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Review Article

A comprehensive review on the role of dopamine in the pathophysiology of tardive dyskinesia

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ABSTRACT

Tardive dyskinesia (TD) is a neurological syndrome characterized by involuntary, repetitive, and unusual movements that primarily impact the orofacial region while also extending to other body parts, encompassing chorea, dystonia, tics, buccolingual stereotypy, and akathisia. This condition stems from iatrogenic factors, particularly the chronic administration of medications that obstruct dopamine receptors. Predominantly implicated are antipsychotic drugs, utilized primarily for schizophrenia and bipolar disorder treatment. These drugs modulate dopamine levels, yet prolonged usage can induce alterations in dopamine receptor sensitivity and disruptions in dopaminergic pathways, consequently fostering TD. Dopamine, a pivotal neurotransmitter governing motor control, motivation, reward processing, and emotional regulation, exerts its effects through distinct dopamine receptor types, of which the D2 subtype assumes particular significance in TD development. The persistent blockade of D2 receptors by antipsychotics prompts a compensatory surge in receptor numbers and sensitivity, ultimately contributing to TD's emergence. In essence, TD reflects a complex interplay between medical intervention and neurological intricacies. The protracted influence of antipsychotics on dopamine receptors highlights the delicate equilibrium essential for optimal brain function. The unconventional movements characterizing TD underscore the intricate role of dopamine and its receptors in orchestrating neural equilibrium.

Keywords: Tardive dyskinesia, Drug-induced movement disorder, Involuntary movements, Dopamine receptor, Atypical anti psychiatric drugs

INTRODUCTION

The movement disorder known as "tardive dyskinesia" (TD) is an iatrogenic illness caused by the use of drugs that dopamine receptors blocked agonists (DRBAS). The movement disorder comprises buccolingual stereotypy, dystonia, akathisia, and tremor.[1] Dopamine receptor blockers, such as antipsychotic medications, are linked to the condition. In addition to an increase in medical morbidity and a poor quality of life, tardive dyskinesia has substantial physical and psychological effects.[2] The orofacial region is frequently affected by recurrent polymorphous movements in TD, but the neck, trunk, and extremities can all be affected. The beginning of TD is frequently delayed, it might be potentially irreversible, and it is controlled by continuing dopamine-receptor antagonist therapy.[3]

With an estimated frequency of 20% in individuals taking atypical anti psychiatric drugs (AAPS), TD prevalence rates differed significantly between studies. The risk of TD is lower with AAPS than with conventional typical

antipsychotics (TAPs), but it nevertheless exists due to the growing usage of AAPS. Age, non-caucasian ethnicity, and length of antipsychotic usage are significant risk factors linked to TD. Supersensitivity of the dopamine receptors and oxidative stress are two theories for the origin of TD, but other neurotransmitters and variables are likely involved as well.[4] Various drugs induce tardive dyskinesia during treating psychiatric conditions, as shown in Table 1. The most typical conditions that are treated with medications linked to the emergence of tardive dyskinesia include schizophrenia, psychosis, and nausea.[5]

When antipsychotic drugs that inhibit D2 receptors are taken for an extended period, tardive dyskinesia frequently develops. Tardive dyskinesia is a result of brain harm brought on by D2 receptor-blocking medications. Various muscles may move involuntarily as a result of this cumulative damage.[3] In this review, we aim to provide an extensive understanding of the role and mechanism of dopamine in tardive dyskinesia.

Role of dopamine in tardive dyskinesia

Dopamine is a catecholaminergic neurotransmitter that regulates everything from voluntary movement and pleasure to hormone regulation and hypertension through its G protein-coupled dopamine receptors (D1, D2, D3, D4, and D5).[7] D2 receptors are found on both pre-and postsynaptic locations in the striatum.[8] D2 receptors, which are inhibitory receptors that are found on striatal medium spiny neurons and inhibit the inhibitory indirect pathway, cause hyperkinetic movements when they become oversensitive.[9] Rodent studies have demonstrated that serotonin receptors, specifically 5-HT2 receptors, which are broadly distributed in the striatum, interact with dopaminergic neurotransmission. Their inhibition inhibits the upregulation of D2 receptors.[10]

Typical antipsychotics have a higher propensity to cause tardive dyskinesia because first-generation antipsychotics bind to dopamine D2 receptors more firmly than second-generation antipsychotics.[11] The caudate-putamen and the nucleus accumbens have the highest concentrations of D2 receptors in the brain, according to data from animal research.[12]

Increased high receptor density in these same brain areas is similarly related to antipsychotic-induced dopamine supersensitivity.[13] In contrast, the number of D2 receptors in the substantia nigra does not consistently alter. The density of D1, acetylcholine, or GABA receptors in the striatum or the number of dopamine transporters in cortical or subcortical regions is likewise unaffected.[14] TD is thought to result from the persistent blockage of antidopaminergics, which causes dopamine D2 receptors to become hypersensitive and to up-regulate. Since D2 receptors block the indirect pathway, hypersensitivity increases the number of result in hyperkinesia.[15] Postsynaptic and presynaptic D2 receptors represent at least two separate populations in the brain. Signals are passed from a dopaminergic neuron to the next neuron via postsynaptic receptors. Dopaminergic neurons' production and release of dopamine are controlled by presynaptic D2 receptors.[8] Presynaptic D2 receptor inhibition causes dopaminergic neurons to release more dopamine. The intracellular levels of free dopamine inside the neurons may rise as a result of this dopamine overflow. This spillover could provide crucial neuronal damage for tardive dyskinesia.[16]

Mechanism of development of tardive dyskinesia

Dopamine receptor hypersensitivity is the most widely accepted hypothesis for the emergence of tardive dyskinesia. The persistent blockade of dopamine receptors, specifically D2 and probably D3 receptors, is thought to contribute to the pathophysiology of TD.[17] This chronic blockade causes overexpression of D2 receptors and postsynaptic dopamine receptor hypersensitivity.[18] Uncontrollable movements are thought to originate from the upregulation of D2 receptors that occurs when D2 receptors are inhibited.[19] This upregulation makes D2 receptors extremely sensitive to dopamine. The D2 receptors should revert to normal and tardive dyskinesia should go away once the medication has been eliminated from the body.[20]

In fact, TD may involve different receptors (e.g., serotonergic receptors). Dopamine (DA) release is significantly influenced by serotonin. For instance, the suppression of DA neurons may be the cause of TD following therapy with selective serotonin reuptake inhibitors (SSRIs). It has been hypothesized that inhibiting serotonin receptors might produce TD by increasing DA release in the raphe nucleus and decreasing DA synthesis in the basal ganglia.[21]

D2 agonists, like dopamine, cause internalization of D2 receptors and a decrease in D2 density. Contrarily, antipsychotics decrease the internalization of D2 receptors and increase brain D2 receptor mRNA, which influences the density of D2 receptors. The intracellular systems G protein-coupled receptor kinase-6 (GRK-6) and β-arrestin 2 are altered as a result of D2 upregulation, which lasts after antipsychotics are stopped working and is crucial for the internalization of D2 receptors.[22]

Free intracellular dopamine oxidizes either spontaneously or as a result of aldehyde dehydrogenase and monoamine oxidase in the mitochondria. The oxygen radicals produced by this oxidation harm the cell. Dopaminergic neurons die when there is too much cell damage.[23]

Tenderness dyskinesia can develop as a result of the buildup of this damage and cell death. Dopaminergic neurons are harmed even when D2 blockers are used for a brief period of time. D2 blockers can cause cumulative harm with prolonged usage, which may end in tardive

dyskinesia. Numerous people on antipsychotic medication have seen this cumulative impact.[24]

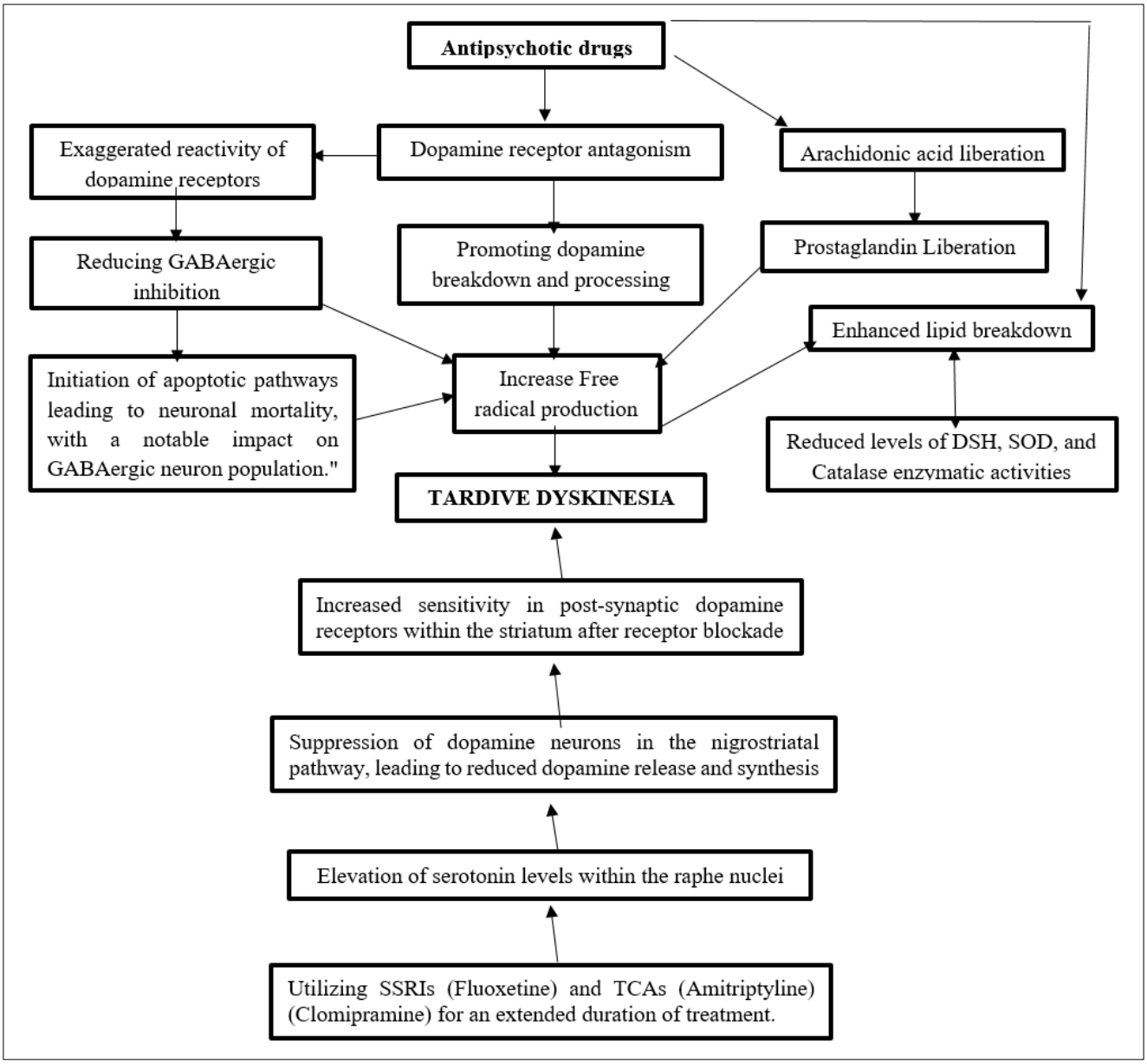

Figure 1: Antidepressant-induced dopamine neuron suppression triggers tardive dyskinesia.[28,29]

SSRIs- selective serotonin reuptake inhibitors, TCA- tricyclic antidepressants, DSH- deliberate self-harm, SOD- superoxide dismutase, GABA- gamma-aminobutyric acid.

Table 1: Antipsychotic drugs that induced TD.

S. no.	Drug class	Drugs
1	Typical antipsychotics	Phenothiazine: Chlorpromazine; Fluphenazine, Perphenazine, Prochlorperazine, Thioridazine, Trifluoperazine, Perazine, Triflupromazine, Levomepromazine, Mesoridazine, Thioxanthene: Chlorprothixene, Thiothixene, Flupentixol, Zuclopentixol
		Dibenzazepine: Loxapine
		Butyrophenones: Haloperidol, Droperidol
2	Atypical antipsychotics	Diphenylbutylpiperidine: Pimozide Dihydroindolone
		Molindone Dibenzodiazepine: Clozapine, Quetiapine

Continued.

S. no.	Drug class	Drugs
		Substitute Benzamide: Sulpiride, Remoxipride, Levosulpiride, Tiapride, Amisulpride Benzisoxazole: Iloperidone
		Dibenzazepine: Asenapine
		Benzisothiazole: Ziprasidone
		Thienobenzodiazepine: Olanzapine
3	Serotonin reuptake or serotonin norepinephrine reuptake inhibitors	Duloxetine, Citalopram
4	Tricyclic antidepressants	Amoxapine
5	Central monoamine oxidate inhibitors	Reserpine
6	Anti-manic agents	Lithium substitute Benzamides, Sulpiride, Veralipride

First-generation antipsychotics bind to dopamine D2 receptors more firmly than second-generation antipsychotics, they are more likely to produce tardive dyskinesia than second-generation antipsychotics.[25] According to certain data, tardive dyskinesia can develop before extrapyramidal symptoms with neuroleptic therapy. The striatal 5-hydroxytryptophan receptors are one of the additional neurotransmitter receptors that may contribute to tardive dyskinesia in addition to dopamine receptors. These receptors are thought to have a role in controlling motor activity through their interactions with dopaminergic neurons.[26]

Tardive dyskinesia can be brought on by the upregulation of dopamine receptors as a result of persistent dopamine blockade, which causes an excessive response to the postsynaptic receptors to dopamine. The striatum and significant area of the basal ganglia experience oxidative stress as a result, which manifests as tardive dyskinesia. Evidence also points to the possibility that antipsychotic drugs and their metabolites may harm neurons directly by inducing oxidative stress.

The condition known as withdrawal dyskinesia is caused when the substance that causes tardive dyskinesia is removed. This is thought to be caused by postsynaptic receptor hypersensitivity and overexpression of the dopamine D2 receptor. This does not, however, explain why tardive dyskinesia persisted for many years after the problematic medication was stopped.

RESULTS

The comprehensive review on the role of dopamine in the pathophysiology of tardive dyskinesia has provided significant insights into the underlying mechanisms of this neurological disorder. The review confirms that brain harm induced by D2 receptor-blocking medications is a major contributing factor to the development of tardive dyskinesia. The cumulative damage caused by these medications leads to involuntary movements in various muscles, resulting in the characteristic rapid and uncontrollable movements observed in affected individuals. These symptoms are identified as common, irreversible, and potentially incapacitating, underscoring the severity of tardive dyskinesia's impact on the quality of life for those affected.

The review emphasizes that medications that block dopamine D2 receptors, particularly antipsychotic drugs, are the most common cause of tardive dyskinesia. The duration and cumulative exposure to multiple D2 receptor-blocking medications significantly contribute to the risk of developing this condition. Although spontaneous onset is possible, the review confirms that medications remain the primary focus of concern when addressing the etiology of tardive dyskinesia.

Furthermore, the review points out a gap in the existing literature, highlighting that prior articles have not sufficiently explored the significance of dopamine receptors in the development of tardive dyskinesia. This emphasizes the need for further research to delve into the specific roles of different dopamine receptor subtypes and their interactions in the pathogenesis of tardive dyskinesia.

Overall, the comprehensive review provides valuable and consolidated information on the role of dopamine in the pathophysiology of tardive dyskinesia. By shedding light on the mechanisms behind the development of this syndrome, the review offers valuable insights for healthcare professionals, researchers, and clinicians working towards improved management and treatment strategies. The findings underscore the importance of cautious prescribing practices, monitoring patients on D2 receptor-blocking medications, and exploring novel approaches that may target specific dopamine receptor subtypes to mitigate or prevent the development of tardive dyskinesia in susceptible individuals.

DISCUSSION

Tardive dyskinesia (TD) is a debilitating neurological syndrome characterized by involuntary and abnormal movements, predominantly involving the orofacial region, but also affecting other body parts. This condition is considered iatrogenic, arising from brain harm caused by medications that block dopamine D2 receptors, particularly antipsychotic drugs.[1] In this comprehensive review, we explored the intricate role of dopamine in the pathophysiology of TD, shedding light on the underlying

mechanisms contributing to its development and progression.

Dopamine is a critical neurotransmitter in the brain, involved in various physiological processes, including motor control, reward processing, and emotional regulation. The dopaminergic pathways play a crucial role in maintaining the balance between inhibitory and excitatory signals in the basal ganglia, which are responsible for fine-tuning motor movements.[4] When dopamine signalling is disrupted due to the antagonism of D2 receptors by medications, this delicate balance is disturbed, leading to dysregulation of motor control and resulting in the characteristic abnormal movements seen in TD.

Vesicular monoamine transporter 2 (VMAT2) inhibitors alleviate tardive dyskinesia by reducing dopamine transport into vesicles, limiting excessive dopamine release in the motor striatum. This rebalancing curtails hyperkinetic movements by dampening excitatory signals ("go" pathways) and enhancing inhibitory signals ("stop" pathways), thereby yielding effective therapeutic outcomes.[27]

One of the primary mechanisms contributing to TD is the up regulation and hypersensitivity of dopamine receptors. Chronic blockade of D2 receptors by antipsychotic drugs can lead to compensatory changes in the number and sensitivity of these receptors. This increased receptor density and sensitivity lead to an augmented response to dopamine signalling, further exacerbating the motor disturbances associated with TD.

Moreover, the duration and cumulative dose of D2 receptor-blocking medications play a significant role in the development of TD. Prolonged exposure to these drugs increases the risk of TD, with patients on long-term antipsychotic therapy being more susceptible to this condition. The cumulative harm caused by multiple D2 receptor-blocking medications further highlights the importance of cautious prescribing and monitoring to prevent or mitigate TD in susceptible individuals.

Although medications are the most common cause of TD, other factors, including genetic predisposition and individual variability, can influence an individual's susceptibility to developing TD. Some individuals may experience spontaneous onset of TD without any apparent medication exposure, suggesting a complex interplay of genetic and environmental factors in its etiology.

CONCLUSION

Tardive dyskinesia (TD) stands as a consequence of cumulative cerebral impairment arising from the administration of D2 receptor-blocking medications, engendering involuntary muscular movements of diverse nature. These swift, uncontrollable motions bear a ubiquitous presence, marked by their irreversibility and debilitating impact. The crux of this condition lies in the gradual aggregation of harm triggered by multiple D2 receptor-blocking drugs, with a primary nexus to medications inhibiting dopamine D2 receptors. Nevertheless, the extant body of research has regrettably fallen short in delving comprehensively into the pivotal role of dopamine receptors in the genesis of tardive dyskinesia. Within this context, our review endeavours to shed light on the intricate interplay of dopamine and its associated mechanisms within this disorder. By doing so, we seek to augment the understanding of the precise involvement of dopamine receptors, thereby fostering a more nuanced comprehension of the underpinnings driving the emergence and progression of tardive dyskinesia. Through a comprehensive exploration of these mechanisms, we aspire to pave the way for novel insights into potential preventative and therapeutic strategies, offering hope for better management and mitigation of this intricate and debilitating neurological syndrome.

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