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Review Article

A Combination of Mechanisms Contributes to the Development of Tardive Dyskinesia: Management Implications

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Abstract

Tardive Dyskinesia (TD) has defiled all forms of therapy and continues to constitute significant clinical problem. Existing hypotheses implicate dysregulations of both excitatory and inhibitory neurotransmitters, with consequent neuronal changes/damage. The present consensus is that a combination of mechanisms contributes to the development of TD. Authors advise on a combination therapy targeted at the cellular phenomena underlying the disease.

Keywords: Tardive Dyskinesia; Hypotheses; Glutamate; Dopamine (DA)

Abbreviations

NMII: Non Muscle Myosin II; BG: Basal Ganglia; TD: Tardive Dyskinesia; Snr: Substantia Nigra Pars Reticulata; Gpi: Globus Pallidus Internus; Gpe: Globus Pallidus Externus; SNc: Substantia Nigra Pars Compacta; DRBAs: Dopamine Receptor Blocking Agents; GABA: Gamma Amino Butyric Acid; SX_c-: Cystine/Glutamate Antiporter System X; AMPARs: A-Amino-3-Hydroxy-5-Methyl-Isoxazolepropionic Acid Receptors; NMDARs: N-Methyl-D-Aspartate Receptors; EAATs: Excitatory Amino Acid Transporters; MSNs: Medium Spiny Neurons; LTP: Long-Term Potentiation; DA: Dopamine

Introduction

Tardive dyskinesia (TD) is a syndrome of involuntary hyperkinetic movement disorder, affecting the face and/or the trunk and extremities. TD develops in association with long-term use of neuroleptic medication. DSM-IV-TR 2000 definition [1] includes: "the essential features of Neuroleptic-Induced Tardive Dyskinesia are abnormal, involuntary movements of the tongue, jaw, trunk, or extremities that develop in association with the use of neuroleptic medication; the movements are present over a period of at least 4 weeks and may be choreiform (rapid, jerky, nonrepetitive), athetoid (slow, sinuous, continual), or rhythmic (e.g., stereotypies) in nature; the signs or symptoms develop during exposure to a neuroleptic medication or within 4 weeks of withdrawal from an oral (or within 8 weeks of withdrawal from a depot) neuroleptic medication; and there must be a history of the use of neuroleptic medication for at least 3 months (or 1 month in individuals age 60 years or older)".

TD symptoms are troublesome or disabling, and impairs quality of life, both physically and emotionally [2,3]. TD has a prevalence of between 20%-40% of the patient population undergoing chronic neuroleptic treatment [4,5], and it is usually persistent and irreversible [5-8]. The annualized persistence rate after discontinuation of the offending conventional antipsychotic medication is 80% [9], or remission rate is 2% [10], and remission rate using VMAT2 inhibitors is 30-40% [10].

TD is fundamentally a disorder of human motor system in the brain, involving cortico- basal ganglionic-thalamo-cortical motor loop [11]. All studies [11-15] of human motor disorders have implicated BG and its nuclei (input, intrinsic and output nuclei) as well as its microcircuit dynamics. A lot of neurotransmitter systems have been implicated too but most prominent among them are glu-

taminergic, dopaminergic, GABAergic, cholinergic, adenosinergic, encephalinergic, dynornphinergic and a few peptides and cannabinoids.

Some of the theories and hyp0theses advanced to explain the pathophysiological basis of TD include: dopamine receptor supersensitivity and receptor upregulation theory; a disturbed balance between dopamine and cholinergic systems; noradrenergic dysfunction; dysfunctions of striatonigral, γ-aminobutyric acid (GABA)ergic neurons; excitotoxicity; neurodegenerative hypothesis; oxidative stress hypothesis; "Maladaptive synaptic plasticity" hypothesis; glutamatergic upregulation hypothesis; and recently Reflex Memory Theory. All these hypotheses focus mainly on basal ganglia, and the effects of neuroleptic medication on D2 receptors of the cortico-basal ganglionic motor loop. However, no candidate theory or hypothesis has offered a convincing explanation, but the consensus is that a combination of mechanisms contributes to the development of tardive dyskinesia [16,17].

In the main text, the author gives a highlight of striatal output pathways, then discusses the effects of dopamine receptor blocking agents (DRBAs, neuroleptic medication) on dopaminergic signaling, and the consequences of the blockade on glutamatergic neurotransmission. The author further discusses cascade of neuronal and astrocytic events that culminate in the development of TD. The author offers a perspective on the mechanisms that combine to cause the endpoint disorder, then suggested management approaches, research directions and draw conclusions.

Highlight on striatal output pathways

BG controls voluntary movement through two GABAergic pathways; the direct (striatonigral) and indirect (striatopallidal) pathways. Both pathways project to the output nuclei (Gpi/Snr). Activation of the 'direct pathway' promotes movement and activation of the 'indirect pathway' limits motor function so that excessive and erratic movements do not occur [18]. DA is the neuromodulator of both pathways, regulating the excitatory and inhibitory neurotransmissions of the neurons.

The 'direct pathway' expresses D1 receptor (D1R), adenosine A1 receptors (A1R) and dynorphin [19] to form an allosteric, antagonistic molecular heteromer, where D1R is excitatory and A1R is inhibitory [20], but dynorphin is the tract stabilizer [21].

The 'indirect pathway' expresses D2 receptors (D2R), adenosine A2A receptors (A2AR), and enkephalin (ENK) [19] to form an allosteric, antagonistic macromolecular heteromer, where D2R is inhibitory and A2AR is excitatory [20], but enkephalin is the tract stabilizer [21]. Striatal A2A receptors at the pre-synaptic glutamatergic terminals boost the efficiency of glutamatergic information flow in the indirect pathway by exerting control, either pre- and/or post-synaptically, over other key modulators of glutamatergic synapses, including D2 receptors [22].

These two pathways work together, though in opposite directions, to control voluntary movement. Figure 1 shows a simplified diagram of these pathways.

Figure 1: graphic model showing the direct and indirect striatal pathways that facilitate normal movement.

Abbreviations: DA: Dopamine; Th: Thalamus; SNr/SNR: Substantia Nigra Pars Reticulata; Gpi: Globus Pallidus Internus; GPe: Globus Pallidus Externus; SNc: Substantia Nigra Pars Compacta; BG: Basal Ganglia; and STN: Subthalamic Nucleus.

All areas marked: red represent predominantly glutamatergic transmission; blue, predominantly GABAergic transmission, and green represents balanced excitation/inhibition. The structures considered to form the basal ganglia network include the striatum,

the globus pallidus externa (GPe) and globus pallidus interna (GPi), the substantia nigra pars compacta [SNc] and substantia nigra pars reticulata [SNr]), and the subthalamic nucleus (STN). These subcortical nuclei are interconnected and form a part of the frontal-subcortical loops. The striatum is a prominent input nucleus to the basal ganglia, which receives glutamatergic projections (shown in red) from virtually every cortical area, and predominantly transmit same to D2 (D2-like dopamine receptors) family receptors, and also dopaminergic inputs (shown in blue) from the SNc. The cortex exerts an excitatory influence over striatal efferent neurons (medium spiny neurons [MSNs]), which project to the basal ganglia output nuclei (GPi and SNr,) via two pathways: The "direct" pathway is predominantly a GABAergic projection (striato-GPi/SNr), expressing: D1 [D1-like dopamine receptors] family receptors (as excitatory modulators); adenosine A1Rs (as excitatory inhibitors) [22]; and dynorphin (as tract stabilizer) [21], where these receptors form molecular heteromers [22], but the final output to the output nuclei (Gpi/Snr) is inhibitory. The MSNs of the indirect pathway (striato-GPe-GPi/SNr), also GABAergic, are under inhibitory influence from D2 [D2-like dopamine receptors] family receptors, but also expressing: adenosine A2ARs (as excitatory enhancers) [22]; and encephalin (as tract stabilizer) [21], to form macromolecular $A_{2A}R$-D_2R heterotetramer-AC5 complex [20], yet the final output to the output nuclei (Gpi/Snr) is inhibitory. The output nuclei of the basal ganglia are also under excitatory influence arising from the cortex via a relay in the subthalamic nucleus (STN, hyper-direct pathway. It is proposed here that, even though the output of both direct and indirect pathways is "inhibitory," and hyper-direct pathway is excitatory, the sum effect is a balanced excitation/inhibition (shown as green from indirect pathway through output nuclei to thalamus, thus cortex), manifesting phenotypically as voluntary, controlled movement; an imbalance may manifest as a disorder. 'Balance' here does not mean 'equal' excitation/inhibition, rather, it means 'basal functional state' of BG motor system. This balance is achieved through the neuro-modulatory effect of DA on glutamate.

Effects of DRBAs on dopaminergic signaling

The Striatum is the most prominent input nucleus to the basal ganglia [18-20], and it is composed of medium-sized spiny neurons (MSNs) which, constitute 90-97% of striatal neurons and are all inhibitory neurons that use GABA as neurotransmitter [13,18,19,20]. The Striatum receives dense excitatory (glutamatergic) projections from cortical areas [13,18,15], and also dopaminergic projections from substantial nigra pars compacta (SNc) [12,19]. The DA modulates the glutamate and the GABA actions in the striatum. DA acts as a neuromodulator regulating the glutamatergic inputs onto the principal neurons, and upon release, DA rapidly influences synaptic transmission modulating both AMPA and NMDA receptors thereby controlling the striatal output [14]. Dopamine input to the striatum is required for voluntary motor movement, and this function is dependent on either excitatory or inhibitory modulation of corticostriatal synapses onto medium spiny neurons (MSNs) [23].

DA acts via D2 receptors to modulate the activity of glutamatergic inputs onto MSNs of the indirect pathway of the dorsal striatum, thereby regulating glutamate release [24,25,23,26,14].

In TD development, dopamine D2-receptor antagonism by neuroleptic medication is a necessary initial step that triggers reactive changes in striatal circuits [4,27]. By blocking presynaptic D2 receptors, neuroleptics enhance striatal glutamatergic neurotransmission [4] because the continuous blockade of D2 receptors results in impairment of the modulatory function of dopamine on the glutaminergic terminals in the dorsal striatum. The neuromodulatory impairment of DA leads to upregulation of glutamatergic neurotransmission and synaptic plasticity of glutaminergic neurons [10], and consequently excitotoxicity, oxidative stress and neuronal damage [4].

Neuronal and astrocytic events that contribute to TD development

Synaptic glutamate release from presynaptic terminals via activation of ionotropic glutamate receptors rapidly increases extracellular glutamate concentrations within the synaptic cleft [28], but under basal conditions, the level declines within milliseconds due to diffusion, and reuptake by the excitatory amino-acid transporters (EAATs) [29].

Because DRBAs enhance striatal glutamatergic neurotransmission by blocking presynaptic D2 receptors, there is an exacerbation or prolonged activation of glutamate receptors at the postsynaptic sites, and this starts a cascade of neurotoxicity, including cationic influx, mitochondrial dysfunction, energetic and oxidative stress, and overproduction of reactive oxygen species (ROS) [30]. The oxidative stress and excessive intracellular ROS can also induce excitotoxicity by stimulating extracellular glutamate release [30]. The presence of ROS has been shown to decrease glutamate trans-

porter activity, impairing synaptic clearance of glutamate further contributing to the increase in extracellular glutamate concentration [30]. Astrocytes are responsible for about 90% of the glutamate clearance from the synaptic cleft and are also responsible for the maintenance of glutamate homeostasis by sustaining its synthesis, uptake and release *via* the glutamate-glutamine cycle, and because of this significant role of astrocytes in glutamate reuptake, impairment of astrocytic glutamate transporters leaves neurons highly susceptible to excitotoxicity [30].

An excess of extracellular glutamate blocks the glutamate/cystine-antiporter system Xc-, depleting the cell of cysteine, a building block of the antioxidant glutathione, and deficiency of glutathione leads to accumulation of reactive oxygen species and eventually cell death [31]. Additionally, excess of extracellular glutamate reduces expression and/or activity of EAATs, setting up vicious cycle of extracellular glutamate accumulation, excitotoxicity, oxidative stress, and weak antioxidant defense system. These events ultimately lead to disruption in the basal ganglia motor system and loss of voluntary control of movement.

Perspective

The current theories/hypotheses implicate D2 dysregulation, enhanced glutamatergic neurotransmission, excitotoxicity, oxidative stress, maladaptive synaptic plasticity and neuronal damage as key events that lead to TD development. Each of these events contributes to the process of TD development, meaning a combination of mechanisms contributes to the development of tardive dyskinesia [16,17].

TD is fundamentally a movement disorder involving the basal ganglia, specifically the motor system. A balanced excitation/inhibition of neurons in the brain ensures voluntary control of movement. Glutamate is the major excitatory neurotransmitter and GABA the major inhibitory neurotransmitter, respectively in this motor system, but dopamine acts as a neuromodulator, modulating both glutamate and GABA.

Blockade of D2 receptors (D2Rs) by neuroleptic medication impairs D2 modulation of glutamatergic activities leading to upregulation of glutamate, and this triggers a cascade of events leading to TD development. The extant observation that striatal dopamine depletion provoked excessive striatopallidal neuronal activity [32] is consistent with the assertion that the 'impairment' of D2Rs in the indirect pathway (striatopallidal neurons) enhanced striatal glutamatergic neurotransmission in the striatopallidal neurons and shifts the balance of excitation/inhibition in favour of excitation. The blockade of D2 receptors may have also 'impaired' the dopamine-facilitated inhibition of the striatopallidal neuron, giving way to the adenosine-facilitated activation of the striatopallidal neurons with consequent excitation of the output nuclei (GPi and SNr). The D1 receptors are excitatory in nature. Therefore, the sum effect of the two pathways on the output nuclei [GPi and SNr) becomes tonic excitation, and this is a complete reversal of the normal BG output, that is, from tonic inhibition to tonic excitation.

Another pointer to glutamate hyperactivity in TD is the finding of higher levels of excitatory amino acid markers in the CSF of schizophrenic patients with TD than in the CSF of those without TD [4]. The increased glutamate activity generated cascade of neural events that led to maladaptive synaptic plasticity of glutaminergic neurons, causing disruption in the BG motor system which, in turn leads to "abnormal basal ganglia output," and "formation of miscoded motor programs" and abnormal movements [9]. Oyigeya [33] proposed that maladaptive memory, otherwise called reflex memory has a role to play in TD pathogenesis, especially the "persistence" and "irreversibility" of the disorder even after discontinuation of the offending neuroleptic medication.

In the author's perspective, the resultant "abnormal basal ganglia output" is the 'reversal from tonic inhibition to tonic excitation', and the "formation of miscoded motor programs", which, in effect means 'maladaptive memory', is phenotypically expressed as the "abnormal movements." Taken together, these endophenotypic dynamics, resulting in the formation of maladaptive memory, eventually manifested phenotypically as the "persistent" and "irreversible" involuntary and uncontrollable movement disorder that characterize TD. (Figure 2) is a proposed model of BG motor system in TD where the BG motor output, to the thalamus, is tonic excitation and mediated by glutamatergic transmission, instead of GABAergic transmission.

All areas marked: red represent predominantly glutamatergic transmission; blue, predominantly GABAergic transmission. The structures considered to form the basal ganglia network include the striatum, the globus pallidus externa (GPe) and globus pallidus interna (GPi), the substantia nigra pars compacta [SNc] and sub-

Figure 2: shows a proposed model of BG motor system in TD. Abbreviations: DA: DOPAMINE; Th: Thalamus; SNr/SNR: Substantia Nigra Pars Reticulata; Gpi: Globus Pallidus Internus; GPe: Globus Pallidus Externus; SNc: Substantia Nigra Pars Compacta; BG: Basal Ganglia; TD: Tardive Dyskinesia; and STN: Subthalamic Nucleus.

stantia nigra pars reticulata [SNr]), and the subthalamic nucleus (STN). These subcortical nuclei are interconnected and form a part of the frontal-subcortical loops. The BG motor system is the most implicated system in TD pathology. The striatum is a prominent input nucleus to the basal ganglia, which receives glutamatergic projections (shown in red) from virtually every cortical area, and predominantly transmit same to D2 (D2-like dopamine receptors) family receptors, and also dopaminergic inputs (shown in blue) from the SNc. The cortex exerts an excitatory influence over striatal efferent neurons (medium spiny neurons [MSNs]), which project to the basal ganglia output nuclei (GPi and SNr) via two pathways: The "direct" pathway (shown in blue) is predominantly a GABAergic projection (striato-GPi/SNr), expressing: D1 [D1-like dopamine receptors] family receptors (as excitatory modulators); adenosine A1Rs (as excitatory inhibitors); and dynorphin (as tract stabilizer), where these receptors form molecular heteromers, but the final output to the output nuclei (Gpi/Snr) is inhibitory. In this model, it is assumed that this pathway is not grossly affected in TD so, it remains predominantly GABAergic.

The MSNs of the indirect pathway, striato-GPe-GPi/SNr (shown in also GABAergic, are under inhibitory influence from D2 [D2-like dopamine receptors] family receptors, but also expressing adenosine A2ARs (as excitatory enhancers); and encephalin (as tract stabilizer), to form macromolecular $A_{2A}R$-D_2R heterotetramer-AC5 complex, yet the final output to the output nuclei (Gpi/Snr) under basal conditions is inhibitory, but in TD the striatopallidal neurons become dysfunctional. The output nuclei of the basal ganglia are also under excitatory influence arising from the cortex via hyper-direct pathway.

In TD pathology, it is proposed that the neuro-modulatory effect of DA on glutamate is 'impaired' because of the inhibitory effect of DRBAs on DA, specifically D2 receptors. Consequently, the inhibitory influence from D2 [D2-like dopamine receptors] family receptors on striatopallidal neurons is weakened, leaving the excitatory influence of glutamatergic transmission, enhanced by A2ARs, to dominate the tract, and the net effect is excitation of striatopallidal neurons, and this is projected to the output nuclei. In addition, the glutamatergic excitatory influence arising from the cortex via the hyper-direct pathway, projecting on to output nuclei (Gpi/Snr) further excites the output nuclei. It is assumed that the sum excitatory influence from the indirect pathway and hyper-direct pathway onto the output nuclei outweighs the inhibitory influence from the direct pathway, and this shifts the balance of excitation/inhibition in favour of excitation, reversing the BG output from tonic inhibition to tonic excitation (shown in red from indirect pathway through to output nuclei, to thalamus, thus cortex). With prolonged domination of glutamatergic transmission in the BG, a state of excitotoxicity is created with consequent maladaptive synaptic plasticity and formation of maladaptive memory, the Reflex Memory. It is further proposed that this information becomes the output of the BG that is relayed to the thalamus, thus the cortex, and then conveyed through the motor neurons to the skeletal muscles, manifesting phenotypically as automatic, involuntary, uncontrollable and hyperkinetic movement termed TD.

The "synaptic plasticity of glutaminergic neurons" caused by the continuous blockade of dopamimergic receptors is maladaptive because it originates from a defect in circuit remodeling [33].

This "maladaptive synaptic plasticity" caused by sustained excitotoxicity may have resulted in loss of selectivity and specificity of microcircuit nuclei of the BG motor system. The neurons may have encoded memory of all these events in the system, and over time recognize the consolidated 'maladaptive memory' as a 'new normal' of motor memory, akin to what Teo and colleagues [9] called "miscoded motor program", and this abnormal motor memory is in turn fed into the cortex through the thalamus.

This processed motor information ('maladaptive memory') in the BG is sent to the cortex through the thalamus and then descends to the brain stem and to the spinal cord through corticobulbar and corticospinal tracts, respectively to control the musculature that are responsible for the conscious or voluntary movements of skeletal muscles. The automatic retrieval of this maladaptive motor memory is expressed phenotypically as involuntary, unconscious, uncontrollable, and hyperkinetic movement termed Tardive Dyskinesia.

The author therefore proposes that the "persistence" and "irreversibility" of TD phenomena, irrespective of its etiopathogenesis, is due to maladaptive (reflex) memory. This memory is otherwise called reflex memory because, unlike normal automatic memories, its retrieval is automatic, reflexive and uncontrollable, and it continually disobeys "inhibition rule" and it does not reconsolidate after retrieval [33] in awake state.

Given the multiple mechanisms involved in the development of TD, the author believes a combination therapy is best suited for TD management, and to be targeted at the underlying cellular phenomena of the disorder instead of specific symptoms [30]. This is because the molecular mechanism that triggers excitotoxicity involves alterations in glutamate and calcium metabolism, dysfunction of glutamate transporters, malfunction of glutamate receptors, particularly N-methyl-D-aspartic acid receptors (NMDAR) and a consequence of other cellular phenomena, such as mitochondrial dysfunction, physical neuronal damage, and oxidative stress [30].

Management implications

Based on this perspective, TD evolves from DRBAs-related glutamate dysregulation with consequent excitotoxicity and maladaptive synaptic plasticity leading to maladaptive memory formation. So, if the glutamate concentration is properly regulated and the excitotoxicity is stopped and the 'temporary neurodegenerative process' is reversed, the BG may return to a healthy state to form adaptive motor memory. This will replace, in form of editing and updating, the earlier maladaptive motor memory formed in association with glutamate-linked pathologies. The new adaptive motor memory will then be relayed to the cortex to update the earlier maladaptive motor memory sent to it during the period of excitotoxicity, for memory is not a stable record of experience, but an ongoing process that allows existing memories to be modified with new information through a reconsolidation-dependent updating process [34].

The author's perspective is that measures aimed at controlling glutamate-linked excitotoxicity may prevent TD development, and measures aimed at erasing the already formed maladaptive memory will provide a cure for established TD.

Measures aimed at controlling glutamate-linked excitotoxicity

At the commencement of DRBAs, all at-risk patients may be placed, as adjuvants, a combination of antioxidants, EAATs enhancers, and drugs known to inhibit excessive presynaptic release of glutamate. With this combination, it is hoped that neuronal excitability may be controlled and glutamate reuptake will continue to be effective, hence glutamate homeostasis may be achieved.

Measures aimed at erasing the maladaptive motor memory

The maladaptive motor memory is acquired, hence epigenetically determined so, its performance can easily be modulated, whether impaired or improved, by epigenetic processes [35]. This primarily involves the use of inhibitors of DNA demethylation and histone deacetylation.

Using Blebbistatin (Blebb), an inhibitor of nonmuscle myosin IIB, researchers achieved selective erasure of dangerous addiction-associated memories in preclinical studies [36-38]. Even though this agent was used on emotional memory, it may work on motor memory too because of the massive neuronal interconnectivity of the brain.

Optogenetics has capacity to target and selectively and reversibly deactivate and reactivate not only relatively new but even very remote, well-consolidated memories [39]. Optogenetics has been used in preclinical studies to selectively erase/inactivate memory by inducing long-term depression (LTD), and also restore/reac-

tivate memory by inducing long-term potentiation (LTP) [40]. Though optogenetic therapies have not yet been employed in patients, it is conceivable that this may one day be a viable treatment option for movement disorders [41], especially now that it has already been approved for its first clinical trials in humans [39].

In TD, neurons remain in excitable state most times, hence labile and unstable and therefore vulnerable to manipulations using pharmacological drugs or optogenetics. Figures 1 and 2, adopted from Andres and Darbin [42], but modified, attempt to differentiate (using colours), basal ganglia motor system in health and in TD, and to further demonstrate the excitable state of BG system in TD phenomena as canvassed in this perspective.

Future research direction

More research works are needed to clearly ascertain the roles of glutamate in the development of TD. There is also a need to confirm or refute the claim that maladaptive motor memory contributes to TD development, and especially, its persistence and irreversibility even after discontinuation of DRBAs.

Conclusion

In conclusion, the present theories/hypotheses offered good explanations of the evolution of TD, but these have not yet translated to a cure for TD. However, it is clear that a combination of mechanisms contributes to TD development, but more research is needed to confirm or refute the prime position of glutamate in this perspective which appears to be a radical deviation from the long-held view of dopamine receptor super sensitivity and receptor upregulation theory. There is also a need to confirm or refute the claim that maladaptive motor memory is responsible for the persistence and irreversibility of TD even after discontinuation of DRBAs. There is a need for combination therapy for TD, targeting primarily, the cellular phenomena underlying the disorder.

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