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Review

The implications of oxidative stress in tardive dyskinesia

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ABSTRACT

Typical antipsychotic drugs are widely used in the treatment of schizophrenia and other psychotic disorders. Unfortunately their use is often associated with the development of behavioural supersensitivity as well as acute and delayed extra-pyramidal side effects (EPS) including Parkinson's like symptoms, tardive dyskinesia (TD) and akathisia. Recently, some of the second generation antipsychotic drugs such as risperidone have also been shown to cause EPS. In pre-clinical animal models, an enhanced behavioural response to dopamine D2 receptor agonists is generally observed following withdrawal of antipsychotic drug administration. Among the EPS, TD is one of the movement disorders most commonly associated with the protracted use of haloperidol and other antipsychotic drugs affecting 20-40% of patients treated with typical antipsychotic drugs. While this disorder has been under investigation for many decades now, the exact underlying cause remains unknown. The dopamine supersensitivity hypothesis was the earliest attempt to explain the pathophysiology of TD but today it is widely acknowledged to be insufficient. The more recent hypothesis implicating increased oxidative stress and neurodegeneration in the basal ganglia is currently gaining increasing support as a mainstream explanation of TD. It proposes that dopamine D2 receptor blockade in the striatum by antipsychotic drugs can induce dopamine accumulation and consequent oxidation to form reactive oxygen species. These reactive oxygen species can be detrimental to lipids, proteins and DNA, and therefore induce neuronal cell death. This review, summarizes our current understanding of abnormal oro-facial movements and TD, oxidative stress induced behavioural supersensitivity and examines the breadth of recent research in this field.

KEYWORDS: tardive dyskinesia, antipsychotic drugs, oxidative stress, free radicals, basal ganglia, striatum, haloperidol

ABBREVIATIONS

Alpha lipoic acid (ALA), Alpha(α)-Phenyl-N-tert-butylnitrone (PBN), α-tocopherol (vitamin E), Anti-oxidant defence system (AODS), Apoptosis inducing factor (AIF), Ascorbic acid (vitamin C), Catalase (CAT), Extrapyramidal side effects (EPS), Globus pallidus internal segment (GPi), Globus pallidus external segment (GPe), Glutathione peroxidase (GSH-Px), Glutathione S-transferase (GST), γ-aminobutyric acid (GABA), haloperidol (HP), Hydrogen peroxide (H_2O_2) Hydroxyl radical (OH^-•), Intraperitoneal (IP), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), NADPH quinine oxidoreductase 1 (NQO1), Reactive oxygen species (ROS), Semiquinone radical (SQ•), Spirulina Maxima (SM), Substantia nigra pars compacta (SNc), Substantia nigra pars reticulata (SNr), Subthalamic nucleus (STN), Superoxide dismutase (SOD) Superoxide radical (O_2•), Tardive dyskinesia (TD), Vacuous chewing movement (VCM)

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INTRODUCTION

Tardive dyskinesia history and symptoms

Tardive dyskinesia (TD) is a devastating side effect of antipsychotic drug treatment, characterized by involuntary movements of the facial muscles, and occasionally the trunk and limbs. Interestingly, the now well accepted association between motor dysfunction and psychotic treatment was not easily first acknowledged in the clinic. In the early 1900s physicians were reluctant to associate antipsychotic drug treatment with a movement disorder (reviewed in [1]). Based on the understanding of antipsychotic drugs at the time, it was difficult to conceive that a drug that affects cognition might also have an effect on motor activity. To further complicate diagnosis, physicians had to then distinguish the movements that were characteristic of the psychosis from those that were involuntary motor disorders.

Schönecker was one of the first to describe TD as a consequence of [typical] antipsychotic drug treatment in the literature (reviewed in [1, 2]). He described the characteristic involuntary facial movements and noted the chronic nature of the disorder as well as symptoms that would persist following discontinuation of antipsychotic drug treatment (reviewed in [1, 3]). The persistence of the symptoms seen by Schönecker distinguished what he saw from the transient dyskinesia's that had been observed in other untreated populations such as the elderly, and untreated psychotic patients. In 1967, Schelkunov reported similar involuntary oro-facial movements in rats and mice treated with typical antipsychotic drugs; this has since become the most widely accepted animal model of TD (reviewed in [4]).

By the 1970s, there were three motor disorders that were associated with antipsychotic drug treatment: Parkinsonism, TD and akathesia [5]. While the term TD was first coined in 1964, it was the last movement disorder to be properly distinguished as a side effect of antipsychotic drug treatment [6]. TD was, and still is, characterized by the involuntary movement of the facial muscles such as tongue protrusions, sucking and protrusion of the lips, and can be accompanied by involuntary movement of the trunk and limbs [7, 8].

In the 1990s atypical antipsychotic drugs were introduced for the treatment of psychoses like schizophrenia [9, 10]. Atypical antipsychotic drugs including Clozapine, offered amelioration of the positive symptoms of schizophrenia with a decreased, but not eliminated, occurrence of TD [9, 11]. However, these drugs brought a new array of challenges including increased incidence of agranulocytosis (acute leukopenia), hypotension, seizures, weight gain as well as potentially abnormal glucose and lipid metabolism [12]. Thus typical antipsychotic drugs continue to be used in the clinic, and TD remains a significant challenge to the medical community today.

The ensuing review will discuss the current understanding of the pathophysiology of TD as a consequence of antipsychotic drug induced oxidative stress.

The basal ganglia and tardive dyskinesia

Research concerning TD has focused on the basal ganglia as a system under dopaminergic control that modulates motor activity. While a specific region of the basal ganglia system responsible for the dyskinetic phenotype continues to be debated, considerable attention has been given to the striatum and its immediate connections as regions of particular interest [4, 13, 14, 15]. These regions have been a focus in part because of the similarity of TD to chorea of Huntington's disease and since control and execution of movement is largely modulated by this system [16].

The connections of the basal ganglia

The basal ganglia contains two major pathways- the direct pathway which is excitatory to the thalamus and the indirect pathway that inhibits the thalamus [17].

In the basal ganglia circuit (Figure 1 (A)), glutamatergic projections from the primary motor cortex, premotor cortex, supplementary motor area, and somatosensory motor cortex converge topographically onto medium spiny neurons in the striatum [18, 19]. These neurons also receive cholinergic input and GABAergic input (γ-aminobutyric acid), from neighbouring inter-neurons as well as other medium spiny neurons of the striatum [20, 21, 22]. This convergence of information is a reflection of the striatum's

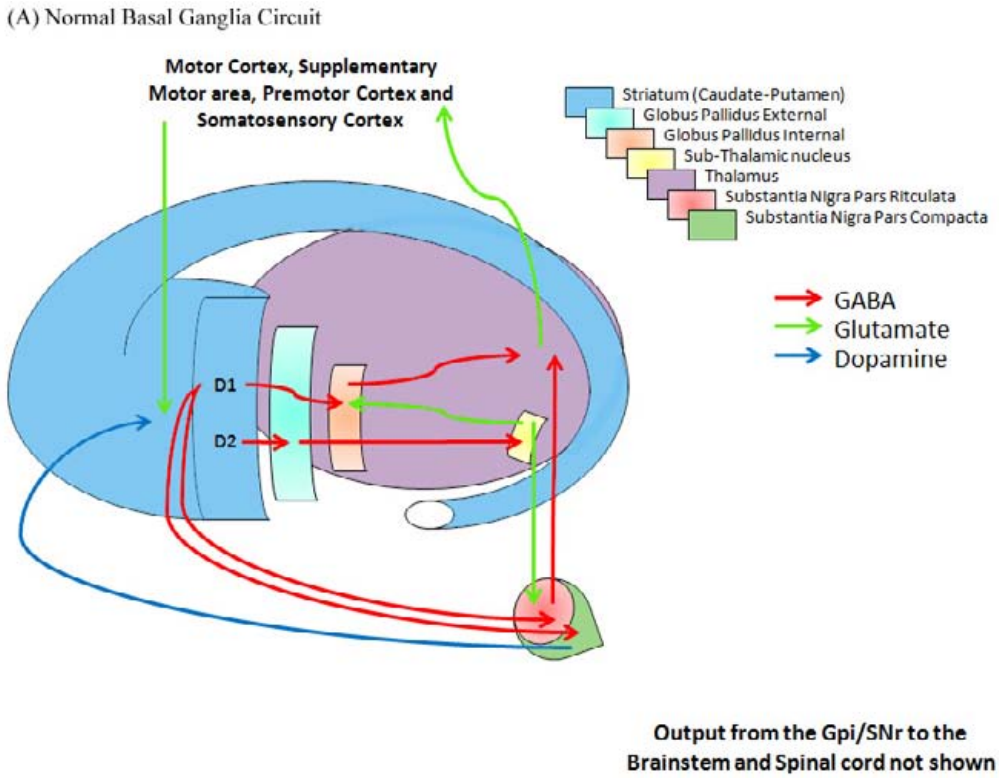

Figure 1 (A). Normal basal ganglia circuit (simplified diagram). The striatum receives glutamatergic input from the cortex and dopaminergic input from the substantia nigra pars compacta (SNpc). Medium spiny neurons which predominantly express dopamine D2 receptors release GABA in the globus pallidus external segment (GPe), which inhibits GABA release into the subthalamic nucleus (STN). The STN sends glutamatergic projections to the globus pallidus internal segment (GPi) and the substantia nigra pars reticulata (SNpr). GABAergic neurons project from the GPi and SNpr to the thalamus. This is the indirect system. In the direct system GABAergic medium spiny neurons in the striatum that express dopamine D2 receptors predominantly project directly to the GPi, and relay unto GABAergic projections to the thalamus. Finally, glutamatergic neurons in the thalamus receiving both direct and indirect stimulation project to the cortex with a final signal concerning motor control. Dotted lines represent decreased signalling, solid lines represent normal signalling, and thick solid lines represent increased signalling.

significant role in information integration [18]. Dopaminergic projections from the substantia nigra pars compacta (SNc), also provides input to the medium spiny neurons of the striatum.

This dopaminergic influence on the neurons of the striatum is thought to alter the neurons' affinity to cortical stimulation, and is dependent on the type of dopamine receptor stimulated. There are two families of dopamine receptors: D1-like and D2-like [23]. Dopamine D1 receptors up-regulate adenylate cyclase, and thus increase the influence of cortical stimulation on striatal neurons. Conversely, dopamine D2 receptor stimulation down-regulates adenylate cyclase and thus decreases the influence of cortical stimulation on these neurons [18, 23].

The medium spiny neurons that make up the direct pathway possess mostly dopamine D1 receptors and are thought to predominantly project to the globus pallidus internal segment (GPi) and substantia nigra pars reticulata (SNr) where they release GABA. Dopamine D2 receptors are predominantly expressed on GABAergic striatal neurons that project to the globus pallidus external segment (GPe). GABAergic neurons from the GPe in turn project to the subthalamic nucleus (STN) where they synapse on glutamatergic neurons that project to the GPi and SNr. This is

the indirect pathway. Output from the GPi and SNr are GABAergic and project to the thalamus, which in turn has glutamatergic projections back to the various cortical regions. According to this model the direct pathway inhibits the inhibition to the thalamus, and thus allows for increased glutamatergic stimulation to the cortex which results in facilitation of movement [18, 23]. In contrast, the indirect pathway promotes the inhibition of the thalamus and thus reduces the glutamatergic stimulation of the cortex resulting in an inhibition of movement [18, 23]. Imbalances between the direct and indirect systems are the most consistently agreed upon etiologies which unify all of the historically identified hypotheses which have attempted to explain TD.

Changes in circuitry with tardive dyskinesia

One of the earliest hypotheses to explain TD was the dopamine supersensitivity hypothesis [24]. Typical antipsychotic drugs predominantly bind the dopamine D2 receptor. Thus it was hypothesized and later established that such treatment could lead to an up-regulation of dopamine D2 receptors in the striatum [25, 26, 27]. Since the dopamine D2 receptor has an inhibitory effect when stimulated, increases in receptor number and sensitivity of these receptors could result in a decreased GABAergic output from the striatum. This would dysregulate the balance of the direct and indirect systems in the basal ganglia, and may account for the motor disturbances that characterize TD. While this may explain some of the features of TD including the worsening of symptoms after removal of the antipsychotic drug as well as the alleviation of symptoms with increasing dosage of the antipsychotic drug, its fast onset does not correlate well with the chronic nature of TD [28, 29].

However, even while the dopamine supersensitivity hypothesis was still the mainstream explanation of TD, other groups had already characterized neurodegeneration in the striatum and substantia nigra, as correlating features of TD in humans and animal models [30, 31, 32]. The concept of neurodegeneration would evolve to offer a far more comprehensive explanation of the chronic nature of TD.

Antagonism of dopamine D2 receptors by antipsychotic drugs like haloperidol has been proposed to initially cause an inhibition of dopamine activity, and consequent up-regulation of the GABAergic signal to the GPe, culminating in an overall decreased output from the thalamus (Figure 1 (B)). These changes have been suggested to account for the early-onset Parkinsons-like side effects [33]. Prolonged dopamine D2 receptor antagonism can result in up-regulation of dopamine synthesis and the build up of dopamine levels in the synaptic cleft, particularly in the striatum wherein there is a high concentration of D2 receptors [34]. High levels of oxygen in the brain can facilitate oxidation of excess dopamine to reactive oxygen species including hydrogen peroxide (H_2O_2), superoxide (O_2•), hydroxyl (OH^-•) and semiquinone (SQ•) radicals [35, 36, 37, 38]. It has been demonstrated that increasing oxidative stress can stimulate mitochondrial membrane permeability and apoptosis predominantly by the apoptosis inducing factor (AIF) pathway, wherein AIF translocates to the nucleus and causes DNA degradation [39]. This may account for a loss of local neuronal cell populations. Thus it is hypothesized that decreased signalling in the striatopallidal pathway will result in increased GABAergic output from the GPe. This increased output will in turn cause a decreased output from the STN and thus decreased inhibition in the thalamus from the GPi and SNr. Consequently there will be increased stimulation to the cortex that can account for the hyperlocomotion characteristic of TD (Figure 1 (C)). These molecular changes are in agreement with work done in cebus monkeys by Mitchell *et al.* (1992) [40].

The exact role of the direct system and dopamine D1 receptors in the oxidative stress hypothesis for the pathophysiology of TD continues to be debated. A recent study by Madsen *et al.* supported the hypothesis that D1 agonists, like SKF, can induce tardive dyskinetic symptoms [41]. This study further suggests a role for the CB1 receptor in modulating this effect, however thus far there has been no implication of the D1 receptor in neurodegeneration and TD, and thus the effects of D1 have only been depicted in this review as a reference, which is in dire need of further exploration.

Numerous studies have demonstrated region specific neurodegeneration in TD which is limited

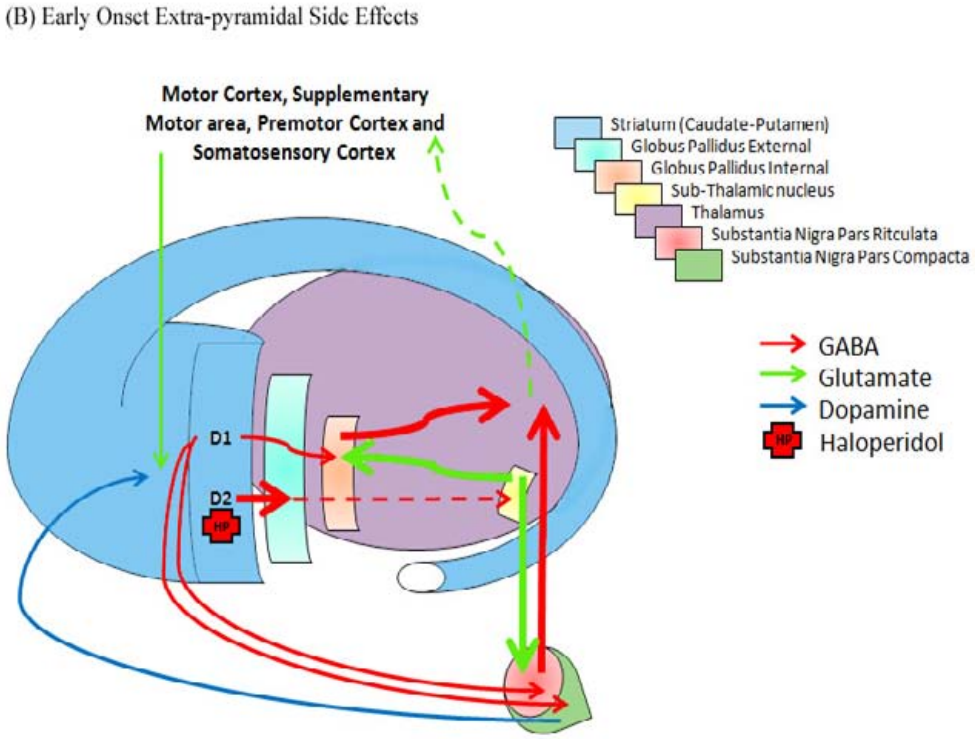

Figure 1 (B). Early onset extra-pyramidal side effects (simplified diagram). It has been proposed that acute blockade of the dopamine D2 receptor by haloperidol, will initially increase GABAergic output from the striatum since the dopamine D2 receptors are inhibitory on this system [33]. Consequently, there will be a decreased GABA inhibition from GPe to the STN and increased glutamate stimulation from the STN to the GPi and SNpr. This will result in increased GABAergic output from the GPi and SNpr to the thalamus. Thus, there will be a decreased stimulation to the cortex and resultant hypolocomotion, characteristic of early onset extra-pyramidal side effect e.g. Parkinsonianiam in humans or catalepsy in animals. Dotted lines represent decreased signalling, solid lines represent normal signalling, and thick solid lines represent increased signalling.

to the ventrolateral striatum [42, 43]. According to the topographical arrangement of the striatum this region is particularly involved in oro-facial control correlating well with the TD phenotype [44]. This provides further support for the oxidative stress hypothesis of TD.

Challenges to the anti-oxidant defence system

Oxidative stress can result from increased levels of free radicals, as well as from potential decreases in the brains defences including the anti-oxidant defence system (AODS). The AODS is composed of a collection of enzymes and molecules that work to neutralize endogenous and externally introduced free radicals. The key enzymes of the AODS are superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) [45]. This system is very effective under normal conditions; with each enzyme complementing the activity of the others (Figure 2). However the AODS can become overwhelmed or thrown off balance if the enzymes are not active in the appropriate proportions. Non-enzyme components of the AODS include albumin, uric acid, bilirubin, GSH, α-tocopherol (vitamin E), ascorbic acid (vitamin C) and β-carotene ([46], reviewed by [47]). These non-enzymatic components are associated with extracellular protection, and are often found in plasma, while the enzymatic components are more often expressed intra-cellularly (reviewed by [47]).

Interestingly, in 1983, it was proposed that the antipsychotic drug haloperidol can increase SOD activity levels [48]. A human study in Poland

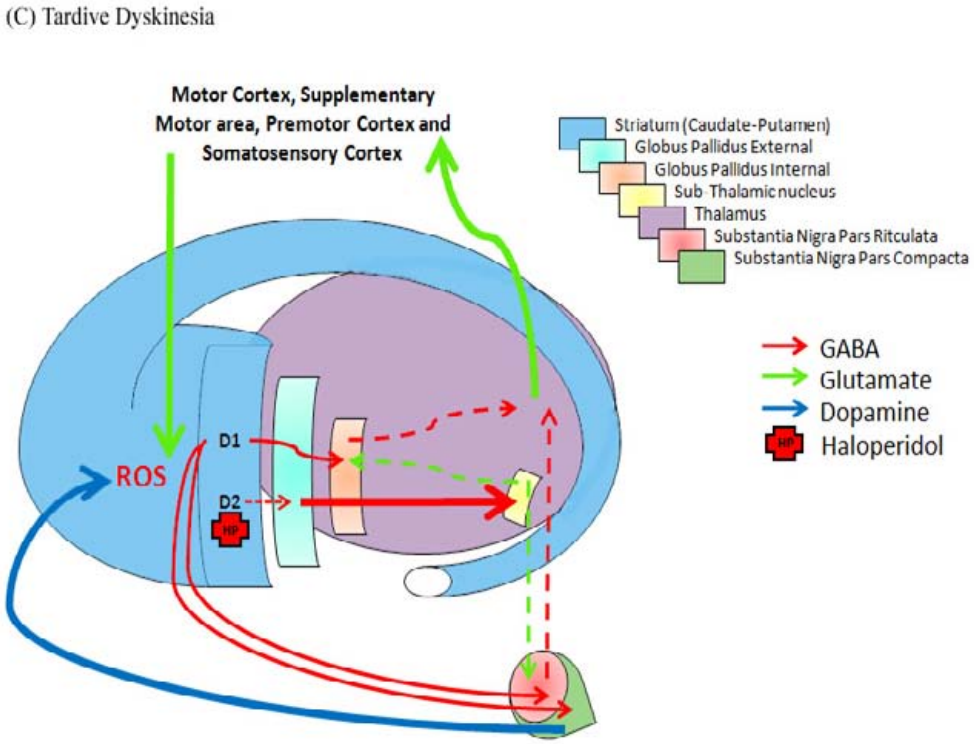

Figure 1 (C). Tardive Dyskinesia (simplified diagram). According to the oxidative stress hypothesis, chronic blockade of the dopamine D2 receptor with haloperidol will result in increased dopamine at the level of the synaptic cleft of these cells (i.e. from SNpc). This dopamine can be oxidized to reactive oxygen species (ROS) which may cause neuronal degeneration. Consequently, there will be decreased GABAergic output from the medium spiny neurons blocked by haloperidol (i.e. the dopamine D2 receptor expressing neurons). In turn, this will increase GABA inhibition to the STN and then decrease glutamatergic stimulation to the GPi and SNpr. Finally, there will be a loss of inhibition at the thalamus and increased glutamatergic stimulation to the cortex. The excess stimulation to the cortex can account for the hyperlocomotion characteristic of TD. Furthermore, it has been demonstrated that there can be increased glutamatergic stimulation from the cortex to the striatum which may also contribute to increased levels of oxidative stress and cell loss in the striatum. Dotted lines represent decreased signalling, solid lines represent normal signalling, and thick solid lines represent increased signalling.

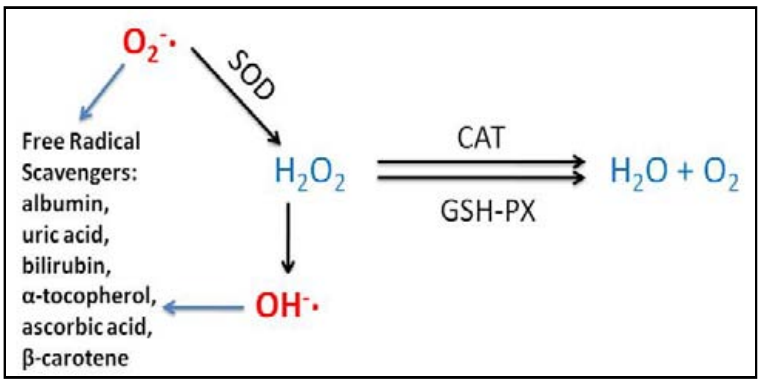

Figure 2. Simplified diagram of interconnections of the antioxidant defense system. Superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) [45].

determined that CuZnSOD (cytoplasmic) is significantly reduced while CAT activity was increased in schizophrenic patients with TD [49]. Zhang *et al*. (2002) [50] found that MnSOD (mitochondrial) was increased in patients with TD. Other groups also implicate MnSOD polymorphisms in the development of TD [51, 52, 53]. Thus, the cellular changes that accompany TD may be concentrated at the level of the mitochondria which may represent an interesting consideration for future study. Other groups have taken this concept a step further, proposing that while antipsychotic drugs can alter the enzymatic components of the AODS, they do not act directly on these components. In contrast the changes that are seen may reflect changes in symptomatology and may not be a direct effect of the antipsychotic drug [45]. It has been widely acknowledged that patients with schizophrenia both on and off antipsychotic drug treatment had an altered antioxidant status when compared to healthy controls ([54, 55, 56, 57]; reviewed in [58]). Together, these studies suggest that the status of an individual's AODS might be compromised in schizophrenia. Therefore, individuals affected by schizophrenia are more vulnerable to antipsychotic drug induced cell death, because of a weakened AODS.

Glutamate excitotoxcity

An increased level of glutamate and oxidative stress was found in the CSF of patients with schizophrenia and TD, providing another possible mechanism of neurodegeneration in TD [59]. The excitotoxcity hypothesis proposes that excess glutamate release from the cortico-striatal pathway may become toxic and induce cell death in the striatum (Figure 1(C)) [59]. The exact mechanism by which glutamate increases oxidative stress remains unknown, but glutamate build-up has been established to cause an increased level of lipid peroxidation, and neuronal cell loss [59].

HPP+ induced oxidative stress

It has been proposed that haloperidol's metabolite HPP+ may also contribute to an inhospitable environment in the striatum [60, 61]. HPP+ has been shown to be more toxic than haloperidol to PC12 cells and its proposed mechanism of action is thought to be analogous to the metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), MPP+, which is neurotoxic in the substantia nigra producing symptoms that closely model Parkinson's disease [62]. HPP+ displayed toxicity to both dopaminergic and serotonergic mesencephalic cells *in vitro*, as well as an ability to inhibit both dopamine and serotonin uptake [60]. While little research has been done to establish the exact role of HPP+ in haloperidol induced neurotoxicity, this remains a possible contributor to the development of TD in both animals and humans.

Current research: using antioxidants as a therapy in tardive dyskinesia

Numerous studies to date have confirmed that increased levels of oxidative stress can result from an antipsychotic drug challenge in humans, animal models and at the cellular level. Specifically, haloperidol has been demonstrated to produce increased free radical production in C6 astroglial cell lines [63]. It has been shown that there is increased lipid peroxidation in the cerebrospinal fluid of human patients suffering from TD [64]. Alpha(α)-Phenyl-N-tert-butylnitrone (PBN) a free radical spin trapping molecule has been demonstrated to prevent vacuous chewing movements (a widely accepted model of tardive dyskinesia, Box 1) in rats [65]. Furthermore, treatments with anti-oxidants, like vitamin E and ebselen, have been demonstrated to offer some therapeutic value in TD in humans and rat models [66, 67]. Consequently, the oxidative stress hypothesis has been increasingly investigated as an explanation for TD. However, recent studies focusing on both the characterization of TD as well as furthering therapeutic measures have yet to reach a consensus on a single cause of TD and an appropriate therapy. Here we will review recent advances in antipsychotic drug induced oxidative stress research for therapeutic use.

Within the oxidative stress hypothesis, a relationship between specific polymorphisms in oxidative stress related genes was considered since this would help provide an explanation for the partial incidence of TD in the antipsychotic drug treated population (i.e. why only a subset of the anti-psychotic drug treated population develop symptoms of TD). A 2009 study by Kang *et al*. [68]

Box 1: Experimental models of TD

The most widely accepted and investigated animal model of human TD is the typical antipsychotic drug induced vacuous chewing movement (VCM) ([91] reviewed in [92]). A VCM is an abnormal opening and closing of the mouth (oro-facial movement), which is not directed at grooming or eating, and is often accompanied by facial grimacing, and tongue protrusions. Since TD is induced similarly in humans, this offers a simple and effective model of TD that is likely caused by a similar pathophysiology to the human correlate. The predominant animal of choice is the rat; due to ease of access and a well established understanding of its physiology relative to other animals. However, the cebus monkey and guinea pig have also been utilized as model animals for inducing TD [93, 94, 95].

Haloperidol and Reserpine are some of the commonly used typical antipsychotic drugs to induce VCMs. Dosages may range from 1-3 mg/kg daily via intraperitoneal injection for haloperidol or subcutaneously every other day for Reserpine, for 3-30 days [96, 97, 98]. At this dose haloperidol will induce a subset of animals to display high counts of VCMs and a subset to display lower counts as early as the first week of drug administration. Consequently most research groups working with haloperidol will divide their subjects in to low and high VCM groups, and perform assessments separately. This characteristic of the disorder may reflect the partial incidence in humans, wherein only 20-40% of treated human patients will develop TD. Similarly, Reserpine may induce VCMs as early as day three, which does not correlate well with the chronic nature of TD [28, 96]. This abnormality was accounted for by Neisewander *et al*. (1994) and others who established in a dose response test with Reserpine, that varying the concentration of drug can alter the onset of symptoms. They demonstrated that lower concentration of drug will take a longer time to induce VCMs but higher concentrations will induce VCMs earlier. Thus it can be argued that the dosages most often administered may be considerably higher in rat physiology than the corresponding dosages in humans. Further support for this model of TD was demonstrated by the administration of Reserpine or haloperidol to animals of varying ages. It was also shown that older animals developed more severe oro-facial abnormalities than younger, which also resembles the human trend [99, 100].

Nonetheless, intraperitoneal injected haloperidol does not always produce a stable and reliable model. The VCMs developed are not always reliable from week to week, and may not persist following discontinuation of treatment, as is observed in the human condition [101]. Thus, many groups have opted to administer haloperidol decanoate intramuscularly, or in drinking water for three or more weeks. The VCMs developed in these models, although phenotypically similar to those previously described, take a longer time to develop but once established persist following drug discontinuation, which closely resembles the human condition [92].

analyzed the Glutathione S-transferase (GST) enzymes: GST-M1, GST-T1, and GST-P1 gene loci in over two hundred schizophrenic patients with and without TD for a possible relationship between polymorphisms in these genes and TD. GST enzymes are responsible for mitigating oxidative stress in cells, raising the possibility that mutations in these enzymes which limited their activity could raise susceptibility to oxidative damage and hence to TD. However, no significant relationship was identified between the existence of polymorphisms in the GST loci and the development of TD [68]. Similar results were seen when the same group failed to show a correlation between polymorphisms in MnSOD (a member of the AODS) or NADPH quinine

oxidoreductase 1 (NQO1) and the development of TD in multiple populations [51]. In contrast, other studies successfully demonstrated some correlation between an oxidative stress related polymorphisms and TD development in schizophrenic specific populations. For example, a 2004 study by Pae *et al*. [69] reported a relationship between a NQO1 polymorphisms and TD. Similarly another study by Hitzeroth *et al*. [70] showed a relationship to MnSOD mutation but this was later contradicted when tested in larger samples as indicated above in 2010 [51]. Finally, while there are several known associations between TD development and polymorphisms in the dopamine D2, D3 and recently even the D4 receptors, little can be meaningfully interpreted from these results to date [71]. The current evidence of mutations in oxidative stress-related genes appears to be precarious and suggest that the onus should be placed on the increased production of reactive oxygen species as opposed to a genetic predisposition.

It has been known for some time that long term haloperidol administration can result in oxidative stress with recent studies confirming increased lipid peroxidation products particularly in the basal ganglia [72]. Thus considerable work has been done to explore the use of a variety of antioxidants to compensate for these changes both in humans and animal models (Tables 1 and 2). *In vivo* work in rat models of antipsychotic drug induced TD has demonstrated that many commonly used antioxidants have promising preventative properties against TD when co-administered with antipsychotic

Table 1. Summary of recent antioxidant studies related to TD. All studies done in rats.
IP: Intraperitoneal, IM: Intramuscular, PO: Per-Oral, SC: Subcutaneous.

Compound (antioxidant)	Methods	Results	Study
Zolpidem (N, N, 6-trimethyl-2-p-tolyl-imidazo (1, 2-a) pyridine 3-acetamideL-(+))	Daily IP injections of haloperidol (1 mg/kg) and zolpidem (1, 2, 5 mg/kg) for 21 days. Lipid peroxidation and VCMs measured.	Zolpidem significantly reduces VCMs and lipid peroxidation compared to haloperidol only treatment. Preventative role.	[73]
Curcumin	Daily IP injections of haloperidol (2 mg/kg) and curcumin administered PO at 200 mg/kg in jello for 14 days. Abnormal-oro facial movements and locomotion assessed.	Curcumin prevented the development of abnormal-oro facial movements but had no effect on locomotor activity. Preventative role.	[76]
Curcumin	Daily IP injections of haloperidol (1 mg/kg) for 21 days. Curcumin administered daily PO at 25 and 50 mg/kg. VCMs, tongue protrusions, facial jerking measured.	Curcumin in both doses largely reduces VCM development, tongue protrusions, facial jerking. Preventative role.	[74]
Alpha Lipoic acid (ALA)	Daily IP injections of haloperidol (1 mg/kg) for 21 days. Acute ALA (suspended in 0.2% carboxy methyl cellulose at a dose of 25, 50 and 100 mg/kg) administered orally by oral gavage 1 h before haloperidol on 21st day of treatment. VCMs measured.	ALA supplementation significantly decreased VCM development at 100 mg/kg and catalepsy dose dependently. Indicative of symptom attenuation following haloperidol administration.	[78]
Morus alba leaf extract	Daily IP injections of haloperidol (1 mg/kg) for 21 days. Co-administiration of Morbus alba leaf extract (100-300 mg/kg, IP)	Morbus alba leaf extract in both doses largely reduces VCM development, Preventative role.	[75]

Table 1 continued..

Ilex paraguariensis (IXP)	haloperidol injected weekly(12 mg/kg/, IM) for 4 weeks. IXP provided ad libitum (50 g/L) for 60 days. VCMs measured.	IXP co-administration prevents increases in VCM induced by haloperidol. Preventative role.	[77]
Ebselen (2-phenyl-1,2 benzisoselenazol-3)	haloperidol was injected SC (12 mg/kg) weekly for 4 weeks. Ebselen was injected IP (30 mg/kg) 5 days before haloperidol for a total of 33 days on alternate days. VCMs measured. (i.e. administered before and during haloperidol treatment).	Ebselen significantly reduces VCMs and lipid peroxidation compared to haloperidol only treatment. Preventative role.	[67]
Spirulina Mazima (SM) (cocktail of antioxidants)	Daily IP injections of haloperidol (1 mg/kg) for 21 days. SM (45, 90 and 180 mg/kg) was administered by gavage along with haloperidol from 21st day to 49th day of treatment. VCMs measured.	Dose of 180 mg/kg of SM shown decreases VCMs. Indicative of symptom attenuation following haloperidol administration.	[79]
Alpha(α)-Phenyl-N-tert-butylnitrone (PBN)	Daily IP injections of haloperidol (2 mg/kg) and PBN (150 mg/kg) for 28 days. VCMs measured.	haloperidol + PBN treatment showed significantly lowered VCMs compared to haloperidol treatment. Preventative role.	[83]
Carvedilol	Daily IP injections of haloperidol (1 mg/kg) or Chlorpromazine (2 mg/kg) and two daily IP injections of Carvedilol were administered to assess a dose response to Carvedilol (0.5 - 2 mg/kg) for 21 days. VCMs measured.	Carvedilol dose dependently lowered haloperidol and chlorpromazine-induced VCMs. Preventative role.	[84]
Quercetin (a bioflavonoid)	Daily IP injections of haloperidol (1 mg/kg) and Quercetin were administered to assess a dose response to Quercetin (25-100 mg kg) for 21 days. VCMs measured.	Dose dependent (25-100 mg/kg) reduction in haloperidol-induced VCMs. Preventative role.	[85]

drugs [73, 74, 75]. A 2008 study by Bishnoi *et al.* demonstrated the protective nature of curcumin, a polyphenol ingredient in turmeric, against the development of haloperidol induced TD in the rat model [74]. These findings have been complemented by a study published by our laboratory in 2011 that confirmed curcumin's potential therapeutic value in preventing haloperidol induced abnormal oro-facial movements [76]. Other polyphenols, such as Ilex paraguariensis have shown promising results and hence warrant further research [77]. Additionally, in 2009, Thaakur and Himabindhu, [78] used a 21 day alpha lipoic acid (ALA) co-administration to show similarly effective results, as did a 2010 study by Nade *et al.* [75] using Morus alba leaf extract to prevent the development of antipsychotic drug induced TD. Interestingly, ALA administered in high dosages immediately following haloperidol treatment was able to decrease VCMs; which may reflect a small window of flexibility in the timing for antioxidant therapy in TD [78]. Similar results were seen by the same group in a 2005 study using a Spirulina Maxima (SM) [79].

As a result, antioxidants are being co-administered with haloperidol treatment in a clinical setting as a possible preventative measure [80]. Notably, vitamin E has been tested clinically in this fashion with encouraging results as a preventative measure, but with little success in reversing symptoms [80]. A growing body of evidence is forming that indicates natural and synthetic compounds with antioxidant characteristics are able to prevent TD when co-administered along with the antipsychotic drug. However, there is little concrete evidence to suggest that antioxidants will offer any reversibility of tardive dyskinetic symptoms. This idea complements the hypothesis proposed earlier,

Table 2. Summary of recent clinical trials and human investigations using antioxidant treatments for TD. Exclusion factors: compound must have some antioxidant capacity. PO: Per-Oral

Compound (antioxidant)	Methods	Results	Study
Vitamin E (α-tocopherol)	A statistical meta-analysis was performed**,** 223 patients were given vitamin E (400-1600 IU/day) to treat TD symptoms, in 12 studies. Most studies used Abnormal Involuntary Movements Scale (AIMS) assessment was used to measure TD.	28.3% showed improvement of TD symptoms. Rarely were clinically relevant side effects observed. Patients who benefited the most from vitamin E therapy had experienced TD symptoms for a shorter duration, suggesting that there may be a small window for the therapeutic role of an antioxidant to treat TD.	[86, 87]
Melatonin	11 men and 11 women, mean age 64. A double-blind, placebo-controlled, crossover was performed: 2 tablets (5 mg each, 10 mg/day) of melatonin or placebo. Washout of four weeks and then cross over. AIMS assessment was used to measure TD.	No adverse side effects observed. 17 of the 22 patients observed improvements with melatonin more than placebo.	[88]
Estrogen	A 3 week long, double-blind randomized clinical trial with 10 post-menopausal women with TD; mean age was 59.1 years, and the mean duration of TD was 32.3 months. AIMS assessment was used to measure TD.	AIMS score decreased by 38% in the estrogen group and 9% in the placebo group.	[89]
Vitamin B6	Five inpatients were assessed. 3 patients has TD, 1 had tardive akathesia and one tardive parkinsonism. PO vitamin B6 was administered at 100mg/day in addition to medications; for 4 weeks. AIMS, Barnes akathesia rating scale (BARS), and Simpson-Angus scale (SAS) was used as assess movements.	4 of the 5 patients significantly improved on AIMS, BARS and SAS. No recorded side effects. Two patients returen to baseline levels of TD 1 week after stopping treatment.	[90]

since cell death is generally preventable but not reversible. (For a review of the clinical uses of vitamin E in TD and Parkinson's disease see [81]). Nonetheless, these studies suggest that there is considerable potential in the clinical setting for the co-administration of antioxidants as a preventative measure against the development of TD.

FUTURE DIRECTIONS AND CONCLUSION

A number of hypotheses have been proposed to explain TD including dopamine supersensitivity, glutamate excitotoxcity and others [59, 82]. We present here the hypothesis that an increased level of oxidative stress in the striatum which induces preferential loss of medium spiny neurons expressing dopamine D2 receptors, and consequent dysregulation of the basal ganglia. This hypothesis can account for dysregulation in movement characteristic of TD and it addresses the chronic and irreversible nature of this disorder. However, it is unlikely that the oxidative stress hypothesis will independently suffice to explain the pathophysiology of TD due to a number of limitations. Firstly, it does not account for the amelioration of symptoms with increasing dosage of antipsychotic drug and it only partially addresses the specificity of neurodegeneration suggesting that the location of DA accumulation (i.e. where there is dopamine D2 receptor blockade) will be the region most significantly affected by increasing oxidative stress. Despite its limitations, the oxidative stress hypothesis presents a promising

approach to clarifying the etiology of TD and with additional exploration may provide a significant building block in a holistic theory of TD.

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