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Review Article

Recent Advances in Therapeutic Targets of Tardive Dyskinesia

Shilpa Rani,[1*] Kanika Sahore[2]

[1]Department of Pharmacology, I.S.F College of Pharmacy, Moga
[2]Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar

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Abstract

Tardive dyskinesia is a hyperkinetic neurodegenerative movement disorder which is severe, debilitate, unrealized and everlasting mainly arises after prolong medication with Dopamine antagonist. The pathophysiology mechanisms of TD mainly consist of dopamine receptor super sensitivity, GABA depletion, cholinergic deficiency, neurotoxicity, changes in synaptic plasticity, and defective neuroadaptive signaling. Tardive dyskinesia is a progressive and potentially irreversible condition which mainly correlates to adverse of dopamine antagonism leading to neurodegeneration and movement disorders like Pill rolling movements of fingers, lip puckering, facial grimacing. Their recurrent factors could allow classify tardive dyskinesia according to their potential, beneficial targets so that it may be used for further initial interventions which are necessary. The focus of this article is a pathophysiology of and an understanding the complex cascade of secondary neurodegeneration.

Key words: Tardive dyskinesia, Schizophrenia, DA-R super sensitivity, vacuous chewing movements, Neurotoxicity, Excitotoxicity

Abbreviations : DA- Dopamine, GABA - γ-aminobutyric acid, GP- Globus pallidus, GP-Globus pallidus internal, GPe- Globus pallidus external, ROS- Reactive oxygen species, NTs-Neuro-transmitters, Nrf2-Nuclear factor 2, ARE - Antioxidant response element, VCMs-Vacuous chewing movements

INTRODUCTION

The patients suffering from Schizophrenia involving involuntary, abnormal movement disorders were never treated with any antipsychotic agent. The risk of tardive dyskinesia is increased, when a person has been taking antipsychotics and the risk also increase with age. The risk of TD is greater with conventional antipsychotics than second-generation antipsychotic drugs[1], which are used for psychiatric, mental and neurological disorders such as Parkinson's disease[2].The term Tardive originates from the French Tardif meaning 'late" while dyskinesia originates from Greek word kinesia related with "motion and movement," while "dys" is related with "insufficient" or "abnormal"[2]. It is irreversible disorder and its prediction is very difficult to do [3]. Negative symptoms and cognitive impairment both are associated with the schizophrenic patients [3].The involuntary movements involves tongue writhing, lip puckering movements, pill rolling of finger movements, purposeless sometimes the limbs or trunk are also effected. Sometimes the legs are so severally affected that walking becomes difficult and different vocal communication[4]. TD mainly affects the proximal muscles resulting in (quick, jerky and non-repetitive movements)are also known aschore form while in some cases results in slow, supple or writhing, and involving distal muscles known as athetoid, or may be sometimes dystonic and stereotypic or a combination of these[5]. Thus Tardive dyskinesia (TD) is one of the complex challenging psychiatric disorder which involves random movements of tongue, lips, jaw, as well as facial grimacing extremities was described, as a significance of long-term experience to first-generation antipsychotic (APD)[6-9].

Risk Factors for Tardive Dyskinesia:-

Tardive dyskinesia occurs after many months or years of Antipsychotics therapy. Other risk factors involving tardive dyskinesia are classified below:-

Table 1: Risk Factors for Tardive Dyskinesia

	Risk factors	Therapeutic Effect
1.	Sociodemographic factors	Aging
2.	Psychiatric disorder	Hopelessness
3.	Drug-related factors	Neuroleptic drugs
4.	Other patient-related factors	History of Diabetes
5.	Genetic factors	50 to 100 gene mutations and variations reported each year as associated with schizophrenia
6.	Non-genetic risk factors	• Infection during fetal life • Brain injury • Anoxia at birth • Trauma in childhood • Abuse of street drugs and steroids • Brain lesions • Psychosocial stress • Isolation, smoking, and excess coffee

Tardive Dyskinesia Deviant

On the basis of pathophysiology and treatment, various forms of TD have been reported and which reveals the important differences from typical TD[1, 10]

Tardive Dystonia

Tardive dystonia is a condition of sustained muscle contractions is due to neuroleptics therapy in which patients show a more generalized involvement and demonstrate a focal or segmental involvement.

Tardive Akathisia

It is described as subjective restlessness along with motor agitation idiomatic distress is a stereotype motor movement attributed to TD and is considered as a subtype of TD. It mainly includes repetitive touching of forehead scalp crossing and uncrossing of legs, pacing, and body rocking repetitive tapping and marching movements.[11]

Tardive Blepharospasm

TD is expressed as a repetitive, forceful, sustained contraction of orbicularis oculi. Blepharospasm is a focal dystonia affecting the motor system of the brain leading to involuntary movement or posture. Meige syndrome which has been presented in TD. Symptoms belong toblepharospasmand accompanied by or mandibular dystonia with manifestations over face, jaw, and neck. The condition mainly induced by long-term exposure to Dopaminergic antagonist and antihistamines[12].

Tardive Myoclonus

Myoclonus is a rare disorder used to describe a brief, light like jerks by the body which presents as sudden brief jerks of muscles in the face, neck, trunk[11a,10,11c,1].

Tardive Tics and Tardive Tourettism

Tardive tics and Tardive tourettism (TTt) resemble Tourette's syndrome and present during or after treatment with dopamine antagonists. Classically TTt begins in individuals elder than 21 years of age, while Tourette's syndrome commonly appears in children by age 7 years.[11a,1,11b,11c].

Tardive Tremor

In a variety of hyperkinetic movement disorder, one of them is tardive tremor which is an attention, deficit hyperactivity movements disorder including chorea, dystonia, myoclonus, or stereotypy [14,15].

Tardive Gait

Tardive gait is a drug-induced motor disturbances which have been classified varients of TD involving movements[16]. Disturbances may occur concurrently[11c].

Pathophysiology of Tardive dyskinesia:-

The pathophysiology of TD is still undefined complex and remains unclear. Multifactor is responsible for TD , to clarify the involuntary and irreversible effects of TD, Various models have been

planned and also on the management of TD[17]. Various inclusive reviews have been surveyed or published [5,18]. Their main aim was to suppress the dyskinetic symptoms. Many mechanisms has been proposed to explain the induction of TD on long-term use of neuroleptics which mainly involves dopamine receptor super sensitivity[19], serotonergic dysfunction [20], GABA deficiency[21], and the oxidative stress theory[22]. The most accurate theory was post synaptic dopamine–receptor hypersensitivity[23]. This model explains the long-standing blockage of dopamine in the receptor leading to permanent receptor hypersensitivity. For the explanation of TD development various neurochemical theory has been planned which include: (i) a concerned balance between dopamine and cholinergic systems; (ii) noradrenergic dysfunction; (iii) dysfunctions of striatonigral, γ-aminobutyric acid (GABA)ergic neurons; and (iv) excitotoxicity.[11c,12a,12b].

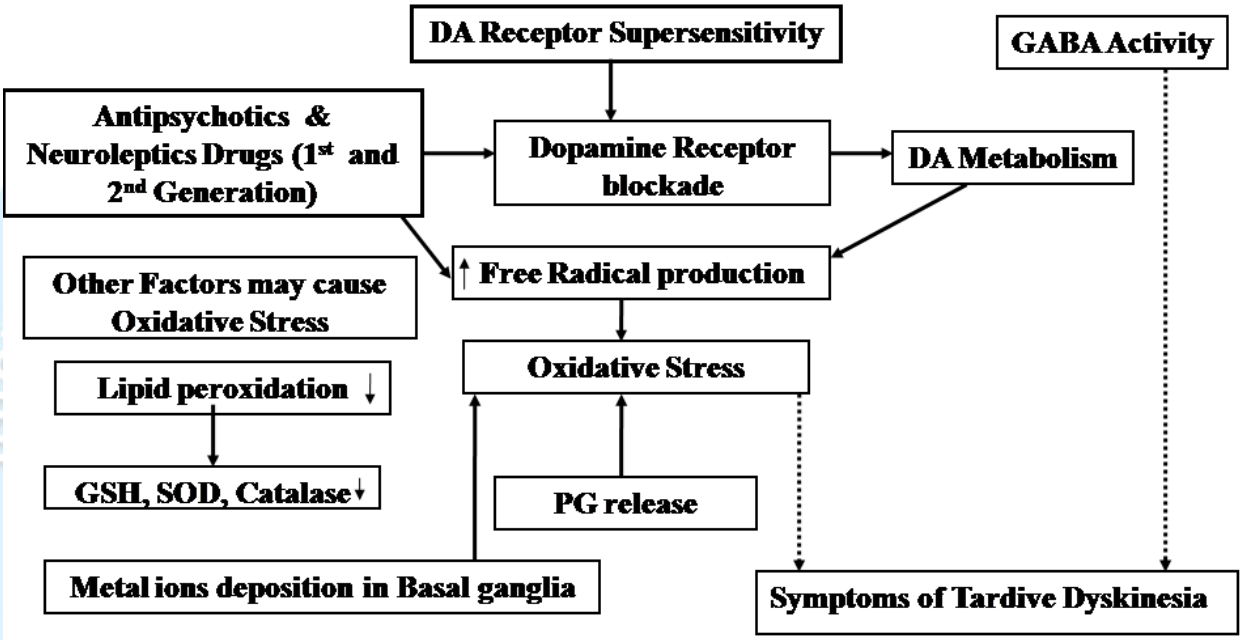

Figure 1: Pathophysiology of Tardive dyskinesia

Beneficial Targets to Improve Tardive Dyskinesia Side Effect

Recognition of novel targets may materialize as a potential therapeutic tool to tactic tardive dyskinesia. DA-R super sensitivity, GABAergic neuronal dysfunction, cholinergic deficiency, Synaptic plasticity, Defective neuroadaptive signaling may provide potential targets to improve Tardive Dyskinesia.

Development of Tardive Dyskinesia and Imbalance of Neurotransmitters

DA-R super sensitivity, GABAergic neuronal dysfunction, cholinergic deficiency has been involved in Development of Tardive Dyskinesia.

Dopamine Receptor (DA-R)super sensitivity

Dopamine super sensitivity theory has approached to studying TD. In the frontal cortex and striatum there is an 8%–30% amplify of D2-Rs, increase solidity in all DA pathway causes neurotic of DA-Rs, chiefly D2 type. [24]Abnormal involuntary movements scales (AIMS) is designed to measure involving movement known as TD by doing study on rat models that shows impulsive vacuous chewing movements (VCMs) with high- dose haloperidol. The pathological involving movement due to hypersensitivity of D2-Rs results in excess of inhibition of the globuspallidus (GP) internus (GPi) and subthalamic nucleus[24a]. In patients with D2-R supersensitivity departure of DA antagonists mainly related to the supersensitivity of dopamine and uncontrolled transmission of dopamine. These transmissions are further blocked by the drugs

blocking the D2 receptor, non-medicated with antipsychotic [25]. The entire antipsychotic mark of DA receptor has been found to be just about normal in the cerebral cortex of patients. According to Oliver Howe's [26] the three dissimilar evolutionary steps involves the progress of the dopamine premise of schizophrenia. The reduction of antipsychotic or its special effects on dopamine metabolism has been recommended as the first contribution of Dopaminergic arrangement[27,28]. The drugs like dopamine antagonists cause psychotics[29] while amphetamine which is dopamine agonist may elevate psychotic symptoms[24b], showing a primary hyperactivity at dopaminergic synapses. This first dopamine theory[30] did not bond hyper-dopaminergic to exact regions of the brain. However, It has paid attention to DA receptor only and also was not able to differentiate between positive or negative symptomatology and didn't clarify the Dopamine - Metabolism, communication and neurotoxicity mechanism, which are necessary to guide to the symptoms experimental in schizophrenia[26].

Regarding dopamine receptor theory " A Customized dopamine theory of schizophrenia" was published in 1991[31], relating the various issues. It has been found in many schizophrenic patients that metabolites of dopamine in the cerebrospinal fluid were not prominent. In few patients, for treating psychotic symptoms the drug clozapine, was superior having low similarity for residence and D2-receptor, elevated levels of D1-receptors in the cortex compared to elevated levels of D2-receptors in the striatum and NAcc gives us different allocation was of different dopamine receptor subtypes.

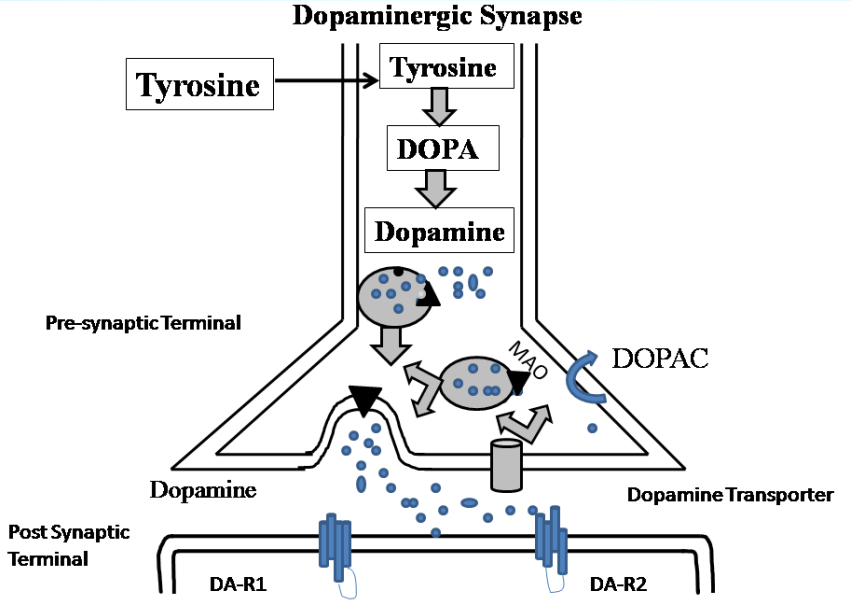

Figure 2: Dopamine Receptor (DA-R) super sensitivity

(a)Dopamine Neurotoxicity(Neurodegeneration)

Another hypothesis is that TD is due to neurotoxicity effect of free radical by products of (C.A) metabolism showing the correlation between neurodegeneration and loss of brain connectivity[32]. The oxidative damage caused by dopamine neurotoxicity is one of the cause of TD while the reason of neurodegeneration is still understood, the neurodegenerative processes found in TD differs from those , found in Alzheimer's disease, as there is no evidence of increased neuronal death or reactive gliosis[33]. Some schizophrenic patients show signs of atypical neurodegeneration, namely reduction of neuronal size and increase in synaptic density[34].

To conquer DA-R blockade, there is the accepted raise in the fabrication of catecholamines, which permits increased breakdown[34j], resulting in neurotransmitters (NTs) cause oxidative stress in the brain. Mainly to striatal interneurons with free radical production causing lipid peroxidation ensuing in a lack of inhibition: the charity of neurotoxicity as a cause of TD[35]. Dopamine stability and abundance neurotoxicity are the two main factors on which dopamine neurotoxicity depends on. The

auto-oxidation of dopamine is, relatively stable within the presynaptic storage vesicles while it is prone in the intra- and extracellular spaces[36]. The difference in the pH inside the vesicles (pH 5.5) as compared to outside main mechanism (pH 7.5) [35a,37]. By interacting with both the DAT and VMAT2 the substance belonging to the amphetamine family act as a potent dopamine releasers from both the synapse and the vesicles[38,36]. Through auto-oxidation and enzymatic degradation, its starts forming reactive oxygen species (ROS) and thus found in abundance in the cytoplasm and the synaptic cleft[39] .In vivo models for neurotoxicity and oxidative stress caused by hyperdopaminergia amphetamines can be considered as pivotal, The excessive oxidative stress results in the damage of Dopaminergic synaptic terminal buttons by the use of methamphetamine that is possibly related to the formation on dopamine derived oxidation products[37, 40]. In post-mortem gas chromatography-mass spectrometry studies showed significantly elevated levels of malondyaldehyde [41,42].

In astrocyte cultures, Dopamine-induced oxidative stress was also reported[43]. There is a significant decrease in dendritic spines in vitro neuronal cultures exposed to dopamine showing oxidative stress [44]. In vitro and in vivo study in mice through treatment with 6-Hydroxydopamine results in the activation of antioxidant genes[45]. The activity of Nrf2 (nuclear factor 2),is also increased by DA, Nrf2 which is a transcriptional factor act by binding to the antioxidant response element (ARE) in the promoter regions of antioxidant genes, through the formation of ROS activates the expression of various antioxidant defense pathways [46].

By equimolar injections of antioxidants like ascorbic acid or glutathione, the neurotoxicity of dopamine injections into the rat striatum, are measured through the death of tyrosine hydroxylase-positive neurons as well as measurements of oxidation products of dopamine, which meets the oxidative capacity of excess dopamine more than likely [47].

When mice were pretreated with rosiglitazone, a PPAR (peroxisome proliferator active receptor)-agonist and activator of antioxidant transduction pathway, the pharmacological model of chronic Parkinson's disease [47] even showed significant reduction of morphological, biochemical and behavioral Parkinson's markers in the treatment of PD[48]. PPAR-agonists has been suggested as therapeutic targets in case of PD[49]. On treatment with various cannabinoids, the same result was found in animals suffering from Parkinson's suggesting that antioxidant capacity of the plant-derived agents protect neurons against dopamine neurotoxicity[50]. Auto-oxidation is one of the biochemical mechanisms of dopamine neurotoxicity while the other is a formation of ROS byproducts during enzymatic degradation. Through enzymatic action presence of metal ions and spontaneous auto-oxidation Dopamine has been shown to form highly reactive quinones, which causing damage to intracellular macromolecules[51]. As the DA oxidizes to quinines faster and reduces back more slowly the formation and therefore the cytotoxic potential is higher in dopamine comparing to catecholamines [52].

Dopamine convened oxidative stress

The derivative $H_2O_2$is created by Dopamine dilapidation through MAOs [53], which has greater impending of producing ROS similar to hydroxyl radicals through the Fenton reaction[51a]. Thus by creating a cruel cycle of positive strengthening between these two pathways of dopamine neurotoxicity through ROS formation results in twists raising the rate of auto-oxidation of dopamine to dopamine-quinone [54]

Impairment of the antioxidant protective mechanism:

As the majority of the energy for the body is supplied through the chemical reaction of oxygen taking place throughout the body, oxygen radical expansion is common[55]. By a four-electron reduction reaction through cytochrome oxidase, all of the oxygen should be condensed to water. However, a small percentage of oxygen may be reduced by one, two or three electrons, and showing in superoxide anion ($O2^{-}$), hydrogen peroxide (H2O2) or the hydroxyl radical. The superoxide anion is the most common free radical formed by mitochondria is $O2^{-}$. Thus, to avoid oxidative damage, intramitochondrial antioxidant systems have to scavenge this free radical which leads to adenosine triphosphate (ATP) production impairment[56]. A very unstable state for the molecule is formed when a free radicals arise an electron exists in an unpaired state. A severe damage to molecules and eventually, to the organism may be results without

careful control of oxidative stress. A lipid peroxidation cascade a chain reaction of free radical generation is inactive when free radicals come in contact with cell membrane fatty acids. Cellular communication disturbance and cell devastation may occur when this chain reaction can break the membrane integrity and can modify the massive numbers of proteins. Superoxide dismutase (SOD) – catalyzes the formation of $H_2O_2$from O_2[57] and is the major enzymes involved in free radical chemistry –H_2O_2 from O_2 – [58,59]. In mitochondria in Manganese in the manganese superoxide dismutase (MnSOD) occurs whereas in cytosol there is copper and zinc (Cu/ZnSOD)[60]. The body defends itself against free radical-induced injury by two mechanisms [61]. Either by chemical antioxidants which render free electrons harmless or by enzymes involvement that catalyze the reaction in which free radicals are distinct to form non-radical structures. Superoxide dismutase (SOD), is the enzyme catalyzes the formation of H2O2 from O2[60a60b], while the creation of H2O2 or O2 from H2O2 is catalyzed by (CAT) and glutathione peroxidase (GSH-Px)[62]. Excessive reactive oxygen species (ROS) free-radical metabolism and the antioxidant protective system. The scavenge excess ROS several enzymes such as SOD, GSH-Px, and CAT are involved which agree to the antioxidant protection mechanism [63].

Increased dopamine turnover and metabolism

There is an increase in the dopamine synthesis and metabolism by blocking dopamine receptors to be used of Antipsychotic medications[26]. The incidence of TD is also affected by producing free radical to diverts dopamine turnover and metabolism process which may directly and indirectly. There is a direct relation between Monoamine oxidase (MAO) and dopamine molecules to oxidative stress leading to the occurrence of TD [64]. Dopamine molecules which are free radicals are formed from dopamine which gets auto-oxidized [65]. Excess free radical are produces in basal ganglia, which is rich in oxidation delivery, polyunsaturated fatty acids and transition metals, resulting in weakening of antioxidant brain defenses[66]. One of the most highly reactive oxygen radical that is H_2O_2 (the hydroxyl radical) is formed with transition metals [67]. In the mitochondria, to a free radical-related mechanism or to the creation of reactive oxygen species, the antipsychotics, such as haloperidol, can be directly destructive. However, the toxic nature of haloperidol and its metabolites to neurons have also been found to a number of study[686970]. An apoptotic cell death, has been noticed while studying the effect of haloperidol and its metabolites to the cell cultures of murine neurons (PC-12)

GABAergic neuronal dysfunction:

In the mammalian brain, γ-Aminobutyric acid (GABA) is a most plentifulneurotransmitter inhibitor. In interneurons modulating neighboring neuronal circuitry, as well as noradrenergic, dopaminergic, and serotonergic neurons GABA is responsible for communication. Emrich *et al* was the first to describe the role of GABAergic dysfunction in mood disorder, for maintaining a balance between the direct and indirect striatopallidal pathways Fast-transfix GABAergic interneurons in the striatum are generally conscientious[24a]. Dyskinesia may be caused by neuroleptic revelation due to annihilation of these drugs [71]. Whereas in animal models of PD has been connected due to an excess of GABA in the GP. Hyperkinetic movements, plus TD have been allied with a decrease of GABA in the GP and substantia nigra[72]. Additional attestation relating GABAergic neuronal dysfunction may lead to the development of TD due to the hereditary relations between the GABA system and TD [73](Figure4)

Cholinergic Dysfunction:

In normal basal ganglia function striatal acetylcholine-dopamine balance has long been measured a key feature[71-74]. Therefore dysfunction various movement disorders, such as Parkinson's disease, Huntington's disease, dystonia and Tourette syndrome is supposed to be triggered by the dysfunction of acetylcholine migration[74]. By targeting acetylcholine receptor disturbs many of this disorder can be treated with pharmacotherapies[75].

Throughout the striatum on a discrete generation of neurons both subtypes of acetylcholine receptors—nicotinic and muscarinic—are uttered. Combined receptor appearance and role consisting of miscellaneous cellular and subcellular localizations are the factors on which practical implications of acetylcholine on movement depends. The medial septal nucleus is counted along with a number of cholinergic projections take place from nuclei of

the basal forebrain in addition to the local striatal innervation. In addition the nucleus basalis of Meynert, the vertical nucleus of the diagonal band and the horizontal limb of the diagonal band nucleus, as well as from the pedunculopontine-lateral dorsal tegmental nuclei, they are also involved[76].

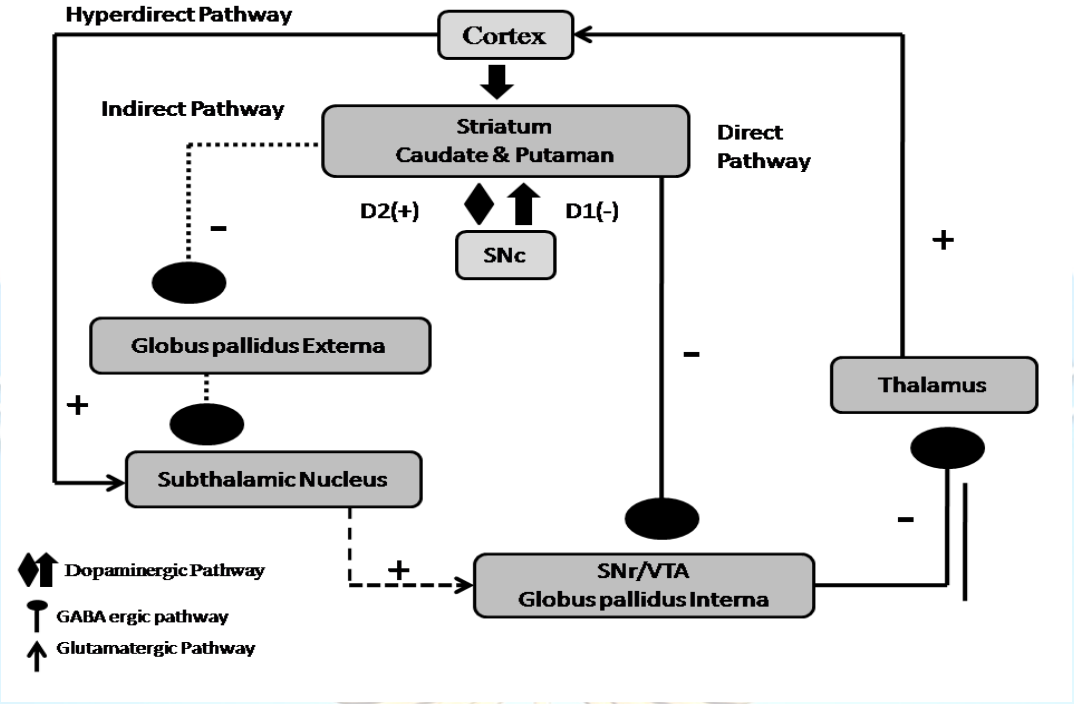

Figure 4: GABAergic neuronal dysfunction

Striatal Acetylcholine-Dopamine Interaction

To innervate with other neurotransmitter system dopamine terminals and ChIs densely the striatum.Articulate the equivalent embarrassment of receptors dopamine terminals express nicotinic receptors (and perhaps M5 receptors), while ChIs similarly express D2 and D5 receptors are expressed through ChIs. In interfacing between these two modulatory systems striatal signaling is probably to involve with the other neurotransmitter system; receptors. Thus, influencing the incorporation, processing and transmission of information along the dual striatofugal systems their great significance of dopamine-mediated regulation of ChIs in modulating striatal outflow. Conventionally the striatal acetylcholine and dopamine systems are viewed as antagonistic. The release of acetylcholine is suppressed by Dopamine through dopamine receptors on ChIs. Through the opening of D2 and D5 dopamine receptors located on ChIs through the modulatory outcome of dopamine on striatal acetylcholine release is achieved. Acetylcholine liberation is inhibited by activation of D2 receptors inhibits while GABA receptors enhance through D5 regulation via protein kinase A (PKA) [77].Dopamine release is similarly suppressed by the acetylcholine while there is an increase in dopamine release indicating the stimulation of nicotinic receptors[78]. In the striatum communication between the dopamine and acetylcholine systems is more multifaceted than the traditional, "see-saw" model would suggest. Likely acting through nicotinic receptor activation the effects of acetylcholine on dopamine liberation appear to be complementary rather than antagonistic while dopamine possibly dampens the acetylcholine release. Additional research to shed further light on their functional interplay is likely to be done using novel techniques to selectively alter particular neurons and particular receptor subtypes.

The parasympathetic nervous system, is said to be almost fully **cholinergic** which uses acetylcholine approximately completely to send its messages. While in a neuromuscular junctions, the preganglionic neurons of the sympathetic nervous

system, the basal forebrain, are also **cholinergic** along with brain stem complexes. In rat models treated with haloperidol due to increased VCMs in the rat the cholinergic insufficiency theory has been occupied in the expansion of TD.

Striatal Dysregulation.

The increased activation of the D1 mediated striatonigral (or "direct") pathway is the final common pathway for dyskinesia showed by various studies on the basal ganglia and movement disorders[79]. Several neuropeptides including substance P and dynorphin are used as co-transmitters along with these intermediate spiny striatal neurons are mainly GABAergic. The internal segment of the globus-pallidus the direct pathway inhibits neurons in the substantia nigra, pars reticulata, and its associated nucleus (Figure 4). These areas, in turned act as a creator for cortical. The net increase (or loss of inhibition) of thalamocortical projections is produced increased inhibition of the inhibitory GABAergic-nigral/pallidal. The D2-mediated striatopallidal (or "indirect") loop also play a major role in outflow tract from the striatum[79]. The neuropeptide enkephalin is also used as cotransmitter pathway. It is medium spiny neurons are also GABAergic. Due to blockade of the inhibitory D2 receptors, the expression of Dopamine and over-activation may facilitate, when the activity of this pathway increase[80]. In rodents study, increases Dopamine agonist-induced dyskinetic mouth movements is suggested as an effect of haloperidol. However such alterations in basal ganglia physiology resulting in TD in the hypothesis which remains unproved, for explaining its role various neurotransmitters for example, D1 and D2 receptors, cholecystokinin (CCK), neurotensin, GABA, Af-methyl-D-aspartate receptors, and opiate receptors play an important role. TD symptoms are also affected by the drugs targeting these transmitter systems. Unfortunately, human studies are limited, using such agents however animal studies have generally been inconclusive.

Management & Treatment of Patients with TD

Based on the still preliminary understanding of the pathophysiology of the disease although a number of drugs have been tried, no effective treatment for TD is currently available. To prevent the worsening of the disorder over time and to minimize its symptoms and reduce ongoing risk factors only suitable attempts are made. a physical and neurological examination, laboratory testing, and a review of the differential diagnosis should be done to medical evaluation, on the first appearance of symptoms of TD [81].

The next biggest issue is whether neuroleptics should be continued or not as most published recommendations suggests that drug withdrawal or marked dose reduction. Another issue affecting is whether additional medications are needed to suppress TD. Sometimes the symptoms which are mild to moderate symptoms are either unnoticed or have little impact. To track symptomatic changes and response to medications routine monitoring of TD is essential. Withdrawal should be considered, the patients who abuse such stimulants as cocaine may develop more severe TD symptom as suggested by Anecdotal reports.

Oppressive Therapies for TD

Dopamine Depletes Alpha-methyl-paratyrosine (AMPT)

In reducing TD severity, medications that work by reducing or depleting presynaptic stores of dopamine have sometimes been helpful. Different mechanisms have been followed by dopamine deplete. The storage of dopamine in presynaptic vesiclesis disrupted by Reserpine and tetrabenazine.

Dopamine Agonists Apomorphine and bromocriptine act directly while amantadine and levodopa act indirectly. Dopamine agonists down regulate dopamine receptors and theoretically could be useful in TD. A major drawback is that they can initially exacerbate both TD and psychotic symptoms. Dopamine auto receptor agonists—for example, *n-N*-propyl- 3-(3-hydroxyphenyl)piperidine (3-PPP)—decrease the release of dopamine and present another possible mechanism to treat TD.

Noradrenergic Antagonists Noradrenergic Antagonists agents like beta-adrenergic antagonist, propranolol, Clonidine, Oxypertine have been used to treat D2 although noradrenergic innervation of basal ganglia structures is sparse and limited primarily to the thalamus.

Cholinergics Deanol, choline, and lecithin, a natu-

rally occurring precursor of choline, Physostigmine, Tacrine. Just as anticholinergics should worsen TD, while cholinergic agonists should improve it. In the 1970s several studies have been conducted with acetylcholine precursors generally disappointing results[82]

GABA Agonists Commercially available GABA agonists have been used Muscimol, another GABA A agonist valproate, diazepam, clonazepam, and baclofen to treat TD, withsome significant success. Some other drugs like Benzodiazepines, 4,5,6,7-tetrahydroisoxazolo-(5,4-c)pyridine-3-ol, a GABAA agonist[83], and gamma-vinyl-GABA, a GABA transaminase inhibitor [84], improved TD.

Antioxidants selegiline and coenzyme Q.
An oxidant vitamin E and free radical scavenger provides one of the more interesting treatments in securing the TD. Neuroleptics produce toxic free radicals that can cause neuronal dysfunction or cell provide a great new treatments.

Conclusion
Tardive Dyskinesia remains a common and potentially irreversible motor complication of chronic Dopamine-Receptor blocking agents. There is no approved treatment for the management of Tardive Dyskinesia. Much has been learned in this area, but our knowledge is still relatively unsophisticated and incomplete .With this increased enterprise of the path biological mechanisms of Tardive Dyskinesia, there is great assurance for future therapies. The diagnosis, understanding and treatment of TD is currently very challenging in nature. As its symptomatic presentation always just changed with individuals among each imbalance of neurotransmitters, Genetic factors, age, and gender. Individuals suffering with TD have a great risk of progression toward others form of neurodegenerative diseases as well as they survive with awareness, severe depression, prolong use of neuroleptics, inadequacy in cognition. Imbalance between Direct or Indirect pathway, Excitotoxicity, cholinergic deficiency, defective neuroadaptive signaling Tardive dyskinesia includes overactivation of dopamine that leads to brain tissue damage. .There are number of potentially beneficial treatment options available to physicians. This review provides detail about the path biological mechanisms of TD, which consist of dopamine receptor super sensitivity, GABA depletion, cholinergic deficiency, neurotoxicity, changes in synaptic plasticity, and defective neuroadaptive signaling, which to date carry with them good expectations and hopes of being part of the future solution to this persistent problem.

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