	.27 (.23–.31)	.20 (.17–.23)	6.1%
10	.43 (.38–.47)	.34 (.30–.39)	4.7%
15	.52 (.46–.57)	.42 (.36–.47)	3.3%
20	.56 (.50–.63)	.49 (.41–.57)	2.1%

TABLE 126.1. CUMULATIVE INCIDENCE OF TARDIVE DYSKINESIA

^aHazard Rate is the rate of tardive dyskinesia occurrence per year among those remaining at risk. The number represents the average yearly hazard rate over the 5-year block of time.

identification of cellular and circuit determinants of dyskinesias in mammalian brain.

The clinical course of TD varies by psychiatric diagnosis, age, sex, and concomitant medical or neurologic illness. Data from a prospective study of 971 young adult psychiatric patients followed for up to 20 years indicated a increasing cumulative incidence rate of TD over the 20-year interval (Table 126.1). The cumulative incidence of persistent TD was lower but increased proportionally (40). These data are consistent with a declining rate of TD over time, illustrated by the declining hazard rate (Table 126.1). A similar pattern develops in the hazard rate over 20 years for persistent TD. A decline in hazard rate over time was also reported by Morganstern and Glazer (46), although their data show a sharper decline after the first 5 years.

Rates of TD are significantly affected by the age and other characteristics of the several samples studied. An increased vulnerability to TD associated with increasing age is the most consistently reported finding in TD research. A prospective study of 261 geriatric patients with a mean age of 77 years revealed cumulative rates of 25%, 34%, and 53% after, 1, 2, and 3 years of antipsychotic drug treatment (74). Similar findings were reported by Jeste et al. (37) and by Yassa et al. (75). In the younger adult sample (40), the hazard rate for TD was lowest for patients in their twenties and thirties at study entry, increased for those in their forties, and sharply increased for those aged 50 to 60 years.

Other variables associated with a significantly increased TD risk in the prospective study (Table 126.1) included the presence of extrapyramidal symptoms during antipsychotic treatment, diagnosis of unipolar depression, the number of peaks in dosage of antipsychotic drug (more than 1,000 mg in chlorpromazine equivalents), and intermittent antipsychotic treatment. Treatment with lithium is associated with a lower risk of TD development.

In this prospective study of 971 psychiatric patients (Table 126.1), the initial episode of TD was persistent for at least 3 months for half of the cases. Of these persistent cases, 68% remitted within the next 2 years. For the half whose initial episode was transient, there was a high risk (32%) of developing a persistent episode within 1 year of

additional antipsychotic exposure. Regardless of the duration of the initial TD episode, if it remitted, there was a high likelihood (61%) of developing a second episode within 1 year.

Preliminary data suggest that prognosis for TD remission is better for patients who are treated for shorter times within the follow-up period after TD diagnosis and for those treated with lower doses of antipsychotic during follow-up (41). These facts about TD encourage future study in animals and humans on TD mechanisms and treatment and facilitate the research by providing a firm baseline and a clear description of course.

FUNCTIONAL HUMAN NEUROANATOMY OF ANTIPSYCHOTIC DRUG ACTION

The human central nervous system (CNS) has been the focus of studies to determine the mechanism of antipsychotic drug action with both acute and chronic antipsychotic drug administration. These antipsychotic data are relevant to TD mechanisms insofar as the localization of the neural pathways subserving antipsychotic drug action can suggest the regions that likely contain the neurochemical disorder underlying TD. The firm association between striatal dopamine-receptor blockade and antipsychotic drug action was established early and has been consistently confirmed in subsequent study (4,7,53). It has been suggested that antipsychotic drugs deliver their full antipsychotic action by blocking the D2 dopamine receptors in limbic cortex (25,54). Alternatively, as argued here, antidopaminergic drugs could deliver their antipsychotic action by altering activity in neuronal populations within the long-loop feedback neurons in the basal ganglia thalamocortical pathways, at least in part, thereby modulating neocortical activity indirectly. The mechanisms responsible for TD may well occur at sites within these modulatory pathways.

Early investigators observed an elevation of neuronal activity in the human caudate and putamen with antipsychotic drug treatment using functional *in vivo* imaging (33, 69). To refine the localization of the signal, our laboratory



FIGURE 126.1. The regions of color indicate quantitatively the areas of regional cerebral blood flow (rCBF) activation (ON-30 day OFF) or inhibition (30 day OFF-ON) with subchronic haloperidol treatment (0.3 mg/kg/day). In the top two figures, at -04 and 00 mm from the anterior commisure/posterior commissure line (ACPC) plane, the basal ganglia show significant rCBF activation with haloperidol. In the bottom two figures, at -04 and +04 mm from the ACPC plane, both the anterior cingulate cortex and the middle frontal cortex show significant diminished rCBF with haloperidol. See color version of figure.

conducted a within-subject crossover study comparing haloperidol (0.3 mg/kg/day for 4 weeks) to placebo (0 mg/kg/ day for 4 weeks), with a positron emission tomography scan using [¹⁸F]fluorodeoxyglucose carried out at the end of each treatment period (35). Regional cerebral metabolic rates of glucose, calculated using the usual analytic techniques, were used for pixel-by-pixel regional comparisons. Haloperidol significantly activated neuronal activity in the basal ganglia (caudate and putamen) and thalamus, whereas the frontal cortex (especially the middle and inferior regions) and the anterior cingulate cortex demonstrated a reduction in regional cerebral metabolic rates of glucose with haloperidol (Fig. 126.1). Activational differences between the on-drug and off-drug conditions were surprisingly restricted to these areas, despite the systemic manner of drug delivery and steady-state kinetic conditions at testing. The striatal changes had been previously reported (6,68). Subsequent evaluation of haloperidol action using regional cerebral blood flow analysis pharmacodynamically verified these regional actions.

The regions identified in the foregoing experiment, whose activity is perturbed by haloperidol, are the same

ones already known to be connected within the basal ganglia thalamocortical pathway (15) and involved in modulation of motor and cognitive function (2). In an animal preparation, Abercrombie and DeBoer demonstrated the principle that a pharmacologic perturbation delivered to a restricted region in the basal ganglia (e.g., striatum) can exert distant neurochemical and functional effects (1). The model of antipsychotic drug action we propose suggests that a primary effect of dopamine-receptor blockade occurs in the caudate and putamen with antipsychotic drug treatment, and the transmission of this primary action through the basal ganglia thalamocortical pathway to limbic and neocortex mediates antipsychotic and motor aspect of the drug actions in humans. The full mechanism of antidopaminergic actions therefore could include altered GABAergic transmission in the globus pallidus (GP), which alters activity in the basal ganglia output nuclei; these changes then modify GABAergic transmission from substantia nigra pars reticulata (SNR) to the thalamus, inhibit thalamic nuclei, and reduce the overall excitatory glutamatergic signal to the cortex. These observations suggest the hypothesis that the same basal ganglia thalamocortical circuits that mediate basal ganglia modulatory influence on prefrontal cortex may also mediate the therapeutic effect of antidopaminergic antipsychotic compounds in schizophrenia. We have reasoned that a drug-induced regional change, occurring over time within this basal ganglia-thalamocortical pathway, associated with a regional increase in the thalamocortical signal could be associated with TD.

ROLE OF THE BASAL GANGLIA THALAMOCORTICAL PATHWAY IN MEDIATING AND TRANSMITTING THE ANTIDOPAMINERGIC ACTION IN STRIATUM TO CORTEX

Basal ganglia and thalamic structures modulate functions of the frontal cortex through parallel segregated circuits, a process that has been most fully studied for motor function. This topic is directly addressed in Chapter 122. For the CNS motor system, specific areas of primary motor cortex, primary sensory cortex, and supplementary motor cortex project topographically to the putamen. These projections are thought to remain segregated but parallel throughout the full course of the circuit, but they are subject to basal ganglia and thalamic influences within each region. Investigators have proposed a family of these frontal circuits whose pathways originate in specific frontal cortex areas, course through the basal ganglia and thalamus, and return to the same areas of cortex, to modulate regional frontal cortical function (3). For the motor system, these subcortical structures appear to contribute to the planning and execution of body movements; for other frontal systems, these same subcortical structures may contribute to maintenance and switching of behaviors and aspects of cognition (2,26).

The thalamus exerts an excitatory effect on frontal cortex pyramidal cell activity, partially delivered within each frontal region by the paired parallel segregated circuit. The basal ganglia output nuclei with their high rates of spontaneous discharge keep their own target nuclei of the thalamus under tonic GABAergic inhibition. These inhibitory output nuclei stimuli are, in turn, regulated by two parallel but opposing pathways from the caudate and putamen, one excitatory and the other inhibitory. The primary cortical signal to basal ganglia is mediated by an excitatory glutamatergic pathway. It would be rational to suspect some role of these parallel segregated motor circuits in antipsychotic drug–induced dyskinesias, as well, especially because the primary action of antipsychotic drugs is D2 dopamine-family–receptor blockade in striatum.

ANIMAL MODELS OF TARDIVE DYSKINESIA

The cause of TD in antipsychotic drug-treated patients is, by definition, long-term drug treatment. Thus, putative

models of the condition have been developed in nonhuman primates and in small animals using long-term administration of antipsychotics and applied to the study of TD mechanisms. The structural and functional brain characteristics of nonhuman primates are reasonably similar to those of human primates; hence, primate preparations may make more valid TD models (9). Yet, it is the reality of nonhuman primate models that many treatment years are required for dyskinesia development (2 to 6 years), and monkey care is involved and expensive. Alternatively, putative rat models have also been proposed; rat oral dyskinesias develop faster with chronic treatment (6 to 12 months), yet they retain many phenomenologic and pharmacologic characteristics of human TD (61,70). These models often provide a more realistic experimental platform, even if not more valid, than the nonhuman primate for developing hypotheses about human TD.

Animal models of all human diseases have been sought for pursuing pathophysiologic hypotheses and for identifying new therapeutics. Investigators have suggested the characteristics of good animal models for an expressed human illness as similarities in (a) origin, (b) phenomenology, (c) biochemical characteristics, and (d) pharmacology (45,73). Similarities of these features provide greater validation of the model. Across all the TD models, both primate and rodent, origin and phenomenology approximate characteristics of human TD. Biochemical determinants are unknown for the TD models as well as for the disease itself. However, extensive similarities exist in pharmacologic response between the human illness (TD) and the model preparations. Because rodent models are more practical to pursue, their pharmacology has been more broadly described than the primate model. It would be obvious to suggest that the use of both rat and monkey models would be ideal, as the efficiency and specificity of the questions dictate.

Nonhuman Primate Models

Antipsychotic treatment in the nonhuman primate has been studied to define the mechanism of acute drug-induced parkinsonism and of chronic drug-induced TD (22,31). Gunne et al. (28,31) showed not only the partial penetration of the syndrome in the nonhuman primate, but also differences in glutamic acid decarboxylase synthesis, the rate-limiting synthetic enzyme for GABA, and GABA levels in GP and SNR between drug-treated monkeys with and without the dyskinesia. Based on these data, Gunne et al. proposed that the mechanism of TD involved a reduction in GABAergic transmission in these regions of the basal ganglia, GP, and SNR. This idea correlated with the known clinical pharmacology of TD, namely, that GABA agonist treatment can improve drug-induced dyskinesias (65).

Rodent Models

Results from many laboratories suggested that rats treated chronically with traditional antipsychotics (e.g., fluphenazine, haloperidol) exhibit seemingly involuntary, irregular, and purposeless oral chewing movements (CMs) over time, often called vacuous chewing movements (13,16,18,23,27,30, 56,61). The phenomenology of CMs resembles TD, in that movements have a gradual onset (61), partial penetrance (34), and a delayed offset, and they are sensitive to stress (49). However, the movements in rats remain limited to the oral region and rarely extend to other body parts. The pharmacology of CMs resembles that of TD: CMs are suppressed by antipsychotics, but not by anticholinergics (52); they are reduced by GABAmimetics (20), and they are attenuated with benzodiazepines. Rat CMs are associated with molecular and cellular changes in CNS histology, including an increase in perforated synapses in striatum and an alteration in relative synaptic number in striatum (47). Administration of the antipsychotic on an irregular schedule can advance the onset and severity of the rat CMs (24). The similarities across phenomenology and pharmacology are close enough between human TD and rat CMs for investigators to pursue the biochemical basis of CMs as a clue to pathophysiology in TD. Moreover, the pharmacology of the two are similar enough for the use of this model as a screen for new antipsychotic drugs to rule out TD potential.

Early pharmacologic studies in the rodent preparation reported that although all traditional antipsychotics are associated with CMs (70,71), clozapine is not (19,27). Subsequently, the other "new" antipsychotics have been tested and have generated results consistent with clinical data, demonstrating low TD potential for the second-generation antipsychotics (29,39). Neither olanzapine nor sertindole produce the CM syndrome at drug doses that produce human therapeutic plasma levels in the animals (21); risperidone at low doses is not associated with CMs, whereas high doses produce haloperidol-like CMs (Gao, unpublished observations). Data using quetiapine or ziprasidone in this animal model have not been reported.

NEUROCHEMICAL CHANGES WITHIN THE BASAL GANGLIA THALAMOCORTICAL PATHWAYS IN A RODENT MODEL OF TARDIVE DYSKINESIA

We designed and carried out a series of studies in a putative rodent model of TD based on the broadly accepted, functional architecture of the basal ganglia and thalamus already described. These studies were based not only on the existence of these theoretic models, but also on early experimental data in nonhuman primates with chronic antipsychotic treatment implicating GABAergic transmission in TD (30, 31). The drug- and time-induced changes in GABAergic transmission in nonhuman primate basal ganglia directly affected the output nuclei, and from there, the thalamic and frontal regions associated with the segregated motor circuit.

With chronic (6 months) haloperidol treatment, some but not all laboratory rats acquired hyperkinetic oral CMs over time (61,63). In comparison, the newer antipsychotics, including clozapine, olanzapine, sertindole, and low-dose risperidone, failed to induce the rat "syndrome" of CMs (21,39). Can these preparations contribute to knowledge of TD pathophysiology? Can they contribute unique information to the mechanism of antipsychotic drug action? Comparison of several different animal treatment groups has been useful in addressing these questions: (a) haloperidol-treated rats, *with* versus *without* rat CMs and (b) haloperidol-treated rats versus newer antipsychotic drug-treated rats.

Chronic haloperidol induces similar D2-receptor up-regulation in striatum in the CM compared with the non-CM rat (Fig. 126.2), a finding discouraging consideration of this feature as a correlate of the CMs. Antipsychotic drugs block the inhibitory D2 receptor and disinhibit the medium spiny neuronal projections to the GP. In these studies, striatal disinhibition is reflected in the glutamic acid decarboxylase mRNA increases in GP, especially in the CM rats (Table 126.2). At the same time, activity in the direct striatonigral pathway appears also to be altered possibly by the haloperidol-induced increase in dopamine release in striatum and its action there on the unblocked D1 receptor (12). In the SNR, a primary basal ganglia output nuclei in the rat, ab-



FIGURE 126.2. Specific binding of ³H-spiperone to D2-family dopamine receptors in the nucleus accumbens of control and chronically haloperidol-treated rats. D2 binding data were similar in the caudate and putamen. Significant dopamine-receptor up-regulation was apparent in the haloperidol-treated rats with chewing movements (CMs) and in those without CMs; there was no apparent difference between CM and non-CM rats in the magnitude of increase. *p < .05.

	Haloperidol	Haloperidol	Olanzapine,	Sertindole,
	+ VCMs	– VCMs	no VCMs	no VCMs
Striatum	D_2 R, GAD	D_2 R, GAD	S1 ↑D₂R No ∆ GAD	No $\Delta D_2 R$ $\uparrow GAD$
Globus pallidus	↓GAD,	No ∆ GAD,	No ∆ GAD	No ∆ GAD,
	↓GABA _A R	No ∆ GABA₄R	No ∆ GABA₄R	↓GABA₄R
Substantia nigra	∱GABA _A R	Tr ↑GABA _A R∆	NI, GABA _A R	NI, GABA _A R ₁
pars reticulata	↓D₁R	No ∆ D₁R	No Δ D ₁ R	No Δ D ₁ R
MD thalamus	↑GABA _A R GABA _A R/ VCM correlation	No Δ GABA _A R No correlation	No Δ GABA _A R No correlation	No Δ GABA _A R No correlation
Right thalamus	∱GAD mRNA	[↑] GAD mRNA	∱GAD mRNA	∱GAD mRNA

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arrow, significant change; D₁R, D₁ family dopamine receptor; D₂R, D₂ family dopamine receptor; GABA_AR, GABA_A receptor; GAD, glutamic acid decarboxylase mRNA; Tr, trend; VCMS, vacuous chewing movements.

normalities also occur. Here the CM rats show reduced nigral D1-receptor numbers, whereas the non-CM treated rats show no change in D1-receptor density (Fig. 126.3). Moreover, this CM-associated receptor change in SNR is blocked (along with the CMs) by concomitant chronic treatment with the GABA agonist progabide (Fig. 126.3), a finding strengthening the association between altered SNR D1 receptors and CMs (45). The reduction in D1-receptor number in SNR could be associated with an antipsychoticinduced increase in the dendritic release of dopamine (Fig. 126.4). D1 receptors in SNR mediate the release of GABA. Hence, an increase in dopamine release within SNR could mediate the release of GABA at striatonigral terminals and subsequently could inhibit activity in the GABA-mediated



FIGURE 126.3. Specific binding of 3H-SCH23390 to D1-family dopamine receptors in the substantia nigra pars reticulata (SNR). D1 binding was down-regulated by chronic haloperidol (HAL) treatment only in the rats that displayed the vacuous chewing movements (CMs). This reduction was blocked by the GABA agonist progabide (P), as were the CMs themselves. Progabide alone had no effect on the D1 binding. *p < .05.

efferent pathway to thalamus. A reduction in GABA-mediated transmission from SNR to the target nucleus in the thalamus could produce a compensatory up-regulation of thalamic GABA_A receptors, hence marking altered SNR activity. In the haloperidol-treated animals, a significant elevation of GABA_A receptor occurred, and a significant correlation developed between the elevated receptor number and CMs in the mediodorsal thalamus (Fig. 126.5). This positive correlation implicates a nigral D1 defect along with an overinhibition of the nigrothalamic efferent GABAergic pathway as an important mediator of CMs in rat (56). The idea that a reduction in the activity of the basal ganglia output nuclei disinhibits the thalamus and is associated with drug-induced rat hyperkinetic oral CMs is consistent with the already established functional models of these interactions (2).

Two second-generation antipsychotics tested in the same animal chronic treatment paradigm differed from haloperidol in their actions. Both olanzapine and sertindole, each at two doses, were compared with haloperidol after 6 months of treatment (56). Neither olanzapine nor sertindole substantially up-regulated striatal D2 binding in the rat, even though we know from human studies that D2 blockade of some strength and duration occurs with each of these drugs (21). Because of the relatively high receptor affinities of these drugs at the D2 receptor, the data suggest that any regional reduction in blockade may occur only at some of the D2 receptors, and the resultant antidopaminergic action is weaker or of a reduced duration than with haloperidol. Nonetheless, olanzapine shows mild, haloperidol-like actions in striatum, and sertindole shows mild, haloperidol-like actions in GP and STN. Still, in SNR, neither new compound is associated with D1-receptor downregulation or GABA_A up-regulation (Table 126.2), nor are GABA_A receptors altered in mediodorsal thalamus by either new drug in contrast to the haloperidol effect. It is possible



FIGURE 126.4. Hypothetical model for the mechanism of chronic haloperidol-induced chewing movements (CMs) in rat. The data collected can be parsimoniously explained by postulating an increase in dendritic dopamine release associated with the development of dyskinetic movements in the CM rats. An increase in dopamine could stimulate the release of GABA presynaptically from the striatonigral GABAergic neurons and thereby increase the overall GABAergic inhibition on the GABA-containing nigral efferent fibers, including those to the thalamus. This alteration would serve to decrease the level of GABAergic inhibition on critical nuclei of the thalamus. This interpretation of the data, even though parsimonious, is speculative.

that the mechanism whereby these two effective antipsychotics (each antidopaminergic) fail to induce CMs is different in striatum, but both result in a common sparing of a critical change in SNR. It may be that the common serotonergic influence exerted within the basal ganglia nuclei by both these compounds spares SNR changes.

WORKING HYPOTHESIS OF THE CM-TD MECHANISM

The data summarized here are consistent with many reports in the literature and confirm the central role of the basal ganglia output nuclei and thalamus in mediating hyperkinetic movements in chronic antipsychotic-treated animals. It would be our current notion that traditional antipsychotic drugs alter the dynamic balance of neurotransmitter activity within the indirect and direct striatonigral pathway. This change, perhaps associated with sustained increase in nigral dendritic dopamine release, results in rodent hyperkinetic oral movements through the feedback of this information to motor regions of neocortex through thalamus. This antipsychotic-induced alteration acutely would merely inhibit activity within the indirect pathway and would be associated with parkinsonism. As treatment progresses and CMs begin, the indirect pathway inhibition could be progressively counterbalanced by direct pathway overactivity in the vulnerable animals. We postulate that the changes in SNR in D1receptor (decrease) and GABAA-receptor (increase) numbers reflect CM-related pathophysiology. These available data so far derive from animal model studies and provide a putative framework for TD pathophysiology. Work now must proceed with the human illness itself, by testing these and other ideas in *in vivo* brain imaging studies and postmortem tissue analysis.



FIGURE 126.5. Correlation of GABA_A receptor density with chewing movements (CMs) in mediodorsal thalamus in rats treated chronically with haloperidol. The significant positive correlation between these two factors suggests their relationship. This correlation supports the hypothesis that CMs are associated with diminished GABAergic transmission from the SNR to significant thalamic nuclei, evidenced by the up-regulation in GABA_A-receptor density associated with the putatively reduced GABAergic nigral signal with CMs. However, no other thalamic nuclei show this type of correlation, even the ventral nuclei traditionally associated with motor control in thalamus.

These findings illustrate not only the basal ganglia mechanisms of one type of dyskinesia, but also one outcome of CNS plasticity in response to chronic dopamine-receptor blockade. The difference between those animals who are vulnerable to develop CMs and those who are not remains obscure, as is the vulnerability to TD with antipsychotic treatment in humans.

TREATMENT APPROACHES

There is still no definitive treatment for TD. Nonetheless, therapeutic strategies are often used for patients with TD symptoms. Prevention, reversal, and suppression or (clinical management) all need to be considered (57). Prevention and reversal used to be only theoretic possibilities, but this is no longer the case. The newer generation of antipsychotic drugs, with their low TD incidence, has introduced these various new options.

Prevention

Patients who require antipsychotic treatment for extended times today have the opportunity of treatment with one of the newer antipsychotic drugs and thus are at reduced risk of developing TD, probably at considerably reduced risk. Clozapine (48), olanzapine (50), risperidone (58), and quetiapine (67) all have been reported to have reduced association with TD. Data are not yet available for new antipsychotic treatment of neuroleptic-naive persons, in whom the expectation may be for an even lower association with the syndrome. However, these data will be generated in time.

Whether treatment with very low-dose traditional antipsychotic drugs will result in the same low incidence of TD is a possibility, but it is nowhere nearly as probable as with the use of the newer drugs. Very low-dose traditional drug treatment, such as haloperidol, 2 to 3 mg/day, is being tested in several centers for efficacy in psychosis and for side effects. However, low-dose haloperidol at 4 mg/day has the same incidence of acute parkinsonism and akathisia as a haloperidol dose of 16 mg/day (76), a finding suggesting that lowdose haloperidol still has considerable potency in modifying motor function. Nonetheless, the economic advantage of traditional antipsychotic treatments, when necessity demands it, deserves thorough testing.

The cellular basis for the advantage of the newer antipsychotics with respect to TD risk is being examined and has been inferred from what is known of their pharmacology. Clozapine has a complex pharmacology, and consequently its TD advantage can be theoretically associated with several transmitter mechanisms (14). The possibilities include a D1 antagonist action, a serotonin_{2A} antagonist action, an antimuscarinic action, particularly at the M1 receptor, and even the antihistaminic action that can spare drug-induced TD. Parsimoniously, because this TD advantage appears to be a property of several or all of the newer antipsychotics, one could propose a common mechanism for the TD sparing. Speculations would then center most strongly on the role of the serotonin_{2A}-receptor blockade in striatum to attenuate the tardive motor effects of the dopamine-receptor blockade. This could be mediated by a blockade of serotonin action on striatal neurons, and a resultant modulation of dopamine-receptor blockade. Alternatively, the newer drugs may modulate dopamine blockade regionally to attenuate the cellular changes produced by the drugs. The results of the chronic treatment experiments in rat would favor this latter explanation. Additional possibilities exist, including a thalamic or cortical action of the drug at the serotonin 2A receptor.

Reversal

Clinical data with traditional antipsychotic treatment suggests that dyskinesia reversal occurs in persons with TD during ongoing treatment (Table 126.1), however, still conferring future risk. Data suggest that this reversal may happen faster with newer drug treatment than with the continued use of traditional drugs. TD reversal occurs frequently, although not inevitably, with cessation of antipsychotic treatment (43). This reversal appears to be more likely in the young rather than in the older patient, presumably because of greater tissue or system plasticity. The reversal occurs over the course of months to years, not in the range of weeks, so the phenomenon is challenging to document. Based on the simplistic formulation that relieving the brain of the inducing agent will allow the drug-induced tissue changes to reverse, then drugs such as clozapine or other newer antipsychotics, which have clinical efficacy with reduced dopamine-receptor occupancy, may reverse existent TD. Clozapine has been tested in a double-blind protocol comparing dyskinesia scores between two treatment populations during ongoing drug treatment (haloperidol versus clozapine) over the course of 12 months (63). Dyskinesia in the clozapine-treated group tended to be reduced after clozapine compared with haloperidol treatment (p < .057). Of some significance is that the rebound dyskinesia with drug withdrawal after a year of haloperidol treatment was significant, whereas after a year of clozapine treatment, the previously sensitive group failed to show any dyskinesia rebound after drug withdrawal, a finding suggesting the lack of system sensitivity (perhaps dopamine-receptor sensitivity) with clozapine. Olanzapine is currently being tested in persons with TD for its ability to relieve dyskinesia symptoms over 12 months compared with haloperidol.

Suppression

The feature that most consistently characterizes the results of suppression trials in TD is the variability within patients and among clinical centers conducting trials. No drugs have been reliably demonstrated to suppress TD across all patient groups and ages, although some drug classes show more promise and consistency in this regard than other approaches (32).

Benzodiazepines most reliably reduce the dyskinesias of TD, even at doses that do not produce sedation (64). Clonazepine has been widely used and seems to be one of the more effective benzodiazepines (51,64,72). Even when effective, clonazepam shows tolerance over time and requires continual dose increases to sustain efficacy. Thus, treatment must be occasionally withdrawn to "resensitize" the system to its effects for treatment to sustain action. The mechanism of therapeutic action has always been thought related to the GABA-enhancing drug action. Because the biology of TD has suggested regional GABA reductions, a GABA agonist is rational as a therapeutic choice.

Based on a continuation of this reasoning, other GA-BAmimetics have been tested in TD (60). It has been challenging to find a therapeutic window for a GABA agonist in TD, in which the GABA agonist action is potent enough to be antidyskinetic but the side effects are not limiting. Valproic acid has not been shown to be an effective therapeutic agent in TD, presumably because of its low potency (44). More potent GABA mimetic, such as γ -vinyl-GABA and tetrahydroisoxazolopyridinol, have shown antidyskinetic efficacy, but in some cases with limiting side effects (62,65). The studies that have shown efficacy of GABAmimetics in TD have used younger patients (i.e., less than 50 years old). Studies in older volunteers have not demonstrated efficacy with GABAmimetics (12). Although the question of age effect on TD reversal has not been directly tested, it is generally believed that symptoms are more likely to be suppressed with a GABAergic drug in the young patient than in the older one.

Other drug treatment strategies include vitamin E (17, 48,59), melatonin (55), noradrenergic-receptor antagonists such as propranolol or clonazepan, amantadine (5), and calcium channel blockers, especially nifedipine (58). Whereas each of these approaches provides clinical interest, none has developed into a therapeutic approach.

Treatments for TD will always be needed, even though the incidence of new cases may fall significantly with time. Treatments will always be more effective in younger than in older patients. Opportunities for drug development are likely to be found in the GABAergic or the glutamatergic neurotransmitter systems.

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