Animal Models of Tardive Dyskinesia

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1 Introduction

Today we are in an era of utmost modernization; technology used in medical science says hats off to human mind. We have left no pebbles unturned in discovering human "BRAIN." Researchers have gone deep into lobes then whether its physiology of brain or vast anatomical features. Irrespective of all the laurels attained in it, there is no suitable treatment for some of the CNS disorders for which patients are paying its cost with their lives. One such example is of schizophrenia from which tardive dyskinesia (TD) occurs as a side effect. Throwing some light on the preclinical work done on TD, a review is presented to put together the toxic agents causing TD. Hoping it could prove fruitful in a process of attenuation or abolition of TD. Schizophrenia was conceived by Eugen Bleuler in 1950. It has its onset during

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puberty and lasts throughout life. Neuroleptics are universally prescribed psychotropic drugs for schizophrenia from which TD emerged as side effect.

Tardive is a French word which means "late onset." TD occurs late after the onset of neuroleptic treatment, also termed as medication-induced movement disorder. It is irreversible offender which persists even after the discontinuation of neuroleptics. TD or orofacial dyskinesia or bucco-lingual masticatory syndrome is a knotty hyperkinetic syndrome playing a role of a complex motor side effect of chronic treatment for prevalent schizophrenia worldwide. TD renders one to socially handicapped, due to irregular abnormal rhythmic movements, tongue protrusions, vacuous chewing movements, licking, smacking, puckering, grimacing, panting. It is characterized by choreiform, athetosis, vacuous chewing movements, tongue protrusions, facial jerking. TD is manifested by dopamine supersensitivity, GABAergic neuronal hypofunction, excitotoxicity, oxidative stress.

Following phenothiazines (chlorpromazine) in 1950s, enormous neuroleptics were produced for next 30 years with extrapyramidal side effects, with a root mechanism of blocking post-synaptic dopamine receptors. Tardive dyskinesia emerged as a major limitation of chronic neuroleptic treatment. TD came into forefront 5 years after the instigation of chlorpromazine. Recent clinical data states that TD has been reported with the involvement of speech.

Dopamine supersensitivity has been reported leading TD, particularly dopamine D2 receptor blockade. Dopamine is released in the basal ganglia circuit, but sufficient receptors are not available to act on it, and here receptors become supersensitive for even a bit of dopamine available leading to dopamine supersensitivity. This hypothesis was put forward by Klawans, but it has not gained much evidence. As dopamine sensitivity occurs after a few weeks of exposure to neuroleptics, but TD occurs after long-term exposure. All the more clinical data adds to it by enumeration of postmortem studies of TD patient showing significant increase in dopamine receptors, but only a portion of them exhibits dyskinesia. Secondly, glutamate excitotoxicity plays a part for TD by excessive stimulation of NMDA receptors through blockage of D_2 receptor on glutamatergic terminals in striatum, leads to persistent enhanced release of glutamate that kills striatal neurons.

Now what cannot be left behind is free radical generation, leading to "malicious oxidative stress" without which a pathogenesis of disease could be completed. Dopamine supersensitivity is correlated with enhanced dopamine metabolism which is natural to take place as sufficient receptors are not available to compensate dopamine, so it will be metabolized by the action of MAO-B leading to reactive oxygen species. GABAergic hypofunction in the striatal neurons is well supported through rodent and clinical data forming basis of TD. Loss of these neurons was confined to ventrolateral striatum (area concerned with innervations of oral musculature). Various assumptions have been laid down by the researchers, like increased smoking by individuals, genetic predisposition, and contrasting results are available about age factor, sex ratio for TD without the availability of sound evidence.

Much of the work has been done on the protective drugs that could be used against TD for which positive as well as conflicting results are available but an adequate one is not yet available. To explore the occurrence, prevalence, and numerous factors, we need animal models to understand the pathological, physiological, clinical manifestations, different pathways followed by different antipsychotics. Moreover, animal models preferably primate models persuade more closely to human condition in terms of therapeutic concern. The prevalence of TD in the society and extending horizons of diseased condition in which antipsychotics are prescribed makes it necessary to understand the pathological role of anatomical factors involved along with the new therapeutic approaches to target it, and the best possible way to achieve it before administrating it to human lives is the use of animal models which is ineluctable.

Word neuroleptic has its roots in Greek, according to which "neuro" corresponds to "neuron" and "leptic" corresponds to "seizure." Neuroleptics or antipsychotic or major tranquilizers are the drugs given to treat psychotic disorder schizophrenia (biological illness). It decreases the intensity of hallucinations and delusions. They have been used in westerly medicines since 1950s. Neuroleptics are targeted in the brain having basal ganglia their main site of action. Basal ganglion is the region involved for motor coordination with the involvement of various inhibitory and excitatory neurotransmitters. Any disturbance in it or any abnormality occurring in the complexity of network of nuclei and neuronal structures present in it which are still not fully elucidated leads to abnormal motor coordination associated with oral dyskinesias. Neuroleptics block membrane's viability for numerous chemical entities by interfering with their signaling. This leads to the generation of plotters and culprits of the pathological condition of patient. Extent of occurrence of extrapyramidal side effects due to antipsychotics is directly related to possession over D_2 receptors. The reason for this is that the antipsychotics have marked targeted action in striatum which is rich with D_2 receptor. It has been proved with proof specs of abnormalities in striatum with the brain imaging technique of TD patients. Neuroleptics also block the complex I of electron transport chain by contributing to the formation of free radicals and generating oxidative stress.

Putting attention on subcategories of neuroleptic discrimination between typical or classic and atypical should be known. Major difference lies on their ability to cause TD at therapeutic doses. In that respect, typical ones occupy the throne recognized with bitter tablets producing "medication-induced movement disorder." They are first to be discovered, first to be used, and first to be regarded as sinners. But nowadays preference is given to atypical for achieving therapeutic treatment along with the minimization of hyperkinetic syndrome.

Typical neuroleptics increase the level of prolactin, but there are no such findings with atypical. Typical neuroleptics cause TD with high affinity for D_2 receptor blocking profile and occur frequently at even low therapeutic doses, whereas atypical neuroleptics do share receptor affinity with D_1, D_2, and serotonergic receptors. Typical neuroleptics increase basal ganglia volume along with changes in cortical areas, whereas atypical neuroleptics produce changes in thalamus. There was a little relief with the atypical ones, but they emerged with a new hindrances

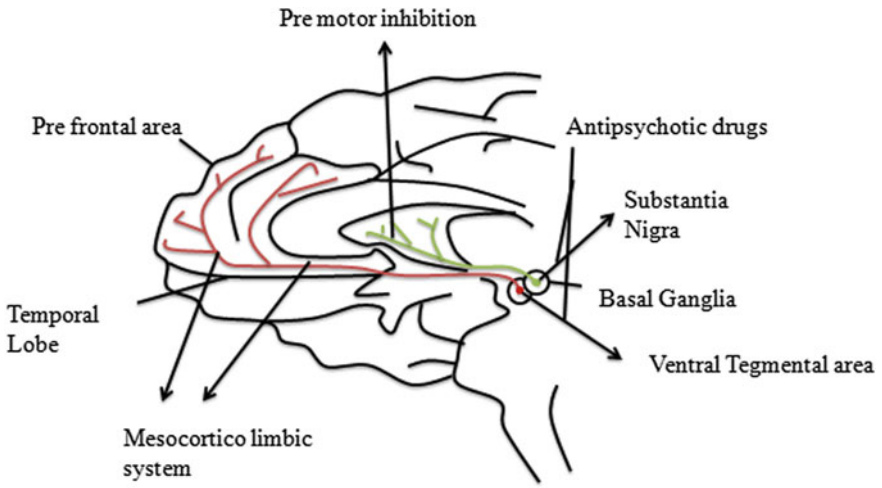

Fig. 1 Antipsychotics action on mesocortical, mesolimbic, and nigrostriatal pathway

which we call in scientific paradigms as adverse effects such as agranulocytosis, seizures, weight gain, sedation, whereas reports with typical ones are missing. After recognizing the drawbacks of typical, researchers felt need for the development of neuroleptics with a modification and then came atypical with an aim to abolish the occurrence of TD. But to our fate researchers were not fully successful in their mission; hence, there was some improvement that atypical ones are efficacious without TD at low doses. Reports of occurrence of TD with them at low doses are less, but at high doses they do share the same pharmacological profile (Fig. 1).

2 Classification of Animal Models of TD (Fig. 2)

2.1 Neuroleptic-Induced TD

Neuroleptics provide an adequate data and represent an excellent model to give an explanatory justification for the occurrence of TD using neuroleptics. Neuroleptics being lipophilic in nature have the ability to change the permeability of various receptors. Clinical data report states about the relevance of neuroleptic treatment in association with TD patients on showing striatal abnormalities during brain imaging. Animals treated with neuroleptics show frequent signs of orofacial dyskinesia (VCM's, TP, and FT). This leads to the alteration in the range of neuropeptide, neurotransmitter, antioxidants, and receptor in basal ganglia of animals treated with neuroleptics showing orofacial movements. Adequate methods have been adopted to quantify them. Different reports are available about the time taken by

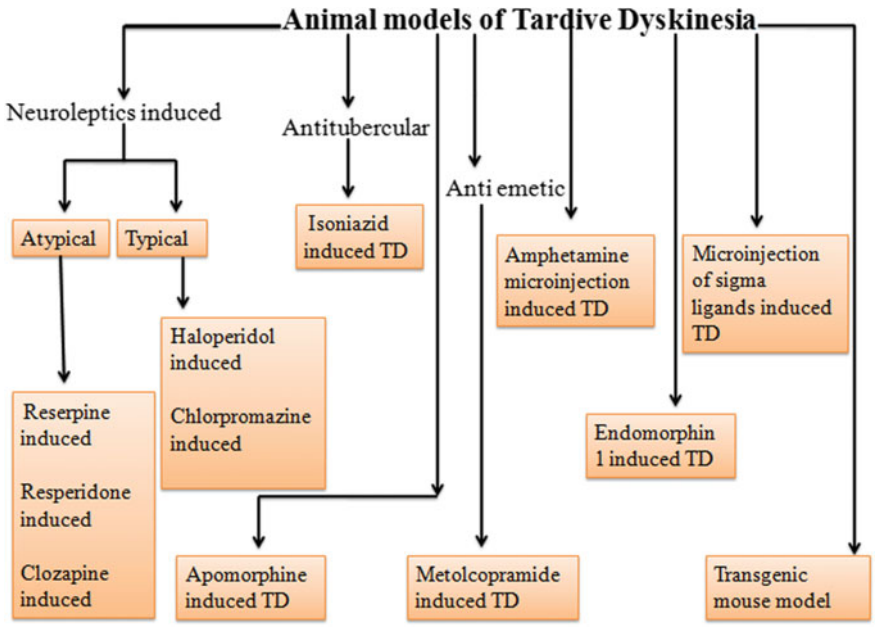

Fig. 2 Classification of Animal Models of TD

neuroleptics showing symptoms of TD from steady occurrence in several months to early onset. No rigid data is available due to variability in various factors age, gender, genetics, hereditary, medical history.

2.1.1 Typical Neuroleptics

Classical neuroleptics typically block D_2 receptors. This pays the path for dopamine hypothesis. Blocking of D_2 receptors is linked with cognition impairment corresponding to extrapyramidal side effects of neuroleptics following a cascade of dopamine supersensitivity, decreased striatal GABAergic and cholinergic neurons. Repetitive and enhanced stimulation of D_2 receptors located on glutamatergic neurons produces excitotoxic levels. They are associated with six times enhanced ROS generation following nigrostriatal dopamine system which has proved to be analogues with the generation of extrapyramidal side effects. They are associated with prominent changes in synaptic areas of basal ganglia. Electron microscopy of basal ganglia region showed altered osmiophilia and decrease in size of mitochondria, cytoplasm of neurons along with their processes.

Chlorpromazine-Induced TD

Principle: Emergence of chlorpromazine brought revolution in psychiatry with a drastic improvement in schizophrenic patients. Soon, its neurobiology is elucidated which showed its association with D_2 receptor blocking agents producing

symptoms of TD. Chlorpromazine is a classic typical dopaminergic D_2 receptor blocker leading to dopamine supersensitivity, enhanced dopamine metabolism. Clinically effective dose of chlorpromazine is 10–25 mg, p.o., 3 times a day. Blocking of D_2 receptor results in dopaminergic supersensitivity, glutamate excitotoxicity due to increased activation of NMDA receptor and reactive oxygen species. This action is responsible for antipsychotic activity along with other neuroleptics which showed extrapyramidal side effects.

Procedure: In preclinical studies, chlorpromazine 5 mg/kg, i.p., is given to animals for 21 days for the induction of TD (VCM's, facial jerking, and tongue protrusions) (Naidu et al. 2002).

Haloperidol-Induced TD

Principle: Haloperidol has been one of the extensively and widely used classical antipsychotics in psychiatry, obstetrics, and anesthesiology. It is one of the preferable drugs for the preclinical studies. Much of the work has been done on it for the elucidation of its complete pharmacological profile. Haloperidol is a dopamine antagonist. It disrupts the activity of neurotransmitter by blocking dopaminergic D_2 receptor which further leads to the cascade of dopamine supersensitivity, enhanced dopamine metabolism, free radical generation (Fig. 3).

Procedure: Haloperidol 1 mg/kg, i.p., is given to animals for 21 days for the induction of tardive dyskinesia. Haloperidol is not teratogenic as evidenced by animal data, but it could lead to embryo toxicity and also found in breast milk.

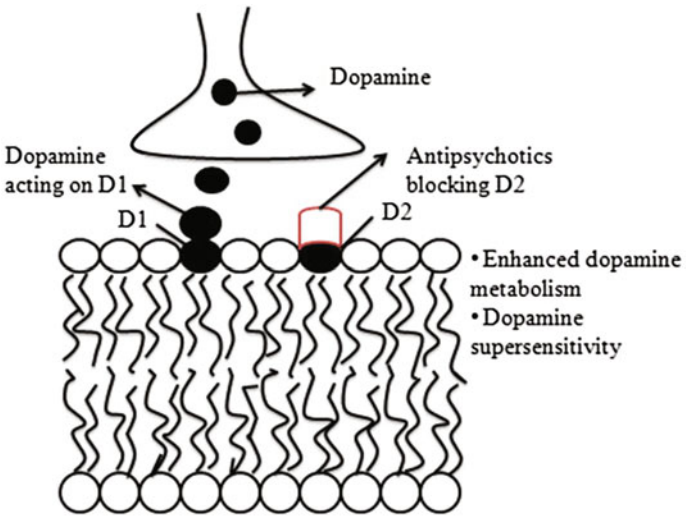

Fig. 3 Hypothetical diagrammatic representation of: (i) antipsychotic action on dopaminergic receptors. (ii) Amphetamine-induced TD

2.1.2 Atypical Antipsychotics

Atypical antipsychotics come under the category of "second-generation" antipsychotics. They are accompanied with minimal risk of causing structural disruption and triggering neurotransmitter alterations contributing to cognition impairment. They follow mesolimbic pathway and block 5-HT_2 and interpret dopaminergic transmission by loosely binding to D_2 receptor. According to the clinical data, available occurrence of TD is more prevalent in females as compared to males for which a possible reason could be the influence of estrogen in females for developing TD. Estrogen may have an additive effect with atypical antipsychotics on dopamine blockade. Declining estrogen in postmenopausal women also precipitate TD by reliving the blockade of dopaminergic receptors. Results of atypical are assessed by scores obtained through "a trend toward greater improvement in Quality of Life Scale and symptom scores." Atypical antipsychotics were developed with the aim to diminish or mimic the side effects of typical one (TD), but researchers were not fully successful in their objectives; hence, we can conclude it by saying through the data yet available that atypical antipsychotics could be preferred over typical antipsychotics.

Reserpine-Induced Tardive Dyskinesia

Principle: Regarding the critical mater of evaluating animal model of TD, reserpine, a monoamine depleting agent recognized for depleting dopamine, serotonin, and norepinephrine nonselectively proved to be better in fulfilling the needs. Reserpine-induced orofacial dyskinesia occurs late during the course of administration with prolonged persistence after the termination of administration. Though reserpine is not categorized as a neuroleptics, yet it is used as an antipsychotic having association with TD, showing similar features to TD. Reserpine-induced orofacial movements are reduced with D2 antagonist and are aggravated with dopamine agonist.

Procedure: Reserpine at a dose of 1 mg/kg, s.c., for 3 days is used for the induction of orofacial dyskinesia (Kulkarni et al. 2001).

Risperidone-Induced Tardive Dyskinesia

Switching over to risperidone one can have a sigh of relief to some extent as the data reports that the occurrence of TD is not associated with low doses of risperidone whereas high doses do not spare minds portion with the plethora of TD. Risperidone is a baby compound obtained by the derivatization of benzisoxazol. Belonging to the family of second-generation antipsychotics, possesses affinity and ability of blocking D_2 as well as 5HT2A receptors.

Procedure: Reserpine at a dose of 6 mg/kg, p.o., for 6 months is used for the induction of orofacial dyskinesia. One advantage as already mentioned above is procuring control model of VCM's at dose of 1.5 mg/kg, p.o., for 6 months.

Clozapine-Induced Tardive Dyskinesia

Principle: Clozapine being a atypical molecule is a drug of choice for schizophrenia. But as we have learnt, atypical antipsychotics do have the propensity

to cause TD. Clozapine has been defined as advantageous and novel by due to its affinity for serotonergic $5HT_{2A}$ and D_4 receptor antagonism along with weak D_2 receptor blockage. Serotonin receptor blockade has shown protective effect in TD which suggests that genetic variations in serotonin functions of schizophrenic patients may alter the risk for TD who are chronically exposed to dopamine receptor antagonist drugs.
Procedure: Dyskinetic movements occur in animals at the dose of 2 mg/kg, i.p., for 21 days (Naidu et al. 2002).

2.2 Antitubercular Drugs-Induced Tardive Dyskinesia

Part played by neuroleptic drugs for the occurrence of TD is not finding a solution yet, when another hindrance came for medical health professionals when an antitubercular drug isoniazid started showing the signs and symptoms of tardive dyskinesia.

2.2.1 Isoniazid-Induced Tardive Dyskinesia

Principle: Isoniazid has a potential of inhibiting GAD (a master component for the synthesis of GABA). Then, automatically it will be rewarded by the name of GABA depletor. As well-established dearth of GABA in the nigral regions contributes to the pathophysiology of TD. Decline in the activity of GAD is in association with the occurrence of characteristic symptoms of TD (Kulkarniet al. 2001).
Procedure: Doses at which dyskinetic symptoms occur are 1, 2, 5, 10 μmol/rat, i.c.v. Highest permissible effect occurs at 5 μmol. Peak of isoniazid is attained after 30 min of administration which remains for 60 min (Kulkarniet et al. 2001).

2.3 Amphetamine Microinjection-Induced TD

Principle: In general, amphetamine is a CNS stimulant. It increases heart rate and blood pressure. It treats attention deficit disorder and narcolepsy. But a research done by Rubovits et al. showed the characteristic ability of amphetamine to induce stereotype behavior in rodents by acting on striatal dopamine level (Fig. 3) (Rubovitset al. 1972).
Procedure: Dose of 20 μg/0.5 μl of amphetamine into confined subregion of striatum produces dyskinetic movements (Rubovits et al. 1972).

2.4 Endomorphin-1-Induced Tardive Dyskinesia

Principle: Endomorphins are endogenous opioid peptides exhibiting agonistic properties for mu receptors. Basal ganglia, a part of the brain, is involved in the locomotor activities and other functions too through various subregions and neurotransmitters involved which are having their influence through direct and indirect

pathway. Globus pallidus (GP) is also one of them containing a heavy number of mu receptor. Endomorphin when administered in the striatum acts as a shooter of dopamine efflux with the involvement of substantia nigra, contributing to the hypothesis of dopamine supersensitivity (Fichna et al. 2007).

Procedure: Endomorphin-1 is administered at dose of 18 pmol bilaterally into GP therefore exhibiting the characteristic features of orofacial dyskinesia.

3 Conclusion

Oxidative stress is surely related to neuroleptics and their use in schizophrenic patient with both typical and atypical ones for which various antioxidant as adjuvants are tried in animal models, but satisfactorily they are not able to diminish the occurrence of TD rather they can only minimize it and that too in specific conditions. TD is not a disease, it is such a horrible side effect of a disease (an outcome of a bitter pill)." Much investigation is yet to be done on it; it is a tiny piece of the literature to throw some light on TD with an aim to develop efficient and possible therapy for TD.

Ethical Statement

All institutional guidelines, national guidelines, state and local laws and regulations with professional standards for the care and use of laboratory animals should be followed. Studies involving animals must state that the institutional animal ethical committee has approved the protocol. For authors using experimental animals, a statement should be made that the animals' care is in accordance with institutional guidelines and animals used have been treated humanely and with regard to the alleviation of suffering. Researchers should treat animals as sentient and must consider their proper care and use and the avoidance or minimization of discomfort, distress, or pain as imperatives. Animal experiments should be designed only after due consideration of animal health. It should be ensured that all researchers who are using animals have received instruction in research methods and in the care, maintenance, and handling of the species being used. All the surgical procedures should be performed under appropriate anesthesia and follow only those procedures which avoid infection and minimize pain during and after surgery.

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