Merging the Pathophysiology and Pharmacotherapy of Tics

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Abstract

Background: Anatomically, cortical-basal ganglia-thalamo-cortical (CBGTC) circuits have an essential role in the expression of tics. At the biochemical level, the proper conveyance of messages through these circuits requires several functionally integrated neurotransmitter systems. In this manuscript, evidence supporting proposed pathophysiological abnormalities, both anatomical and chemical is reviewed. In addition, the results of standard and emerging tic-suppressing therapies affecting nine separate neurotransmitter systems are discussed. The goal of this review is to integrate our current understanding of the pathophysiology of Tourette syndrome (TS) with present and proposed pharmacotherapies for tic suppression.

Methods: For this manuscript, literature searches were conducted for both current basic science and clinical information in PubMed, Google-Scholar, and other scholarly journals to September 2018.

Results: The precise primary site of abnormality for tics remains undetermined. Although many pathophysiologic hypotheses favor a specific abnormality of the cortex, striatum, or globus pallidus, others recognize essential influences from regions such as the thalamus, cerebellum, brainstem, and ventral striatum. Some prefer an alteration within direct and indirect pathways, whereas others believe this fails to recognize the multiple interactions within and between CBGTC circuits. Although research and clinical evidence supports involvement of the dopaminergic system, additional data emphasizes the potential roles for several other neurotransmitter systems.

Discussion: A greater understanding of the primary neurochemical defect in TS would be extremely valuable for the development of new tic-suppressing therapies. Nevertheless, recognizing the varied and complex interactions that exist in a multi-neurotransmitter system, successful therapy may not require direct targeting of the primary abnormality.

Keywords: Tourette syndrome, tics, pathophysiology, neurotransmitters, treatment

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Introduction

Tourette syndrome (TS) is a neuropsychiatric disorder whose primary symptoms include motor and vocal tics. Tics are defined as quick, rapid, recurrent, non-rhythmic, brief movements or vocalizations that have a waxing and waning course. Tics are common in the pediatric population, with estimates of their presence in about 20% of children.¹ For the diagnosis of TS, an individual must have multiple motor and at least one vocal tic, a waxing and waning course, and a duration of tics for greater than 1 year. Affected individuals with only motor or vocal tics for more than a year are labeled chronic motor or vocal tic disorders and those with a tic history of less than 1 year, a provisional disorder. Tics are typically exacerbated by stress, anxiety, and fatigue and, especially in older children and adults, are preceded by a premonitory sensation or urge. Therapeutically, there is no cure for tics, and symptomatic treatment is recommended when tics are causing psychosocial difficulties, physical discomfort, or other lifestyle disruptions. Behavioral therapy has been effective,² but many individuals continue to require tic-suppressing pharmacotherapy. Recognizing a variability in physician selection, first-tier pharmacotherapies often include the alpha-adrenergic agonists (clonidine, guanfacine) and
anticonvulsants (topiramate), and second-tier the atypical (aripiprazole, risperidone, ziprasidone, quetiapine) and typical (pimozide, fluphenazine, haloperidol) antipsychotics as well as vesicular monoamine transporter type 2 (VMAT-2) inhibitors (tetrabenazine) Table 1. The efficacy of current pharmacotherapeutic agents and future therapies for tics should be understood in the context of the pathophysiologic model underlying this movement abnormality.

The goal of this review is to integrate our current understanding of the pathophysiology of TS with present and proposed pharmacotherapies for tic suppression. In the following sections, we review the proposed anatomical pathways (cortical-basal ganglia-thalamo-cortical [CBGTC]), and the hypothesized alterations of neurotransmitter systems located within these circuits. We review the mechanism of action and efficacy of standard and emerging pharmacotherapeutic agents used for tic suppression. Our hope is that integrating the biochemical alteration(s) underlying tics with knowledge of the mechanism of drug action will ultimately lead to better treatment.

Overview of the CBGTC circuit

A fundamental understanding of CBGTC circuitry and its integrated neurotransmitter systems are essential for understanding potential pathophysiologic mechanisms and therapies in TS. As will be described, involved circuits represent a dynamic web of interlinked reverberating inhibitory and excitatory influences providing potential multiple sites of influence (Figures 1 and 2). Essential individual components include the following:

1) Cortex: Multiple regions within the cortex provide the striatum (caudate and putamen) with excitatory glutamatergic input: e.g., pyramidal neurons within frontal associative/cognitive regions project to the caudate; pre-motor/supplementary motor areas (SMAs) project to the putamen; and emotional (limbic) regions to the ventral striatum. These projecting cortical neurons are themselves influenced by various neurochemical afferent inputs from interneurons (gamma-aminobutyric acid [GABA]), the ventral tegmental area (VTA, dopamine), median raphe (serotonin), locus coeruleus (catecholamines), and other intracortical connections. In addition to the sites within the striatum, cortical regions also send projections to the subthalamic nucleus (STN), VTA, substantia nigra, thalamus, and via the pontine nucleus to the cerebellum.

2) Basal ganglia: Within the striatum, GABAergic medium-sized spiny neurons (MSNs), giant aspiny cholinergic interneurons, and several subtypes of medium-sized GABAergic interneurons receive cortical glutamatergic inputs. Striatal MSNs and interneurons also receive glutamatergic afferent input from motor cortex and intralaminar thalamic nuclei; dopaminergic projections from the substantia nigra pars compacta (SNpc) and VTA; GABA, substance P, and enkephalin input from other MSNs; and acetylcholine, GABA, or peptidergic input from striatal interneurons. The STN, populated mainly by glutamatergic projection neurons, receives its major afferents from the cerebral cortex, thalamus, globus pallidus externa (GPe), and brainstem. A direct input from the inferior frontal and dorsomedial frontal cortex to the STN has a “reactive inhibition” role. Outputs from the STN project not only to the globus pallidus interna (Gpi)/substantia nigra pars reticulata (SNpr), but also to the GPi, striatum, and pedunculopontine tegmental nucleus (PPTg).

3) Thalamus: The motor thalamus (Mthal, i.e., ventroanterior and ventrolateral nuclei) is part of a closed loop, receiving input from cortical associatives, premotor and motor areas, basal ganglia (SNpr and GPi), and the cerebellum (dentate nucleus). It provides excitatory (glutamatergic) innervation to dendrites of cortical pyramidal neurons located in layers I and II and to a lesser extent in layer V. In addition, short subcortical loops exist between the thalamus and the striatum: motor information entering to the striatum from the Mthal and sensory information from the intralaminar nuclei.

Possible location of the primary abnormality within the CBGTC circuit

Prior reports have typically presented pathophysiologic hypotheses for tics based on potential abnormalities in: 1) direct and indirect motor pathways; 2) as a favored alteration within a particular CBGTC region/neurotransmitter; or 3) the concept of a complex circuit in which a failure anywhere along the pathway can alter cortical excitability and enable the tic.

1) Direct and indirect motor pathways: One commonly presented, but overly simplistic, model of motor behavior suggests interplay of two distinct pathways, the “direct” and “indirect” pathways (Figures 1 and 2). The direct pathway transmits striatal information monosynaptically from GABAergic MSNs, containing dopamine receptor type 1 (D1), M1/M4 muscarinic cholinergic, and histamine receptors, to the GABAergic Gpi/SNpr region – this pathway thus inhibiting the inhibitory Gpi/SNpr output. The indirect pathway, in contrast, conveys information from MSNs, containing dopamine receptor type 2 (D2), M1, and adenosine A2 adrenergic receptors, to the GABAergic GPi, from the GPi to the glutamatergic STN, and then on to the Gpi/SNpr; this pathway thus stimulates the inhibitory Gpi/SNpr output. In turn, both pathways have a reverse effect on spontaneously firing thalamocortical neurons and ultimate motor activity, i.e., activation of the direct pathway facilitates motor activity via disinhibition of thalamocortical neurons whereas activation of the indirect pathway reduces motor activity by increasing the inhibition of thalamocortical neurons. While studies in some non-human primates suggest that concurrent activation of projection neurons in direct and indirect pathways produce contraversive movements, they fail to recognize the complex nature of other interactions within the basal ganglia including communications between D1 and D2 receptor striatal MSNs; MSNs with collaterals in both the Gpi and GPi; GPi projections going back to the striatum; Gpi/SNpr projections, not only to the thalamus, but to the PPTg, habenula, and the superior colliculus, as well as a checks and balance functionally dynamic system regulated by mesolimbic and dopaminergic neuronal circuits.

2) Alteration within a particular CBGTC region: An additional pending question in TS is which region within the CBGTC circuit represents the primary originating physiologic abnormality? As will be briefly described, there is potential supporting data for several areas.
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<th>Pharmacological Agent</th>
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<th>GABA</th>
<th>Hist</th>
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a) Cortex: Evidence supporting a primary cortical involvement in tics includes: 1) the frequent association of tics with neuropsychiatric comorbidities, e.g., executive dysfunction,13,14 cognitive inhibitory deficits,15 attention deficit hyperactivity disorder (ADHD), obsessive–compulsive disorder (OCD), anxiety, mood disorder, and disruptive behaviors,16 2) the presence of a preceding sensory premonitory urge that is associated with activation in mesial and lateral premotor areas, the insula, SMAs, anterior cingulate cortex, and primary sensorimotor cortex;17 3) post-mortem studies demonstrating a greater number of changes in prefrontal regions (Brodmann area 9) than in caudate, putamen, or ventral striatum;18,19 4) volumetric magnetic resonance imaging (MRI) studies reporting larger dorsal prefrontal and parietal-occipital areas,20 changes in prefrontal, frontal, sensorimotor, cingulate, and temporal areas,21 and alterations of the corpus callosum; 5) functional connectivity studies showing increased connections between cortical-basal ganglia networks or widespread immature functional connectivity; 6) demonstrated areas of cortical hypermetabolism in positron emission tomography (PET) studies; 7) reduced inhibition within the motor cortex as demonstrated by transcranial magnetic stimulation (TMS); and 8) various animal models showing that disruption of cortical function leads to tic-like behaviors.

b) Basal ganglia: Evidence supporting a basal ganglia involvement includes: 1) its association with other movement disorders; 2) postmortem studies showing reduced density of parvalbumin positive interneurons, choline acetyltransferase positive cholinergic interneurons, and MSNs in the striatum;22,23 3) inconsistent imaging studies of the caudate and putamen;24–26 4) studies in human primates, rats, and mice, demonstrating that the disruption of the glutamate/GABA balance within the striatum causes tic-like behaviors.27–30

c) Other potential regions: Although many investigators focus on alterations within cortical and basal ganglia regions, there is preliminary imaging and animal model support for the involvement of the amygdala, hippocampus, ventral striatum, thalamus, and cerebellum. The ventral striatum, composed of the nucleus accumbens (NAC) and olfactory tubercle, serves as an integrating site for emotion, motivation, vigor, and attention, via inputs from the prefrontal cortex, anterior cingulate gyrus, hippocampus, and amygdala. Ultimately, these inputs culminate in the dorsal striatum where they influence motor output through alterations in the levels of glutamate, GABA, histamine, and dopamine.5,31 The Mthal is a major node linking cortical-striatal-basal ganglia and cortical-cerebellar networks. In three subjects receiving deep brain stimulation therapy, electrophysiological recordings showed that spontaneous motor tics are preceded by repetitive coherent thalamo-cortical discharges.32 Lastly, the cerebellum has been implicated as a site of abnormality based on animal models demonstrating that neurons in the cerebellar cortex and dentate nucleus have both increased abnormal discharges and blood flow immediately preceding tics.33 The latter has been used to counter hypotheses suggesting that tics are sensory driven. A cerebellar role...
is also supported by computational model analyses that reproduce anatomical and functional features of the Cortical-basal ganglia-thalamo-cortical and basal ganglia-cerebellar-thalamo-cortical networks.34

**CBGTC neurotransmitters: their pathophysiologic role and pharmacotherapy**

At the biochemical level, proper conveyance of messages through CBGTC circuits and the maintenance of stable connections require functionally integrated neurotransmitter systems. In the following sections, we discuss the role of specific neurotransmitters within the CBGTC; evidence implicating a specific transmitter’s pathogenic role in causing tics; and the selection and utilization of pharmacologic agents that address the proposed abnormality. Specific neurotransmitters to be reviewed include dopamine, glutamate, GABA, norepinephrine, serotonin, histamine, acetylcholine, endogenous opioids, and cannabinoids. In general, evidence associating a particular neurotransmitter with tics includes clinical responses to specific classes of medications; genetic protocols; measurements in blood, urine, and cerebrospinal fluid (CSF); imaging protocols (PET, single-photon emission computed tomography [SPECT], and magnetic

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**Figure 1. Cortical-Basal Ganglia-Thalamo-Cortical Circuit and their Interconnected Pathways.** Abbreviations: CM-PF, Centromedial-parafascicular Nucleus; GPe, Globus Pallidus Externa; GPi, Globus Pallidus Interna; Hypo, Hypothalamus; Mthal, Motor Thalamus; NAc, Nucleus Accumbences; SMA, Supplemental Motor Area; SNT, Subthalamic Nucleus; SNpc, Sustainia nigra paras compacta; SNpr, Sustainia nigra paras reticulate; PN, Pontine Nucleus; PPTg, Pedunculopontine Tegmental Nucleus; VTA, Ventral Tegmental Area.
Figure 2. **Neurotransmitters within Cortical-Basal Ganglia-Thalamo-Cortical and Interconnecting Pathways.** Abbreviations: ACh, Acetylcholine; CM-PF, Centromedial-parafascicular nucleus; Glu, Glutamate; GABA, Gamma (γ)-aminobutyric acid; GPe, Globus Pallidus Externa; GPi, Globus Pallidus Interna; Hypo, Hypothalamus; Mthal, Motor Thalamus; NAc, Nucleus Accumbences; SMA, Supplemental Motor Area; SNT, Subthalamic Nucleus; SNpc, Sustantia nigra pars compacta; SNpr, Sustantia nigra pars reticulate; PN, Pontine Nucleus; PPTg, Pedunculopontine Tegmental Nucleus; VTA, Ventral Tegmental Area.
resonance spectroscopy [MRS]); neurochemical assays on postmortem brain tissues; and/or animal studies. Although each neurotransmitter is discussed independently, it is essential to recognize that there are significant interactions among the multiple neurotransmitters and an alteration in one system could effectively modify a second or third agent (Figure 2). For example, in the striatum, both D1 and D2 MSNs receive input from cortex and thalamus (glutamate), local GABAergic and cholinergic interneurons, reciprocal connections with neighboring MSNs (GABA, encephalin, substance P), neuromodulators (dopamine, serotonin, noradrenaline), and from histaminergic neurons located in the hypothalamus. It is also important to recognize that studies in patients can be influenced by age at evaluation, gender, presence of existing comorbidities, current and prior medication use, and nuances of the selected methodology.

**Dopamine**

Dopaminergic pathways include three primary systems: nigrostriatal (from SNpc to dorsal striatum and basal ganglia); mesocortical (from VTA and some dorsal caudal extensions within the dorsal raphe nucleus [DRN] and ventrolateral periaqueductual grey regions to the frontal cortex), and mesolimbic (from VTA and some dorsal caudal extensions to the ventral striatum). Although not designated a specific system, both the SNpc and VTA provide dopaminergic input to the thalamus. Immunohistochemical studies have also identified a nigro/ mesothalamic dopaminergic system in human and macaque monkeys with greatest dopamine innervation to the ventral lateral and ventral anterior motor nuclei.35,36 Further, depending on the dopamine receptor subtype, a post-synaptic dopaminergic effect can be either excitatory (D1) or inhibitory (D2).6,35,37,38 Dopamine has a long-standing established role in motor activity, various movement disorders, temporal processing, regulating reward and reinforced learning, sensorimotor integration, cognitive function, and aversion.39-42 Evidence supporting a dopaminergic abnormality in TS is extensive and includes the recognition that the most effective tic-suppressing medications are dopamine receptor antagonists. Further, recognizing that tics have been labeled as a habitual behavioral disorder,43,44 studies in animal models have shown that increasing dopaminergic activity enhances the progression from goal-directed to habitual behaviors. Nevertheless, despite a strong sense that dopamine is involved in tic pathophysiology, due in part to inconsistent studies, hypothesized abnormalities have ranged from 1) an increased number of postsynaptic dopamine receptors or a greater dopamine receptor affinity; 2) increased dopamine innervation; 3) a presynaptic dopamine abnormality; and 4) an increased release of dopamine.

CSF studies in TS patients performed four decades ago identified reduced baseline levels of the dopamine metabolite homovanilllic acid (HVA) and its elevation following treatment with haloperidol.45 Unconjugated plasma HVA levels, however, did not correlate with tic severity scores46 and concentrations of dopamine, HVA, and 3, 4-dihydroxyphenylacetic acid were not elevated in post-mortem striatal samples.47 Protocols quantifying dopamine receptor binding in different brain regions have included both post-mortem tissue assessments and in vivo (PET or SPECT) methodologies. Unfortunately, results have been inconsistent. Labeled binding to the dopamine transporter or to the VMAT-2 have been utilized to identify excess dopamine innervation. Again, studies have produced variable results. In a single report, an excess accumulation of [18F]-fluorodopa led to suggestions of upregulation of dopa decarboxylase activity;48 however, a subsequent study found no differences.49

Proposed abnormalities of dopamine release have included both tonic (low basal) and phasic (burst firing) dopamine release systems.50 Confirmation of an alteration of tonic release would be expected to be associated with a change in baseline D2 receptor binding; e.g., increase tonic release would lead to a down regulation of post-synaptic dopamine receptors. However, as noted previously, there is great variability in receptor binding data. Several studies have quantified phasic dopamine release by assessing differences between sequential ([11C]-raclopride or [11C]-FLB457) PET scans, the first following an intravenous injection of saline and the second after an intravenous injection of amphetamine. Using this methodology, increased phasic release was documented in the putamen, medial frontal gyri, and anterior cingulate cortex.31 PET studies in TS patients, following symptom improvement using deep brain stimulation, have suggested that clinical improvement is associated with a decrease in dopamine release and an upregulation of dopamine receptors.32 A conflicting dopamine release study has been published in TS patients without OCD;53 however, differences are possibly explained by variations in PET acquisition and amphetamine administration. Clinical data supporting an increased phasic burst hypothesis also include the exacerbation of tics by stress and anxiety, a suggested exacerbation by stimulant medications, and tic suppression with very low doses of dopamine agonists. In summary, DA is a crucial factor in the dynamic modulation of the motor output of the CBGTC circuit and further studies are required to clarify its precise role in TS.

1) **Dopamine-modulating pharmacotherapy in TS:** Dopamine modulating pharmacotherapies for tic suppression, although effective, are generally not the initial prescribed medication, due to their potential side effects. Several recent reviews provide in-depth updates on the efficacy and safety of this therapy.34,55 Recognizing the varied pathophysiology hypotheses discussed above, it is not surprising that approaches to therapy have included the use of dopamine antagonists, VMAT-2 inhibitors, and dopamine agonists.

a) **Dopamine antagonists:** Medications in this category fall broadly into two categories: typical and atypical antipsychotics.

i) **Typical antipsychotics,** i.e., primary dopamine antagonists, can be subdivided based on their effect on a particular dopamine receptor. The two US Food and Drug Administration (FDA)-approved drugs in this category pimozide (a diphenylbutylpiperidine derivative) and haloperidol (a butyrophenone derivative) are both D2 antagonists with potential influences on the indirect pathway, plus numerous other dopamine sites. Pimozide is generally preferred, because of fewer side effects. Sulpiride and tiapride, substituted benzamides, have been
beneficial in European trials, but are not available in the United States. A new D1 receptor antagonist, ecopipam, via a possible effect on the direct pathway (or other), has been shown to be beneficial in adults and children, with TS. Fluphenazine, a phenothiazine derivative and combined D1 and D2 receptor inhibitor, has also been shown to be effective in several small studies and a retrospective chart review. Metoclopramide, which differs from other typical dopamine antagonists because of its lack of neuroleptic-like effects in the prefrontal, entorhinal, and ventral striatal cortices, was effective and well tolerated in a small controlled study.

ii) Atypical antipsychotics (aripiprazole, risperidone, olanzapine, ziprasidone, quetiapine, paliperidone) are characterized by a relatively greater affinity for 5-HT2 receptors than for D2 receptors, fewer extrapyramidal side-effects, and a potential benefit for behavioral comorbidities (anxiety, mood, disruptive behaviors). Aripiprazole, approved by the FDA for the treatment of tics, differs from other atypical neuroleptics by acting as a partial agonist at D2 post- and presynaptic receptors, the latter decreasing dopamine release. It also binds to 5-HT, histamine, and z-adrenergic receptors. Risperidone, a 5-HT2 receptor antagonist at low doses and D2 antagonist at higher doses, has moderate affinity for z-2 and histamine-1 receptors, and is effective in reducing tics. Long-term side effects seen in patients receiving either typical or atypical antipsychotics include weight gain, sedation, drowsiness, hyperprolactinemia, extrapyramidal symptoms, tardive dyskinesia, and QTc prolongation. It has been suggested that tardive dyskinesia is an uncommon side effect in TS patients treated with antipsychotics.

b) VMAT-2 inhibitors exert their effect by blocking the transport of dopamine into presynaptic vesicles and depletion of the level of dopamine at the synaptic terminal. Tetrabenazine, a benzoxquinolizine derivative, has been shown to be beneficial in open label trials. Concerns, however, exist regarding its use in individuals with depression and suicidality. Two new VMAT-2 inhibitors, approved for use in tardive dyskinesia, are currently being evaluated for the treatment of tics. Deutetrabenazine, a deuterated form of tetrabenazine, provides several pharmacokinetic advantages to tetrabenazine including a longer half-life and improved absorption. Valbenazine, a purified parent drug of the (+)-α-isomer of tetrabenazine has a half-life of about 24 hours. Preliminary studies suggest that both valbenazine and deutetrabenazine have fewer side effects than tetrabenazine, but which will be more effective for tic-suppression remains undetermined.

c) Dopamine agonists: Dopamine agonists (ergolide, ropinirole, pramipexole) have been considered as potentially therapeutic approaches for treating tics, based on their ability to presynaptically inhibit the release of dopamine. A multicenter randomized placebo-controlled trial with pramipexole was ineffective in suppressing tics in adolescents and children. In general, there have been relatively few studies and pergolide has been withdrawn from the US market because of serious potential side effects.

Glutamate

Glutamate, the brain’s primary excitatory neurotransmitter, has essential roles in CBGTC circuits. It is the neurotransmitter of projecting neurons in the cortex (to the striatum, thalamus, cerebellum, STN, VTA, SNpc, DRN; thalamus (to cortex, striatum); STN (to GPe, GPi, striatum, PPTg); PPTg (to basal ganglia); and cerebellar nuclei (to thalamus, red nucleus, vestibular nuclei).

Evidence supporting a role for glutamate in TS is derived from 1) a small postmortem investigation showing reduced levels of glutamate in the GPi, GPe, and SNpr. 2) MRS: using field strength of 3T, limited by an incomplete resolution of glutamate and glutamine, children had no change within the dorsal striatum or anterior cingulate whereas in adults Glx (glutamate and glutamine) was reduced in the striatum and thalamus. Using high field spectroscopy at 7T, 5–12 year olds with TS had elevated glutamate in the premotor cortex, but not striatum. The interpretation of MRS measurements of both glutamate and GABA is restricted; values represent the gross concentration of the substance in the entire voxel (includes neurons, glial, synaptic and extrasynaptic spaces, and cytoplasmic and organellar zones) and differences may be related to voxel placement or editing/fitting methods. 3) Animal models: in rodents, disrupting the balance between glutamate and GABA within cortical-striatal pathways induced tic-like activity and damaging N-methyl-D-aspartate (NMDA) receptors, located on dopaminergic nigrostriatal neurons prevented habitual, but not goal-directed learning. Lastly, accumulating evidence from studies employing optogenetic and chemogenetic methodologies support a role for glutamatergic output neurons and their targets in tic behaviors.

1) Glutamate modulating pharmacotherapy: Glutamate-altering medications have been reported to have a beneficial therapeutic effect on obsessive-compulsive symptoms. In a small TS study, neither a glutamate agonist (d-serine) nor a glutamate antagonist (riluzole) significantly improved tics compared with a placebo control group.

N-Acetylcysteine (NAC) is an amino acid supplement, which following its conversion to cystine, causes the release of glutamate from glial cells and, in turn, a reduced glutamate release from neurons. In a single 12-week add-on trial comparing the addition of NAC to placebo, no significant benefit was observed. Clonidine, although defined as an alpha-adrenergic agonist and discussed under “norepinephrine,” also influences the release of glutamate and regulates spontaneous and glutamate-modulated firing activity in medial frontal cortical pyramidal neurons.

GABA

GABA, the primary inhibitory neurotransmitter, is utilized by striatal synaptic projection neurons, striatal and cortical interneurons, the G Pi, and GPe. GABAergic neurons located within the VTA regulate learning behaviors through control of dopamine and cholinergic systems.
An alteration of GABAergic function in TS is supported by postmortem, MRS, PET, TMS, and animal studies. 1) Postmortem anatomical studies of the striatum show a reduction in the number of GABAergic parvalbumin-containing interneurons. 2) Cortical MRS results are variable with differences between data obtained at 3T and 7T. For example, there are reported reductions in the primary sensorimotor (SM1) cortex and anterior cingulate cortex; normal levels in premotor, ventral medial prefrontal, and dorsolateral prefrontal cortex, SM1 and primary visual cortex; and elevated values in the SMA.\textsuperscript{69} Within the striatum, a single MRS study, using 7T, reported no changes.\textsuperscript{64} 3) PET: a single PET imaging of GABAA receptors using \textsuperscript{[11C]}-flumazenil showed decreased binding bilaterally in the ventral striatum, globus pallidus, thalamus, amygdala and right insula.\textsuperscript{76} 4) TMS: a deficiency of cortical inhibitory interneurons is suggested by a reduction of short-interval intracortical inhibition.\textsuperscript{77} 5) Animal models: studies in human primates, rats, and mice have demonstrated that the local disruption of striatal GABA, via the injection of bicuculline or picrotoxin, can cause tic-like behaviors.\textsuperscript{27–30,78} This abnormal behavior can, however, be reduced or abolished by re-correction of the corticostriatal GABA/Glutamate balance.

1) GABA-modulating pharmacotherapy: Baclofen, a GABAB receptor agonist, has been variably effective as a treatment for TS. In an open-labeled trial, with doses ranging from 10 to 80 mg/day for 4 weeks, significant decreases were noted in motor and vocal tics.\textsuperscript{79} In a double-blind, placebo-controlled crossover study, baclofen in doses of 20 mg three times a day, statistically improved overall well-being, but did not reduce motor or vocal tic activity. Clonazepam, a benzodiazepine, is widely used for tics, despite limited studies confirming its tic-suppressing effect. In two single-blind comparison studies, one showed clonazepam was superior to clonidine for tic suppression,\textsuperscript{80} and the second that clonazepam was better than haloperidol, but only in patients with a high red blood cell to plasma choline ratio.\textsuperscript{81} As with all benzodiazepines, its use is limited by tolerance and adverse reactions including sedation, short-term memory problems, ataxia, and paradoxical disinhibition.\textsuperscript{82} Topiramate is a broad-spectrum anticonvulsant medication that enhances the activity of GABA and antagonizes the glutamate \textit{x}-amino-3-hydroxyl-5-methylisoxazole-4-propionic acid but not the NMDA receptor. In a single randomized study, topiramate was superior in reducing tics when compared with placebo.\textsuperscript{83,84} Levetiracetam is another antiepileptic drug with atypical GABAergic effects; enhances chloride ion influx at the GABAA receptor complex by reducing the effect of zinc and beta carbolines, which interrupt the chloride flux.\textsuperscript{85} In contrast to other GABAergic medications, levetiracetam was not beneficial for tics as measured in both a crossover trial comparing the drug to placebo\textsuperscript{86} and in a randomized, double-blind, crossover study with clonidine.\textsuperscript{87}

Norepinephrine

Noradrenergic fibers project widely to the cerebral cortex from the locus coeruleus and modulate frontal subcortical circuits implicated in TS. For example, the stimulation of central \textit{\alpha}2-adrenergic receptors causes decreased release of catecholamines through a GABA modulated feedback.\textsuperscript{88} Strong evidence for a norepinephrine mechanism in TS is lacking. Assays of norepinephrine or its metabolite 3-methoxy-4-hydroxyphenylethylene glycol have been normal in post-mortem cerebral cortex and basal ganglia as well as in plasma.\textsuperscript{47,100} Evaluations of norepinephrine in CSF have been variable, ranging from increased to normal values. The excretion of urinary norepinephrine in response to stress (i.e., lumbar puncture) was increased in TS subjects.\textsuperscript{96} Lastly, quantification of alpha-2 adrenoceptors in TS platelets were normal, but variable in post-mortem cortex.\textsuperscript{19,99}

1) Noradrenergic modulating pharmacotherapy: Therapeutically, two alpha-adrenergic agonists (clonidine and guanfacine) have tic-suppressing beneficial effects.\textsuperscript{81} Both have been shown to be more effective than placebo in reducing tic severity and to have a beneficial effect on ADHD symptomatology. A study comparing extended-release guanfacine to placebo did not, however, confirm a clinically meaningful effect size within the guanfacine group.\textsuperscript{92} Nevertheless, guanfacine is known to inhibit excitatory glutamatergic transmission of the pyramidal cells in the prefrontal cortex.\textsuperscript{73} Common side-effects include sedation, fatigue, drowsiness, orthostatic hypotension, dry mouth, and irritability.

Serotonin

Serotonergic afferents arise from the DRN and median raphe nucleus (MRN) in the midbrain. The DRN projects to the prefrontal cortex and MRN to the striatum, SNpc, VTA, and NAc. dorsal raphe nucleus (DRN) 5HT neurons receive monosynaptic input from multiple brain regions including the prefrontal cortex (glutamatergic) and the lateral habenula (GABAAergic).\textsuperscript{94,95} The brain serotonergic system is involved in reward processing and has been targeted in the treatment of depression, anxiety, and schizophrenia. It has been suggested that 5HT mediates some of its action by antagonizing the effect of dopamine\textsuperscript{86} and that dopamine denervation can lead to increased overall 5HT in the basal ganglia.\textsuperscript{97} Evidence suggesting a role for serotonin in TS is derived from serum, CSF, PET, and animal studies. Serotonin and its precursor tryptophan have been reported to be reduced in serum\textsuperscript{86} and 5-HHAA (a serotonin metabolite) to be decreased in CSF\textsuperscript{99} but normal in the cortex.\textsuperscript{89} [\textsuperscript{123I]}-\textit{\beta}-2-beta-carbomethoxy-3-beta-(4-iodophenyl) tropane (CIT) binding to the serotonin transporter has variable; one report identified a negative correlation between binding in the midbrain and vocal tic severity,\textsuperscript{101} and in a second, a trend towards a negative correlation between binding ratios and the severity of associated Obsessive Compulsive Behavior (OCB).\textsuperscript{102} \textit{[\textsuperscript{18F]}-Altanserin PET showed increased 5-HT2A receptor binding in multiple brain regions, including those not believed to be involved in the disorder.\textsuperscript{103} PET of tryptophan metabolism has demonstrated decreased uptake in the dorsolateral prefrontal cortical regions and increased uptake in the caudate nucleus and thalamus.\textsuperscript{104} In a mouse model, the injection of a 5-HT2A, 5-HT2B, and 5-HT2C receptor agonist \textit{(2,5-dimethoxy-4-iodoamphetamine produced a repetitive}
head twitch.105 This movement was altered by treatment with a variety of neurotransmitter (glutamate, GABA, dopamine, cannabinoids, acetylcholine, norepinephrine, and adenosine) altering agents, suggesting wide ranging and complex interactions.

1) Serotonin modulating pharmacotherapy: Other than studies with atypical antipsychotics, which have 5-HT2A receptor antagonism, there have been minimal reports. In general, selective serotonin reuptake inhibitors do not suppress tic activity.

**Histamine**

Histamine is a monoamine neurotransmitter synthesized from histidine by the enzyme L-histidine decarboxylase (HDC).106,107 Histaminergic neurons are in the tuberomammillary nucleus of the posterior hypothalamus and send projections throughout the CNS, including the forebrain and striatum. Histamine 3 (H3) receptors are found in high concentration in the cortex, striatum, amygdala, substantia nigra, and hippocampus, as well as on both histamine nerve terminals and postsynaptic cells.106,108 Furthermore, it has been demonstrated that D1 receptors on striatal MSNs in the direct pathway form heterodimers with H3 receptors (D1–H3) to exert complex inhibitory influences on the neurons within the direct pathway.109 In general, the histamine system is involved with the pre and post synaptic regulation of neurotransmitter release for dopamine, glutamate, GABA, serotonin, acetylcholine, and some neuropeptides.106

The link between histamine and TS was initially based on a genetic analysis in a two-generation autosomal dominant pedigree, in which a rare nonsense mutation (Trp317X) was identified in the HDC gene;110 an uncommon finding in the TS population.111 In animal models, a HDC knockout mouse, with negligible histamine levels, exhibits stereotypic movements and spontaneous tic-like symptoms after the intraperitoneal injection of amphetamine.112 Similar movements were produced in this model following H3R receptor activation in the dorsal striatum with both r-aminomethyl-histamine and immepip. The value of the HDC mouse as model for TS and related conditions has been recently reviewed.113

1) Histamine modulating pharmacotherapy: Data on H3 receptor agonists/antagonists and their usefulness in reducing tics is limited. In a single patient with TS and cataplexy, the medication pitolisant, an inverse agonist of the H3 receptor, did not decrease tics.114 A recent trial with AZD5213, a histamine H3 receptor antagonist, showed a 2–3-point decrease in the Total Tic Severity Score compared to placebo.115

**Acetylcholine**

Cholinergic fibers project from the basal forebrain to the cortex and from the lateral tegmental area to the locus coeruleus. In the striatum, large aspiny cholinergic interneurons innervate MSNs and other interneurons. It has been suggested that these cholinergic interneurons co-opt dopamine terminals and drive GABA release.40 Data from a rodent model, evaluated with electrophysiological recordings combined with optogenetics, suggest that nicotinic acetylcholine receptors affect striatal neurotransmission via excitatory inputs onto MSNs.116

The strongest evidence supporting involvement of this neurotransmitter in TS are post-mortem reports showing that the regional density of choline acetyltransferase (ChAT) containing interneurons is reduced in the caudate and putamen.23 In adult TS post-mortem frontal, temporal and occipital brain regions, no significant differences were identified for ChAT activity109 and receptor-binding for muscarinic cholinergic ([3H]-quiniclidinyl benzilate, QNB) receptors showed no generalized impairment. In contrast, using circulating lymphocytes as a method to quantify changes in CNS muscarinic receptors, [3H]-QNB binding was reduced in untreated TS patients.117 In CSF, measurements of acetylcholinesterase and butyryl-cholinesterase activities did not differ from controls.118 In mice, ablation of 50% of cholinergic interneurons in the dorsomedial striatum caused no effect. However, ablations in the dorsolateral striatum plus a stressful stimuli or amphetamine challenge caused tic-like stereotypical behaviors.119

1) Acetylcholine-modulating pharmacotherapy: Results of pharmacological studies in TS using agents that affect cortical nicotinic and muscarinic receptors are inconsistent. The administration of cholinergic precursors, including choline, lecithin, and dimethylaminoethanol (deanol) had little effect on motor tics.117,120–122 In contrast, anti-cholinergic agents (physostigmine) reduced the frequency of motor tics but exacerbated vocal tics.117 In an 8-week trial using mecamylamine, a nicotinic acetylcholine antagonist, the drug was not superior to placebo for reducing tic severity.123

**Opioids**

Opioid receptor agonists (i.e., endogenous β-endorphins, enkephalins, and dynorphins, as well as morphine) exert their pharmacological effects by binding to the G-protein coupled opioid receptors mu, delta, and kappa. Mu and kappa receptors are primarily located in basal ganglia regions and thalamus, whereas delta receptors are predominant in the striatum, STN, and GP.124 MSNs in the indirect pathway express enkephalin and those in the direct pathway express dynorphin.125 Endogenous opioids are believed to exert a reciprocal control between direct and indirect motor pathways via alteration of the excitability of MSNs expressing D1 and D2 dopamine receptors types. Although their exact mechanism of action remains unclear, the opioid system dynamically modulates other neurotransmitters. For example, endogenous opioids have been proposed to modulate the release of dopamine by activating presynaptic receptors on GAB Aergic interneurons in the mesolimbic-mesocortical dopaminergic system126–129 (Figure 3).

Primary evidence of a role for opioids in TS includes postmortem and CSF measurements of dynorphin. In a postmortem study, dynorphin {1-17} immunoreactivity was decreased in striatal fibers projecting to the GPi in a severely affected TS patient.130 In CSF, dynorphin-A {1-18} was increased in TS patients and the concentrations of this opiate correlated with the severity of obsessive compulsive symptoms, but not with tic severity.131 Studies in multiple animal models have suggested a functional communication between opioid receptors and the dopaminergic system. Pharmacological studies, in a wide variety of primate and non-primate species, have highlighted the
induction of stereotyped behaviors by apomorphine and morphine. Dual acting opioid receptor agonist and antagonist combinations (i.e., nalbuphine, nalorphine, pentazocine, butorphanol, and related compounds) have been used to selectively treat levodopa-induced dyskinesia. For example, macaques, receiving intravenous nalbuphine, a mu receptor antagonist and kappa receptor agonist, had resolution of their levodopa-induced dyskinesia.

1) Opioid-modulating pharmacotherapy: Clinical trials of naloxone, an opioid receptor antagonist, in TS have produced conflicting results. Some investigators found dramatic improvements in OCD, whereas others identified only a rare responder. In one double-blind randomized clinical trial of naltrexone, subjects reported reduction of tics compared to the placebo control group. The unmasking of TS-like symptoms following withdrawal from opiates has been cited as further evidence for their possible role in TS. Clearly, additional double blind, placebo-controlled studies are required to further establish the usefulness of opioids in TS. Concerns regarding the potential use of opioid therapy include addiction, decreased gastrointestinal motility, sedation, dyspnea, euphoria, anorexia, urinary retention, and dysphoria.

Cannabinoids

The endocannabinoids, N-arachidonoyl ethanolamine (AEA), and 2-arachidonoyl glycerol (2-AG), are naturally occurring compounds that bind to cannabinoid receptors (CBRs), specifically cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2). CB1 receptors, based on immunoreactivity assays, are located in the prefrontal cortex near glutamatergic fibers and within the striatum, cerebellum, and GP near pre- and post-synaptic GABAergic interneurons. CB2 receptors, initially believed to be solely peripheral, have been identified in the striatum, VTA, hippocampus, and thalamus. Both AEA and 2-AG are synthesized on demand from post-synaptic membrane phospholipids, which diffuse and bind to the pre-synaptic CBRs, and inhibit neurotransmitter release via retroactive feedback inhibition.

The presence of CBRs on dopaminergic axons remains controversial, and the functional interaction between cannabinoids and the dopaminergic system is subject of current investigations. In general, the endocannabinoid system exerts a broad neuromodulatory effect within the CBGTC circuitry through 2-AG and AEA retroactive feedback inhibition and via recruiting several second messenger systems (adenosine triphosphate [ATP], cyclic adenosine monophosphate, nitric oxide, and hydrogen peroxide [H₂O₂]) that also cause a decrease in neurotransmitter release.

Evidence for endocannabinoid involvement in TS comes from a very limited number of SPECT studies quantifying CB1 receptor binding using [123I]-AM281141 and the results of therapeutic trials (discussed below). In addition, a study has linked cannabis use in the last 2 months of pregnancy with an increased risk of TS in children. In mice lacking CB1 receptors, animals had difficulty learning a habit-based protocol. In a 2,5-dimethoxy-4-iodoamphetamine-induced head twitch mouse model, cyclohexyl-carbamoyl acid 3’-carbamoylbiphenyl-3-yl ester (URB597), an indirect cannabinoid agonist that enhances endogenous AEA levels, mitigated the tic-like head movements.

1) Cannabinoid-modulating pharmacotherapy: Several case reports and two small placebo-controlled studies have suggested that cannabinoids (smoking marijuana or using oral delta-9-tetrahydrocannabinol (THC)), has a beneficial effect on tics in TS patients. For example, a 6-week double-blind placebo controlled trial of THC in 24 TS patients showed a significant reduction in a self-reported severity scale. Additionally, in two case studies, individuals with severe comorbidities and complex TS reported a positive response to treatment with nabiximol, a combination of THC and CBD. Nevertheless, the use of cannabis-based pharmacotherapy remains controversial. Medical marijuana, Marinol® (dronabinol, THC) and Epidiolex® (CBD) are manufactured under FDA-regulated guidelines. Production guidelines, however, may vary in other regions of the world. Marinol® has been marketed for anorexia and as an acentiemic, whereas Epidiolex® was recently approved by FDA as a treatment of rare forms of epilepsy. Neither drug has received approval as a treatment for TS. The most common side effects are sedation, dizziness, headaches, “high” (euphoria feelings), red eyes, increased appetite, psychosis, depression, and cognitive impairment. To date, it is generally accepted that there is insufficient evidence to recommend the use of cannabinoids in TS.

A second investigative approach to cannabinoid therapy involves attempts to modulate the endocannabinoid system. In a recent phase 1B study, increasing the levels of 2-AG, by inhibiting its degradative enzyme monoacylglycerol lipase (MGLL), using the selective compound ABX-1431, reduced motor tics and premonitory urges. Although describing a new and unique approach, additional studies containing a larger sample size, longer therapeutic period, and controls for prior cannabinoid usage, are required.

Conclusions

As summarized, there has been an extensive effort devoted to clarifying the underlying pathophysiology of tics. Nevertheless, to date, the precise anatomical site of origin and primary underlying neurotransmitter abnormality remains undetermined. Potential explanations for the slow advancement are varied and include the complex nature of TS, with unpredictable and fluctuating motor and vocal tics that are confounded by the presence of multiple neuropsychiatric comorbidities. Discrepancies in anatomical, biochemical, imaging, and therapeutic trials are often attributed to subject age, gender, variable scales, prior or ongoing therapies, study design, methodologies, specificity, data analysis, etc. Concerns regarding animal models include a failure to recapitulate the human situation, the inclusion of non-tic movements, and anatomical differences between animal models and human subjects. Although it is important to note these limitations, it is essential to acknowledge the ongoing scientific advancements in our understanding of the complex and intricate interactions within the CBGTC circuits.
Figure 3. Diagram Showing the Interactions of Pharmacological Agents Used for Tic Suppression, and their Proposed Pre and Post-Synaptic Effects. α2-Agonists exert their effects on the pre and post synaptic α2-receptors while allosterically enhancing the affinity of GABA for the GABA-receptor complex (GABA-R). Post-synaptically, α2-Agonists enhance the synaptic impulses in recipient neurons by closing the hyperpolarization-activated cyclic nucleotide gated (HCN) channels and decreasing the cation ion efflux. Pre-synaptically, α2-Agonists inhibit excitatory glutamatergic transmission of the pyramidal cells in the prefrontal cortex. The effects of D1 and D2 receptor agonist/antagonist interactions have been recently reviewed. The mechanistic effects of D1-H3 and D2-H3 receptor heterodimers are inhibitory at the post-synaptic terminals. Dopamine has been shown to exert an inhibitory control over medium-sized spiny neurons (MSNs) when acting through D1-H3 heterodimers. This is in contrast to D1 receptor functionality in the direct pathway, where dopamine has an excitatory effect on D1 expressing MSNs. Cannabinoid receptor type 1 (CB1), on the glutamatergic and GABAergic corticostriatal projections is activated by 2-AG and AEA binding. These endocannabinoids are released by post synaptic membrane phospholipids. One intracellular effect of presynaptic CB1 activation on GABAergic interneurons is the increased production of mitochondrial H₂O₂. This H₂O₂ diffuses to adjacent axonal release sites, where it activates H₂O₂-sensitive KₐTP channels, leading to synaptic depression. Opioid receptors (mu, kappa, and delta) are activated by endogenous and exogenous opioid agonists. Although the exact mechanisms are unknown, however, the endogenous opioids are proposed to decrease the GABAergic tone within mesolimbic-mesocortical system by inhibiting voltage-sensitive Ca²⁺ channels, enhancing the outflow of K⁺ ions, and inhibiting the intracellular adenylyc cyclase.
In terms of localization, there is a general tendency to favor a site or component of the CBGTC circuit, rather than noting its multifaceted, interactive nature. For example, recent studies have emphasized the potential importance of an expanding list of cortical inputs with both excitatory and inhibitory roles; the emotional and motivational impact of the ventral striatum; the essential integrating role for the M1thal, interconnections with the cerebellum, and an ever-expanding number of feedback loops.\(^{155}\) Hence, while we await future scientific advances and more definitive data, our working model is that a disruption anywhere within the CBGTC circuit, or even one involving regions inputting to the circuit, can lead to an aberrant message arriving at the primary motor cortex.

At the biochemical level, the identification of the definitive primary neurochemical abnormality remains a challenge. In this report, we describe potential evidence supporting proposed abnormalities of nine different neurotransmitter systems. Although controversial,\(^ {156,157}\) the authors favor a functional involvement of the dopaminergic system, likely an alteration of phasic release. This bias is based on involvement in prior PET and laboratory studies and the overwhelming evidence that dopamine-modulating agents are the most effective tic-suppressing medications. Despite this claim, we readily note numerous studies, especially in animal models, that identify imbalances in other neurotransmitter systems. Once again, it is essential to recognize that these are complex integrated systems. For example, a change in one neurotransmitter has a significant effect on the functional activity of other interconnected systems. Hence, a future important goal will be to determine whether an identified abnormality is a primary or secondary phenomenon, i.e., the cause of or response to having tics.

In this manuscript, we have reviewed standard and emerging pharmacologic agents in TS based on their primary effect on a specific neurotransmitter. Clearly, a greater understanding of the underlying neurochemical defect in TS will lead to the development of new tic-suppressing therapies. Nevertheless, it is important that investigators carefully review existing data before eliminating a potential treatment. For example, preliminary studies can be influenced by atypical placebo effects, sample size, prior medication usage, etc. Finally, when dealing with a multi-transmitter, heavily inter-reactive system, a successful therapy may not need to directly target the primary abnormality.

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