Review

Dopaminergic Disturbances in Tourette Syndrome: An Integrative Account

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ABSTRACT

Tourette syndrome (TS) is thought to involve dopaminergic disturbances, but the nature of those disturbances remains controversial. Existing hypotheses suggest that TS involves 1) supersensitive dopamine receptors, 2) overactive dopamine transporters that cause low tonic but high phasic dopamine, 3) presynaptic dysfunction in dopamine neurons, or 4) dopaminergic hyperinnervation. We review evidence that contradicts the first two hypotheses; we also note that the last two hypotheses have traditionally been considered too narrowly, explaining only small subsets of findings. We review all studies that have used positron emission tomography and single-photon emission computerized tomography to investigate the dopaminergic system in TS. The seemingly diverse findings from those studies have typically been interpreted as pointing to distinct mechanisms, as evidenced by the various hypotheses concerning the nature of dopaminergic disturbances in TS. We show, however, that the hyperinnervation hypothesis provides a simple, parsimonious explanation for all such seemingly diverse findings. Dopaminergic hyperinnervation likely causes increased tonic and phasic dopamine. We have previously shown, using a computational model of the role of dopamine in basal ganglia, that increased tonic dopamine and increased phasic dopamine likely increase the propensities to express and learn tics, respectively. There is therefore a plausible mechanistic link between dopaminergic hyperinnervation and TS via increased tonic and phasic dopamine. To further bolster this argument, we review evidence showing that all medications that are effective for TS reduce signaling by tonic dopamine, phasic dopamine, or both.

Keywords: Antipsychotics, Dopamine, Dopamine agonists, Hyperinnervation, Positron emission tomography, Tourette syndrome

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Tourette syndrome (TS) has long been thought to involve dopaminergic disturbances (1,2). Many aspects of dopaminergic function have been probed in TS (3,4), but existing accounts of dopaminergic disturbances in TS remain fragmentary, addressing only some findings while ignoring or even being contradicted by others. In this article, we develop an integrative account that links the various findings. Specifically, we show that the hypothesis that TS involves dopaminergic hyperinnervation provides a parsimonious explanation for all existing findings from positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies of the dopaminergic system in TS. Such hyperinnervation likely causes increased tonic and phasic dopamine (DA); we show that all medications commonly used to treat TS reduce signaling by tonic DA, phasic DA, or both. We have previously shown computationally how increased tonic and phasic DA explain many of the characteristics of TS (5,6).

EXISTING HYPOTHESES CONCERNING DOPAMINERGIC DISTURBANCES IN TS

Existing hypotheses concerning dopaminergic disturbances in TS are sometimes divided into four (3,4): 1) supersensitive receptors, 2) tonic–phasic dysfunction, 3) presynaptic dysfunction, and 4) dopaminergic hyperinnervation. As shown next, the first two hypotheses, in their current formulations, are contradicted by existing evidence; the last two hypotheses are not contradicted by existing evidence but have so far been used to address only small subsets of findings.

Supersensitive Receptors

The hypothesis that TS involves supersensitive DA receptors emerged from early findings that homovanillic acid (HVA) in cerebrospinal fluid (CSF) was reduced in TS and was normalized by haloperidol treatment (1,4). Under the premise that CSF HVA levels reflect brain DA levels, these findings were considered inconsistent with a hyperdopaminergic view of TS; the effectivity of antipsychotics was therefore attributed to supersensitivity of DA receptors (1). The premise that CSF HVA levels are a proxy for brain DA levels is problematic, however, because HVA and DA levels do not always correlate positively; for example, amphetamine increases DA but decreases HVA (7,8). This example is noteworthy because high doses of amphetamine can worsen tics (9) and induce stereotypies across species (10) that are akin to tics (11). Notably, following amphetamine administration, there is a close temporal association between DA increases, HVA decreases, and stereotypy increases (7). The
Inference that DA is reduced in TS because CSF HVA is reduced may therefore be flawed. Furthermore, chronic haloperidol administration increases HVA while decreasing striatal DA (12–14). The increase of CSF HVA with haloperidol treatment therefore seems unlikely to reflect an increase in striatal DA.

As reviewed below, many studies have investigated D2 receptors in TS and failed to find consistent evidence for increased D2 density or binding. In fact, as discussed below, the findings from that work seem more consistent with increased DA—the opposite of the idea that prompted the supersensitive receptor hypothesis.

D1 receptors have received surprisingly little attention in TS, with the exception of postmortem studies (15–17). Two postmortem studies found no consistent alterations in D1 binding (15,17); another study found increased D1 density in motor cortex, premotor cortex, and Brodmann area 12 (16). These studies, however, had very small samples with marked exposure to medication. Additional research on the D1 receptor in TS is needed.

**Tonic–Phasic Dysfunction**

The tonic–phasic hypothesis adapted to TS early ideas about the roles of tonic and phasic DA in schizophrenia (18). According to this hypothesis (3,19), TS is due to an overactive DA transporter (DAT), which prevents DA spillover to the extrasynaptic space, thereby reducing tonic DA. Reduced tonic DA, in turn, decreases autoreceptor-based inhibition, thereby increasing phasic DA responses, which are amplified further by the excessive DA stored in presynaptic terminals due to increased reuptake.

This account runs into multiple difficulties. First, if TS was due to an overactive DAT, then psychostimulants or antidepressants that strongly inhibit the DAT, such as bupropion, should be prime treatments for TS. No treatment guidelines suggest that to be the case; in fact, the controversy has always been whether psychostimulants have deleterious or no effects on tics (20,21). Psychostimulant treatment of comorbid attention-deficit/hyperactivity disorder (ADHD) in TS is now considered safe (20,22,23), but bupropion (24) and amphetamine at high doses (9), even if not at more common doses (20), seem to exacerbate tics—the opposite of what the tonic–phasic hypothesis would predict. Second, the idea that TS involves low tonic DA would make the effectiveness of anti-phasic hypothesis would predict. Second, the idea that TS involves low tonic DA (19) was based on the findings of reduced CSF HVA in TS (1); we discussed above the problems with this inference.

**Presynaptic Dysfunction**

The presynaptic dysfunction hypothesis is simply a restatement of the finding, in a single study, of increased DA synthesis in TS (33). This hypothesis is not contradicted by any evidence, but it does not explain the multiple other findings (reviewed below) regarding the DA system in TS.

**Hyperinnervation**

The dopaminergic hyperinnervation hypothesis is based on findings of increased DAT and vesicular monoamine transporter 2 (VMAT2) in TS (reviewed below), under the interpretation that such findings reflect an overabundance of dopaminergic terminals. The main limitation of this hypothesis is that it is typically used only to address those findings. As we will see, however, proper consideration of this hypothesis provides an integrated explanation for the various findings of PET/SPECT studies of the DA system in TS and for the mechanisms of action of all medications typically used to treat TS.

**Review of PET and SPECT Studies of the Dopaminergic System in TS**

To thoroughly assess the evidence from published PET and SPECT studies of the dopaminergic system in TS, we searched PubMed for all such studies using the following search string: Tourette AND dopamine AND (“positron emission tomography” OR PET OR “single-photon emission computed tomography” OR “single-photon emission computerized tomography” OR SPECT OR SPET). We last repeated this search in October 2017. Here, we review these findings (which are summarized in Figure 1).

**DA Transporter**

The DAT has been the most frequently studied dopaminergic marker in TS (Figure 1A). Several studies have reported increased DAT binding in vivo in TS in caudate and putamen (34–37), including in patients who were unmedicated (35), unmedicated and clonidine and antipsychotic naïve (37), and medication naïve (34). DAT binding in basal ganglia as a whole has also been found to be increased in medication-naïve children with TS (38). A similar number of studies failed to find differences between unmedicated patients and control subjects in caudate or putamen (39–42), including in medication-naïve patients (41,42), and other studies also failed to find differences in striatum or basal ganglia as a whole (43–45), including in medication-naïve patients (45). With a single exception (39), however, these studies were quite small [mean n (± SD) = 9.91 (± 3.39) patients and 9.55 (± 3.67) control subjects, excluding the single larger study]. The probability of type II error was therefore substantial, so the finding of increased DAT across multiple studies may indicate a true effect. The largest study did not reproduce that increase (39), but patients were not antipsychotic or stimulant naïve and were taking other medications at the time of study. Furthermore, the control group had a substantially greater proportion of female individuals than the patient group did (50% vs. 24%). In the age range of the
Figure 1. Findings from molecular imaging studies of the dopaminergic system—specifically, the dopamine transporter (DAT) (A), vesicular monoamine transporter 2 (VMAT2) (B), dopamine (DA) release (C), DA synthesis (D), and D₂ receptors (E)—in the striatum of patients with Tourette syndrome (TS) compared with healthy control subjects (HCs). Studies are color coded in green, yellow, or red depending on whether they reported increases, no significant differences, or decreases of the corresponding marker in patients relative to HCs, respectively. Studies are color coded in lime or orange if their results refer to DAT binding between patients and HCs in caudate (Cau) or putamen (Put) at baseline, but it reported greater DAT binding in patients than in HCs in right Cau following butyrophenone radioligand, which may be less sensitive to competition from endogenous DA (61). D₂ receptors in the left of studies with adults, if the medication was comparable, because the former are less likely to reflect compensatory changes. Antipsy, antipsychotics; AS, associative striatum; BG, basal ganglia; Cau, caudate; MS, motor striatum; Put, putamen; VS, ventral striatum. aThis study reported no differences (40). A & indicate mixed findings, but significant differences (40). B This study compared pairs of twins concordant for TS diagnosis but discordant for TS severity. It reported increased D₂ binding in Cau in the more severely affected twins, as compared with the less severely affected twins, but this finding could be due to prior exposure to antipsychotics. The study did not include HCs. cThis study found no significant differences between patients and HCs for D₂ binding or density, but 4 of the 20 patients for whom density values were available were antipsychotic naive and others were not antipsychotic at the time of study—not that the findings were obtained for two samples, one of naive patients and another of patients off antipsychotics. Studies with children are shown to the left of studies with adults, if the medication was comparable, because the former are less likely to reflect compensatory changes. Antipsy, antipsychotics; AS, associative striatum; BG, basal ganglia; Cau, caudate; MS, motor striatum; Put, putamen; VS, ventral striatum. dThis study reported similar binding potential, but decreased density and increased affinity, in patients compared with HCs. The study is color coded in yellow because binding potential is the most relevant measure given that it combines the effects of density and affinity (binding potential = density × affinity). These studies did not find significant differences between unmedicated patients (G1) and HCs, but their plots suggested that D₂ binding might have been decreased in patients relative to HCs, and that difference was significant in a subsanalysis with a subset of unmedicated patients in George et al. (57). Both studies reported decreased D₂ binding in medicated patients (G2) relative to HCs, but such differences likely resulted from competition between the medication and the D₂ radioligand, so their relevance may be limited.

Subjects in that study, female individuals have greater DAT binding than male individuals do (46,47), so the greater proportion of female individuals in the control group could have masked an increase in DAT binding in patients. This confound may also have played a role in another study with null findings (40). A postmortem study provided converging evidence for increased DAT binding in caudate and putamen in patients with TS (15). Other postmortem studies found increased DAT binding in frontal cortex (16,17).

Vesicular Monoamine Transporter 2

Two studies assessed VMAT2 binding in striatum (39,48) (Figure 1B). The first study (48), in mostly medicated patients [some results of which had been published earlier (49)], found...
increased VMAT2 binding in ventral striatum (VS). Binding was also slightly increased, albeit only at trend level, in caudate and putamen. The second study (39) failed to find any significant differences in a larger sample of patients free of antipsychotics or stimulants, although several voxels in VS showed increased VMAT2 binding prior to correction for multiple comparisons. This study, however, is the same study mentioned above that also did not find differences in DAT binding but was confounded by a greater proportion of female individuals in the control group.

The VMAT2 is present not only in dopaminergic terminals but also in serotonergic terminals. Striatal serotonin transporter binding is decreased in TS (40); to the extent that such decrease reflects reduced serotonergic innervation, decreases in VMAT2 due to serotonergic hypoinnervation might mask increases in VMAT2 due to DA hyperinnervation. Interestingly, serotonergic hypoinnervation might be caused by DA hyperinnervation: striatal DA denervation in animals increases striatal serotonergic innervation (50), so DA hyperinnervation might, conversely, decrease serotonergic innervation.

**DA Release**

Amphetamine-induced DA release is increased in unmedicated patients with TS in putamen (19) and VS (40) (Figure 1C). Furthermore, in a study in which amphetamine increased tics, such increase correlated with DA release in ventral caudate (51). A study of extrastriatal amphetamine-induced DA release reported significant DA release in unmedicated patients but not in control subjects in primary motor and somatosensory cortices, anterior cingulate cortex, and prefrontal cortex (52). However, that study did not directly compare patients with control subjects, so it is unclear whether these findings reflect significant group differences.

A small study piloted the use of levodopa to induce DA release but did not detect striatal release in either control subjects or patients with TS (53). In some regions, levodopa decreased DA in patients, which is difficult to interpret.

**DA Synthesis**

Two small studies assessed DA synthesis in TS using [18F]fluorodopa (F-DOPA) PET (33,54) (Figure 1D). One study found increased F-DOPA in left caudate and, at trend level, in right midbrain of unmedicated patients with TS (33). The other study, with adults, did not find alterations in F-DOPA accumulation in caudate or putamen, but most patients were on antipsychotics (54).

**D2 Receptors**

Multiple PET and SPECT studies have investigated D2 receptors in TS (Figure 1E and Supplemental Table S1). Several studies using iodobenzamide and raclopride reported similar striatal D2 binding in patients and control subjects (19,44,54,55). Two raclopride studies reported decreased D2 measures in putamen in patients: one study reported decreased binding (51), and the other reported decreased density (Bmax) although together with increased affinity (1/Ki) (40). In two iodobenzamide studies, patients also seemed to have reduced D2 binding in striatum (56) and basal ganglia (57), although this difference was not significant in the first study (56) and was significant in only a subanalysis in the second (57). Two studies using radioligands appropriate for extrastriatal regions also found reduced D2 binding in patients in multiple regions (52,58).

All of the aforementioned studies used benzamide radioligands, which are sensitive to competition from endogenous DA (59). The reduced binding in patients found in some studies could therefore reflect increased DA. Increased DA could also cause D2 receptor internalization (60). Consistent with these ideas, the only study that used a butyrophenone radioligand (N-methylspiperone), which may be less sensitive to endogenous DA and may even show a paradoxical increase in binding with increased DA (61), reported that most patients did not differ from control subjects and that 4 of the 20 patients even had caudate Bmax values above the prediction interval for control subjects (62).

Postmortem studies, unlike PET and SPECT studies, have reported that patients have increased D2 density in frontal cortex (16,17) and slightly increased D2 binding in striatum (15). Patients in these studies, however, had substantial antipsychotic exposure, and antipsychotics increase D2 density and binding (63). Antipsychotic-driven D2 upregulation might also explain why one study found that, in monozygotic twin pairs with TS, the more severely affected twins had increased D2 binding in caudate (64); half of the twins in that study had been treated with antipsychotics; the study did not report which ones, but it seems plausible that the more severely affected twins had more antipsychotic exposure.

All the aforementioned PET and SPECT studies used radioligands that cannot discriminate between D2 and D3 receptors (65,66). A small study tried to investigate specifically D2 receptors in TS using the D2-prefering radioligand [11C]-(+)-PHNO (55). However, in striatum, which was the focus of that study, most [11C]-(+)-PHNO signal results from D2 binding, not D3 binding (67). The (null) findings of that study therefore provide little, if any, specific information about D3 receptors.

**A NEW SYNTHESIS**

There is a tendency in the literature for different findings to spawn different, narrowly conceived hypotheses. For example, the finding of reduced CSF HVA prompted the hypothesis that TS involves low tonic DA, the F-DOPA findings prompted the presynaptic dysfunction hypothesis, and the DAT and VMAT2 findings prompted the hyperinnervation hypothesis. Parsimony (Occam’s razor), however, is a fundamental guiding principle in science (68). An ideal hypothesis would provide a parsimonious, integrated explanation for all the PET/SPECT findings that, moreover, also explained various other aspects of TS.

A consideration of the possible interrelations among the various PET/SPECT findings suggests that the hyperinnervation hypothesis parsimoniously explains all of them (Figure 2). The hyperinnervation hypothesis implies that TS likely involves increased tonic and phasic DA. Recently, we demonstrated computationally that increased phasic DA and increased tonic
Figure 2. Possible explanations for the findings of studies that have investigated the dopaminergic (DA) system in Tourette syndrome (TS) using positron emission tomography (PET) or single-photon emission computerized tomography. The existing empirical findings, indicated in blue, point to increases in dopamine transporter (DAT) binding, amphetamine-induced DA release (DArel), [18F]fluorodopa (F-DOPA) accumulation, and vesicular monoamine transporter 2 (VMAT2) binding in the striatum of patients with TS (although these findings have not always been replicated; see text). Not all of these findings have been reported for all striatal subdivisions; currently, however, it is often unclear whether findings that were reported as significant for some striatal subdivisions and not for others truly were anatomically specific or simply failed to reach significance in some subregions. Some characteristics of the DA system, in fact, could make it easier to find significant findings in some striatal subregions; for example, greater DA innervation of sensorimotor and limbic striatum relative to associative striatum (136) might make it more difficult to detect differences in the latter. Thus, for simplicity, we assume that these findings may reflect general disturbances in DA function that apply across striatum, and we consider possible unifying explanations for all of the findings. There are three such possible unifying explanations [A–C]. The hypothesized primary disturbance for each is indicated by a surrounding red texture. Postulated primary or secondary disturbances that cannot be observed directly are indicated in green. Solid arrows indicate causal relations; the dashed arrow indicates a possible but unlikely causal relation. (A) A disturbance that would straightforwardly and directly explain all of the empirical findings is striatal DA hyperinnervation—that is, an increase in the number of DA terminals in striatum. The increased number of terminals would be reflected in increases in presynaptic markers such as the DAT and VMAT2, would cause greater DA

, and would lead to overall greater F-DOPA accumulation. In addition, the hyperdopaminergia caused by excessive innervation would also explain the finding of reduced striatal D2 binding in some studies (Figure 1E and Supplemental Table S1) because the excessive DA would compete with the radioligand (61) and could even cause D2 internalization (60). (B) Instead of reflecting an increase in the number of DA terminals, the increased DAT binding in TS could instead reflect increased DAT expression per terminal. Given that amphetamine increases DA primarily by reversing transport through the DAT (131), this increase in DAT would cause increased DArel. Indeed, mice with DAT overexpression have increased amphetamine-induced DA release (28). In addition, the increased reuptake would decrease extracellular (e.c.) DA. Stimulation of D2 autoreceptors decreases tyrosine hydroxylase and DOPA decarboxylase activity (132,133); conversely, blocking D2 receptors increases the activity of both enzymes (13,133), thereby increasing DA synthesis. Indeed, acute haloperidol administration has been shown to increase DOPA decarboxylase activity using F-DOPA PET in animals (134). By decreasing autoreceptor stimulation, reduced e.c. DA could therefore increase DA synthesis and F-DOPA accumulation. Hypothesis B seems less likely than hypothesis A to provide a direct explanation for the increase in VMAT2 binding (gray box), although the VMAT2 is subject to complex regulation (135), so it is difficult to make any statements about possible causes of VMAT2 alterations without a substantial degree of uncertainty. Hypothesis B also would not explain the findings of reduced D2 binding in some studies (Figure 1E and Supplemental Table S1). The evidence for both VMAT2 increases and D2 binding decreases is weak and inconsistent (see text), so these explanatory gaps would not per se be particularly damaging for this hypothesis; as discussed in the text, however, several other considerations make it unlikely that the primary disturbance in TS is an overactive DAT. (C) A third possibility is that the primary disturbance in TS is increased DA synthesis, which would be reflected directly in increased F-DOPA accumulation. The increased DA synthesis would create more DA available for release, which could increase DArel and potentially e.c. DA. Intuitively, the increase in e.c. DA could, in turn, upregulate the DAT as a compensatory mechanism to decrease DA (dashed arrow), but that seems unlikely for at least three reasons. First, DA causes DAT internalization, leading to less DAT, not more DAT, in the plasmalemmal membrane (136). Second, chronic levodopa (L-DOPA) administration in healthy and MPTP-treated monkeys, which of course increases L-DOPA and DA synthesis, does not increase DAT binding (137); in rodents, in fact, it decreases it (138). Third, patients with schizophrenia, who have increased striatal DA synthesis (139), do not have increased striatal DAT binding (140). Hypothesis C is therefore unlikely to explain the increased DAT binding (hence the blue-gray gradient for the box “↑ DAT per terminal”). If it did, however, the increase in DAT could further increase DArel for the reasons mentioned above. Hypothesis C would fail to explain the increase in VMAT2 binding (gray box): increased DA synthesis should, if anything, decrease VMAT2 binding due to increased competition from vesicular DA (141). Hypothesis C would explain the reduced D2 binding found in some studies because the increased synthesis could increase e.c. DA. An additional limitation of hypothesis C is that F-DOPA PET does not assess the rate-limiting step in DA synthesis, which is tyrosine hydroxylase, not DOPA decarboxylase; F-DOPA PET may therefore not provide a true measure of DA synthesis. A variant of hypothesis C would be to assume that the primary disturbance is an increase in VMAT2, which would cause increased DA storage in vesicles. The increased vesicular DA would cause increased F-DOPA accumulation in PET and make more DA available for release, thereby increasing DArel and potentially e.c. DA. Finally, the increase in e.c. DA could upregulate the DAT, which in turn would further increase DArel. This variant, however, also assumes that the increase in DAT binding is a consequence of increased e.c. DA, which may be problematic for the reasons already noted. A fourth possibility, not shown because it seems less plausible, would be that DA release would be increased by mechanisms other than increased DA synthesis or VMAT2 uptake. Such postulated increased DA release would, tautologically, explain the increased DArel, and it could also increase e.c. DA, which in turn could upregulate the DAT. Such an account, however, would not explain the increased F-DOPA accumulation or VMAT2 binding, and it also shares the limitation of assuming that the increase in DAT binding is a consequence of increased e.c. DA.
DA cause an increased propensity to learn and express tics, respectively, explaining various aspects of TS (5). A link can therefore be established between DA hyperinnervation and various aspects of TS. DA hyperinnervation also explains why all medications commonly used to treat TS decrease DA neurotransmission, as reviewed below.

The idea that TS involves increased tonic DA is also supported by the findings that increasing tonic stimulation of DA receptors by intrastriatal infusion of DA (69), of the nonselective DA agonist apomorphine (70), or of a combination of D1 and D2 agonists (71,72) causes stereotypes in animals. Notably, these stereotypes are aggravated, rather than abolished, by lesions of DA neurons in substantia nigra (73) or of striatal DA terminals (74), which suggests that they are due to direct tonic stimulation of postsynaptic DA receptors (rather than to any indirect effects on phasic release by presynaptic terminals).

**MECHANISMS OF ACTION OF THE MEDICATIONS USED TO TREAT TS**

Many medications have demonstrated efficacy to treat TS. Despite their varied mechanisms of action, they all reduce DA neurotransmission (Figure 3).

**Antipsychotics**

The antipsychotics haloperidol, pimozide, and aripiprazole are the only medications approved by the U.S. Food and Drug Administration for TS. Antipsychotics are often considered the first-line pharmacological treatment for TS, particularly in chronically, may desensitize D2 autoreceptors (88) (dashed green arrow ending in a circle) and therefore result in a net increase in postsynaptic D2 stimulation (89). In addition, chronic pramipexole decreases DA reuptake through its action on D2 autoreceptors (90,91). Chronic pramipexole may therefore, if anything, increase dopaminergic neurotransmission, which likely explains why it failed in a clinical trial for the treatment of TS (87). Although pergolide also acts on D3 receptors and the DAT is predominantly located extrasynaptically (135); in the figure, DA receptors and the DAT are shown in a synapse-like arrangement just because of the increased familiarity of that representation. (A) Most antipsychotics are D2 antagonists (63). They act on both presynaptic D2 receptors (not shown) and postsynaptic D2 receptors, but their beneficial effects for TS are most likely due to the postsynaptic action (5). (B) Low doses of the DA agonist pergolide likely act mostly on D2 autoreceptors (82). The stimulation of D2 autoreceptors reduces DA neurotransmission by inhibiting tyrosine hydroxylase and DOPA decarboxylase activity (132,133), DA neuron firing (83), and DA release (135) and by stimulating DA reuptake through the DAT (135,144). Pergolide acts on both D2S and D3 autoreceptors, but its beneficial effects for TS might be due to its action on the former and not the latter (Figure 4). (C) Low doses of the DA agonist pramipexole, administered
Figure 4. Relative efficacies ($E_{\text{max}}$), potencies ($1/EC_{50}$), and affinities ($1/K_i$) of various dopamine (DA) agonists that have been, or potentially could be, used to treat Tourette syndrome (TS). DA agonists are color coded in green if they have shown effectiveness in clinical trials (pergolide and ropinirole, although the latter was tested only in an open-label trial), in red if they have failed clinical trials (pramipexole and talipexole), and in yellow if they have not yet been tested in clinical trials for TS. $E_{\text{max}}$ and $EC_{50}$ values were obtained from (97), and $K_i$ values were obtained from (98) (Supplemental Table S2). (A) Relative efficacies, potencies, and affinities for $D_3$ vs. $D_2$ short ($D_{2S}$) receptors for the medications that have been tested in clinical trials for TS. Greater values in the $x$, $y$, and $z$ axes indicate greater relative efficacy ($E_{\text{max}}$), potency ($1/EC_{50}$), and affinity ($1/K_i$) for $D_3$ receptors as compared with $D_{2S}$ receptors. The $y$ and $z$ axes are plotted using a logarithmic scale. The two successful medications (pergolide and ropinirole) cluster together close to the origin, indicating less relative action at $D_3$ vs. $D_{2S}$ receptors. The two unsuccessful medications (pramipexole and talipexole) are substantially farther from the origin, reflecting more relative action at $D_3$ receptors. The clustering together of pergolide and ropinirole in this space contrasts with the clustering obtained when using the binding profile of DA agonists to multiple receptors; in the latter case, ropinirole is most similar to pramipexole and fairly different from pergolide (98). These findings may indicate that the effectiveness of DA agonists for TS depends more on their relative $D_3$ vs. $D_{2S}$ effects than on their broader effects across multiple receptors (although an important limitation of the clustering based on multiple receptors is that it used only affinities). DA agonists with less relative action at $D_3$ receptors may be more effective for TS because chronic $D_3$ stimulation induces neuroadaptations that likely increase DA, thereby counteracting the beneficial effects of $D_{2S}$.
Europe, with atypical antipsychotics often preferred because of their better side effect profile (22,75). Most antipsychotics are D2 antagonists (63) (Figure 3A); aripiprazole and related compounds are an exception and are discussed separately below. Typical and atypical antipsychotics have comparable efficacy in TS (25), which suggests that D2 antagonism is central to their beneficial effect. At the doses used in TS (76), antipsychotics block a large percentage of postsynaptic D2 receptors (77), which likely mediates their initial beneficial effect (5). The beneficial effect of blocking postsynaptic D2 receptors is consistent with the idea that TS involves increased tonic DA because D2 receptors are particularly involved in tonic signaling (26). Furthermore, chronic antipsychotic use decreases both tonic DA and stimulation-evoked (phasic-like) DA release (14,27,78).

### DA Agonists

Low doses of pergolide, a DA agonist, are also effective for TS (79–81). At low doses, pergolide acts mostly on D2 autoreceptors (82), thereby inhibiting DA neuron firing (83), suppressing DA synthesis (84), and reducing striatal tonic DA (85) (Figure 3B). Consistent with the idea of a predominantly presynaptic effect in the TS studies, the doses used were approximately 5- to 15-fold lower than those used in Parkinson’s disease, where a postsynaptic effect is desired. This dose difference is consistent with animal studies showing that low doses of pergolide decrease motor activity, whereas doses that are 5-fold or more increase motor activity and induce stereotypies (82,86).

Another DA agonist, pramipexole, did not prove to be beneficial for TS (87). A possible explanation for this finding is that whereas short-term pramipexole administration inhibits DA neuron firing, chronic administration causes DA neuron firing to return to baseline, likely because of autoreceptor desensitization (88). Chronic pramipexole administration may even increase stimulation of postsynaptic D2 receptors following the normalization of DA neuron firing, given its agonistic action (89).

Furthermore, chronic pramipexole may increase DA because it reduces DA reuptake through its action on D3 receptors (90,91) (Figure 3C). Thus, whereas low doses of pergolide decrease DA, thereby ameliorating TS, chronic pramipexole treatment, even at low doses, may increase stimulation of postsynaptic D2 receptors and DA. Consistent with these ideas, low doses of pergolide and pramipexole may aggravate (92) and treat (93) Parkinson’s disease, respectively.

Low doses of two other DA agonists have been tested in TS: ropinirole, which reduced tics in a small open-label trial (94), and talipexole, which did not prove to be beneficial (95). The factors determining which DA agonists are effective for TS are unknown. One possibility is that DA agonists with less action at D3 autoreceptors relative to D2 short (D2S) autoreceptors may work best (Figure 4).

### Aripiprazole

Most antipsychotics have their beneficial effects by blocking postsynaptic D2 receptors, but they also block D2 autoreceptors (96), which is counterproductive. DA agonists have their beneficial effects by stimulating D2 autoreceptors, but stimulation. Indeed, chronic D3 stimulation has neurotrophic effects on DA neurons, increasing their number and dendritic arborization and even increasing striatal dopaminergic innervation (148,147)—the opposite of what one would want if TS involves DA hyperinnervation. Furthermore, prolonged D3 stimulation reduces DA uptake and DAT plasmalemmal expression (148), and chronic pramipexole administration reduces DA reuptake through its action on D3 receptors (90,91) because D3 autoreceptors inhibit DA neuron firing (132,133,144); prolonged D2S stimulation, in contrast, would inhibit the indirect pathway, which would likely be detrimental (5). Successful medications, however, do not appear to cluster close to the origin. In fact, although it is possible to imagine a plane separating the successful and unsuccessful medications, such separation seems much less demarcated than the one observed in panel (A). One possible explanation for these seemingly counterintuitive findings is that the relative effects on D2L vs. D2S receptors do not vary substantially across these medications: unlike in panel (A), all axes have small ranges. This small variability in D2L vs. D2S effects across these four medications, compared with the much larger variability in D2 vs. D3 effects, may explain why the latter may have a more preponderant role in determining which of these medications work for TS. (C) Relative efficacies, potencies, and affinities for D3 vs. D2 receptors for all DA agonists, including several that have not yet been tested in clinical trials in TS (yellow circles). The representation is equivalent to that in panel (A), with axes ranges adjusted to show all medications. The idea that the effectiveness of DA agonists for TS depends on their action at D2S receptors relative to D2 receptors, if correct, suggests a strategy to select DA agonists to test in future clinical trials: prioritize those with greater action at D2S receptors relative to D2 receptors (i.e., those closer to the origin in the plot). Such trials seem timely because pergolide, the only DA agonist for which there is solid evidence of effectiveness in TS (79–81), increases the risk of heart valve disease (149). This panel shows that none of the untested DA agonists have D2 vs. D3 EC50 ratios as favorable as those of pergolide and ropinirole, but they all have substantially more favorable EC50 and K1 ratios than pergolide and ropinirole (see also Supplemental Table S3). Thus, with the possible exception of bromocriptine, whose EC50 ratio is quite unfavorable, all of the other untested DA agonists shown may conceivably be helpful for TS. Ropinirole should be the first DA agonist to study in a randomized, double-blind, placebo-controlled trial because it showed effectiveness in an open-label trial (94) and, like pergolide, has a favorable profile of action at D2S receptors relative to D2 receptors. Other DA agonists with potentially favorable D2S vs. D2 profiles include cabergoline, lisuride, piribedil, and terguride. Cabergoline is an ergot-derived DA agonist, like pergolide, and it also increases the risk of heart valve disease (149), so it is not an appealing alternative. Lisuride, piribedil, and terguride, however, may be worth testing. Although lisuride and terguride are ergot derived, they seem not to increase the risk of heart valve disease (149). Piribedil is not ergot derived and reduced tics in a case study (150). (D) Relative efficacies, potencies, and affinities for D2L vs. D3 receptors for all DA agonists considered in panel (C), including the ones that have not yet been tested in clinical trials in TS (yellow circles). The representation is equivalent to that in panel (B), with axes ranges adjusted to show all medications. Two of the untested medications have D2S vs. D2L ratios that are better than those of pergolide and ropinirole: terguride and lisuride. Terguride is ideal in this respect because it has no effect on D2 receptors (EC50 = 0), so it may act only presynaptically. Lisuride is not as good as terguride, but it has a more favorable profile than both pergolide and ropinirole in all three measures (i.e., in each of the three dimensions). Piribedil also has a reasonably favorable D2L vs. D2S profile. Terguride, lisuride, and piribedil also have promising D2 vs. D3S profiles (D), so they may be worthy of investigation in TS clinical trials.
most also stimulate postsynaptic D2 receptors (97,98), which again is counterproductive. Aripiprazole may combine the best of both medication types, acting as a partial agonist (or even antagonist) at striatal postsynaptic D2 receptors and as a strong agonist at striatal D2 autoreceptors (99,100) (Figure 3D). Moreover, consistent with the idea that stimulation of D2s autoreceptors but not of D2 autoreceptors may be helpful for TS (Figure 4), aripiprazole may act substantially more on D2s autoreceptors than on D2 autoreceptors in conditions that mimic those in vivo (96). Newer antipsychotics with mechanisms of action related to those of aripiprazole (101) may also be promising for TS.

\(\alpha_2\) Agonists

In North America, \(\alpha_2\) agonists are usually considered the first-line pharmacological treatment for TS because of their greater tolerability (23,75). A meta-analysis found that antipsychotics have a medium effect size, whereas \(\alpha_2\) agonists have a more modest effect size, in TS (25). Furthermore, co-occurring ADHD strongly moderated the effect of \(\alpha_2\) agonists but not of antipsychotics. In fact, in trials requiring comorbid ADHD, \(\alpha_2\) agonists had a moderate to large effect, whereas in trials that excluded patients with ADHD, the effect was small and nonsignificant (25). Thus, \(\alpha_2\) agonists may be indicated only for TS with comorbid ADHD.

Notably, \(\alpha_2\) agonists reduce DA neurotransmission (Figure 3E). Indeed, \(\alpha_2\) agonists inhibit striatal DA release elicited by electrical stimulation in brain slices and by electrical stimulation of the medial forebrain bundle in vivo, likely via \(\alpha_{2A}\) receptors (102,103). This inhibition of DA release occurs with stimulation using a small number of pulses at high frequency (102) and with several seconds of low-frequency stimulation (103), suggesting that \(\alpha_2\) agonists may inhibit both phasic and tonic DA release. Indeed, \(\alpha_2\) agonists decrease tonic DA in striatum and frontal cortex, again likely via \(\alpha_{2A}\) receptors (104–106).

Other Medications That Reduce DA Neurotransmission

Open-label trials suggest that other medications that reduce DA neurotransmission may also be effective for TS. These medications include VMAT2 inhibitors (107) (Figure 3F) and ecopipam (108), a selective D1 antagonist (109) (Figure 3G). A small pilot study also showed a beneficial effect of blocking DA synthesis (2) (Figure 3H).

Synthesis

Consistent with the idea that TS involves DA hyperinnervation and consequent increases in tonic and phasic DA, all aforementioned medications reduce signaling by tonic DA, phasic DA, or both. In that context, ecopipam is noteworthy because it is the only one that may act mostly, or exclusively, on phasic signaling, given that D1 receptors are stimulated mostly by phasic DA because of their low affinity (26). Whether this preferential action on phasic signaling provides the same level of symptom control as medications that also strongly affect tonic signaling remains unknown.

DEVELOPMENTAL COURSE OF TS

TS tends to worsen until periadolescence (around 10 years of age) and then improve throughout adolescence and young adulthood (110). The improvement throughout adolescence and young adulthood is consistent with the idea that TS results from striatal DA hyperinnervation and consequent hyper-dopaminergia because virtually all markers of the striatal DA system decrease during that period (111–115). Conversely, the worsening of TS until periadolescence may conceivably result from increased activation of the striatal DA system; studies in rodents show that DA neuron firing, striatal D1 and D2 receptors, and striatal DAT binding all peak during periadolescence (116,117). The evidence in humans is more mixed but much sparser. Some evidence suggests that striatal DA (111) and DAT (115) also increase from childhood until periadolescence in humans; other evidence suggests that several DA system markers (111–115), possibly including the DAT (111), peak during late infancy or early childhood. Additional research is needed to resolve these inconsistencies. DA system development, moreover, may conceivably follow an atypical trajectory in TS.

OTHER NEUROCHEMICAL DISTURBANCES

Although we focused on DA, other neurochemical disturbances have also been implicated in TS (4,118–120). Hyper-dopaminergia increases long-term potentiation and excitability in the direct basal ganglia pathway relative to the indirect basal ganglia pathway (121,122), which likely explains its role in TS (5,121). Other disturbances that affect the balance of these pathways similarly may be alternative pathogenetic routes for TS. For example, reduced numbers of striatal fast-spiking interneurons (118) may preferentially disinhibit the direct pathway relative to the indirect pathway (5).

LIMITATIONS AND FUTURE DIRECTIONS

Most studies of dopaminergic disturbances in TS used small samples, and results often conflict across studies. Substantial uncertainties therefore remain even for aspects of the DA system that have been probed in TS. Important studies, moreover, have never been done—for example, assessing baseline DA levels through DA depletion (123) and assessing DA synthesis with better radioligands (124).

Consistent with the hyperinnervation hypothesis, the influence of substantia nigra activity on striatal activity is increased in TS (125). Assessing the nigrostriatal pathway using diffusion tensor imaging would help further test the hyperinnervation hypothesis. Given imaging’s resolution limitations, however, the best test of the hyperinnervation hypothesis would be visualization and quantification of labeled DA terminals and synapses in postmortem studies (126). Postmortem studies should also assess whether the number of DA neurons is increased in TS, given the imaging findings of increased midbrain gray matter (127,128). Furthermore, the number of DA neurons in substantia nigra correlates with striatal DAT binding (129), so an increased number of such neurons would be consistent with the findings of increased DAT binding.
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CONCLUSIONS
The hyperinnervation hypothesis provides a parsimonious and integrated explanation for the various findings of PET/SPECT studies of the dopaminergic system in TS. This hyperinnervation likely causes increased tonic and phasic DA, which explains why all effective medications for TS reduce signaling by tonic DA, phasic DA, or both. Recently, we also showed computationally that increased tonic DA and increased phasic DA likely cause propensities to express and learn tics, respectively, and that such an account explains multiple clinical findings in TS (5). Overall, then, a simple pathogenic hypothesis—DA hyperinnervation—provides a parsimonious and integrated account of a wide range of findings in TS.

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