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Neurobiological Basis of Dyskinetic Effects Induced by Antipsychotics: the Contribution of Animal Models

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Abstract: Tardive dyskinesia (TD) is a movement disorder characterized by abnormal involuntary facial movements induced by chronic therapy with classical antipsychotic medications. Currently, there is no satisfactory pharmacotherapy for TD, which represents a major limitation to therapy with classical antipsychotics. In order to develop or optimize therapies for TD, and to develop new APDs with lower indices of motor side effects, the pathology underlying TD must first be understood. The use of animal models has been used to further this objective. Here, we review different preparations that have been used to model TD and discuss the contribution of neuroimaging studies conducted in these models. Studies in animal models have lead to several hypotheses of TD pathology, although none has yet emerged as the ultimate underlying cause of this syndrome. We discuss alterations in functional indices, neuron and synapse morphology and changes in specific neurotransmitter systems that have been described in animal models of TD, and outline how these findings have contributed to our understanding of antipsychotic-induced dyskinesias. We conclude that several non-mutually exclusive theories of TD are supported by animal studies, including increases in oxidative stress leading to structural and functional changes in specific neurotransmitter systems. Elucidating the mechanisms underlying TD neuropathology partly through the use of animal models will lead to the development of APDs with superior side effect profiles or more effective therapies for TD.

Keywords: antipsychotic medications; brain; butyrophenones; haloperidol; drug-induced motor symptoms; preclinical models; tardive dyskinesia.

1. INTRODUCTION

Tardive dyskinesia (TD) is a movement disorder characterized by abnormal involuntary movements of the head, neck, face, tongue and jaw, and in extreme cases, may involve the limbs or extremities [1-2] TD is induced by chronic therapy with classic antipsychotic medications (APDs), such as haloperidol (HAL), at a rate of approximately 5% per year of treatment [3-4] While second generation APDs are associated with a lower incidence of TD, motor complications have still been reported, and the mechanisms that account for their superior motor side effect profile remain unclear. Moreover, second generation APDs are associated with rapid weight gain and potentially fatal complications, such as diabetic keto-acidosis [5] [6] and so first generation antipsychotics remain in clinical use, and TD remains a significant clinical problem. Due to the large proportion of existing APD-treated patients and the potential irreversibility of TD in some cases, it is also a syndrome of significant ethical concern [7]. Currently, there is no therapy for TD that is consistently effective [8] and specific mechanisms underlying the pathogenesis of TD remain unknown.

The use of animal models has contributed significantly to the understanding of TD pathology and has been used to establish proof-of-concept of surgical interventions and pharmacotherapies for TD [9] [10] [11]. In this review, we focus on two animal models of TD, the non-human primate model and the vacuous chewing movement rodent model. In rodents, long-term administration of classical APDs, such as HAL, leads to a syndrome of vacuous chewing movements (VCMs), which are jaw movement in the vertical plane, not directed at a specific object, accompanied or not by tongue protrusions. These VCMs are considered analogous to orofacial dyskinesias occurring in human TD [12] [13]. Shorter HAL treatment times have also been used to model TD [14] [15][16]. However, VCMs emerging in the first 3 weeks of HAL treatment are pharmacologically and functionally distinct from late VCMs, which arise only after prolonged treatment ([17] (Table **1**). It has been suggested that early occurring VCMs may more accurately model extrapyramidal side effects (EPS) associated with *acute* rather than chronic HAL treatment, and therefore attention must be paid to duration of treatment in interpreting data from HAL-treated rodent studies [14] [17] [15][16].

Non-human primates treated chronically with classical APDs develop grimacing and tongue protrusion similar to clinical TD [18][19]. Both rat and non-human primate models are highly similar to clinical TD in etiology, symptoms, and response to treatment. The time course and variability range seen in non-human primates are closer to those seen in humans, making the non-human primate a homologue model of TD [20]. The variability seen in treated rodents (e.g. distinctions between low-VCM and high-VCM rats) has also been useful to separate brain effects specifically associated with dyskinesias from general effects of medications, e.g. [21][22].

Studies in animal models have led to several hypotheses of TD pathology, although none has as yet been confirmed as the ultimate underlying cause of this syndrome [20] [23] [24]; [25]. Although dyskinesias occur with most first-generation APDs [13], most of the studies have used chronic HAL as a prototypical inducing drug. We discuss alterations in functional indices, neuron and synapse morphology and changes in specific neurotransmitter systems that have been described in animal models of TD, and outline how these findings have contributed to our understanding of antipsychotic-induced dyskinesias.

2. MORPHOLOGICAL, NEUROPLASTIC AND DEGENERATIVE CHANGES

The delayed onset and permanent nature of TD suggest that long term or neuroplastic changes may underlie the dyskinetic effects of chronic HAL. Neuroplastic changes may take the form of altered shape and strength of synapses, degeneration of specific populations of neurons or gross structural changes in specific brain areas.

2.1 Structural Changes

One theory of TD pathophysiology suggests that TD is due to structural abnormalities secondary to neurotoxicity [5][20] [24]. However, several studies have failed to find gross structural

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Table 1. Summary of Animal Models Commonly Used to Study TD[a].

Species	Antipsychotic Treatment	Motor Symptoms	Common features with clinical TD	
			Latent time Course	Inter-subject variability
Rat (acute)	Haloperidol hydrochloride 0.25-2.0 mg/kg i.p. daily 1-21 days	Repetitive purposeless jaw movements or vacuous chewing movements (VCMs)	No	No
Rat (chronic)	Haloperidol decanoate ~ 21 mg/kg, i.m / 3 weeks 12-30 weeks	Repetitive purposeless jaw movements or vacuous chewing movements (VCMs)	Yes	Some
Non-human primate (Cebus or macaque monkeys)	Fluphenazine decanoate 0.1-3.2 mg/kg, i.m. / 3 weeks 12 months OR Haloperidol 0.5mg/kg, p.o. daily 3-12 months	Jaw movements, tongue protrusions and facial grimacing	Yes	Yes

[a]In the rat, acute VCMs are pharmacologically distinct from chronic VCMs. Acute VCMs are thought to better model acute extra-pyramidal symptoms than tardive dyskinesia.

changes as a result of chronic APD treatment [26][27] [28] and other studies have reported *increases* in striatal volume in rats and non-human primates following chronic HAL treatment [29] [30] [31]. The mechanisms underlying striatal hypertrophy are unknown, and it has not been linked to changes in specific populations of neurons. Of note, striatal hypertrophy does not preclude neurotoxic processes in the same area [32] [31] [33].

2.2 Synaptic Plasticity

Evidence of changes in synaptic proteins is controversial and conflicting. Examinations of synaptic proteins have reported either no change [34], decreases [35] [36][37] or increases [38][39] [40] [41] in pre- or post-synaptic proteins in the striatum. This inconsistency in results may be due to differences in HAL dosing regimen, length of treatment and withdrawal period [42] [43] [44]. Studies that use chronic intramuscular HAL depot have generally reported no change in multiple pre- and post-synaptic proteins at the tissue, cellular or synaptosomal levels [34], whereas increases have been reported in studies using daily sub-chronic HAL treatment [45][40]. There are also discrepancies between results obtained with mRNA profiling and data from protein expression studies, with changes in mRNA levels, but not proteins, being reported. Lidow *et al.* [46] found no change in levels of synaptophysin protein in any of several cortical regions after chronic HAL, but did detect a decrease in spinophilin levels in all regions with the exception of the motor cortex. Similarly, Nakahara *et al.* detected no significant changes in levels of synaptophysin or SNAP 25 mRNA in the prefrontal cortex of HAL-treated rats [44]. The latter results contradict those of Eastwood *et al.*, where both 2- and 16-week HAL treatments were found to up-regulate synaptophysin mRNA as assessed by *in situ* hybridization [47] [42]. Nakahara *et al.* attributed the discrepancy to the use of RT-PCR and a possible loss of anatomical resolution upon extraction of total mRNA from the striatum. Of note, while Eastwood *et al.* (1997) found an increase in synaptophysin mRNA, these authors reported no statistically significant change in the levels of synaptophysin protein following 16 weeks of HAL treatment. This discrepancy between mRNA and protein levels suggests that chronic HAL may induce a shift in the position of synaptic contacts from dendritic spines to dendritic shafts, without significantly changing the density of synaptic contacts and thus synaptic protein or mRNA levels [48] [45] [39].

Consistent with these findings, electron microscopy studies generally report no changes in number of neurons following HAL-treatment. In cases where HAL-induced changes in neuronal number or morphology have been reported, changes are subtle and localized to the striatum or substantia nigra (SN). Two studies described an association between histopathological damage in the SN after chronic HAL treatment and VCMs [49] [50] and thus provide mechanisms by which dopamine (DA) release could be affected in TD.

The majority of studies addressing morphological changes other than cell loss have focused on the caudate-putamen (CPu). Increased size of axon terminals [48] [51] [39][52], increased numbers of vesicles per synapse [26, 48], synaptic rearrangements [53][39] and decreased synaptic density [36] [27] have been described. A consistent finding is no change in presumed DA synapses in the striatum [54] [40] with described mixed effects on acetylcholine (ACh) neurons [47] [55] [56]. A significant (~50%) increase in the number of perforated synapses has been consistently described after chronic HAL treatment [51][52][57][58]. These synapses refer to glutamatergic input to the striatum [37], reflecting increased or facilitated glutamatergic or potentially excitotoxic input to the CPu. Despite the variety of reported changes in synapse morphology, most have been found not to correlate with severity of VCMs, and are likely not involved in dyskinetic effects [49]. However, populations of GABAergic striatal interneurons have been identified to be lost after HAL treatment and are differentially affected in high- and low-dyskinetic rats after HAL treatment [59][60][61]. There is a selective loss of pre-prosomatostatin-positive striatal neurons which has been inversely correlated with severity of VCMs [49][62] Enkephalin density was upregulated by HAL treatment, accompanied by an increase in the number of striatal neurons expressing pre-proenkephalin (ppENK) in low-VCM rats, but not high-VCMs rats [63]. This suggests that dyskinetic rats fail to generate or maintain an elevated number of ppENK-positive neurons, possibly due to innate mechanism that prevent the increase or to an excitotoxic process that kills neurons and thus obscures this regulation [63][41]. These neurons have GABA as a co-transmitter and receive glutamatergic projections, making this hypothesis consistent with the GABA insufficiency, excitotoxic or oxidative stress hypotheses of TD. Further linking changes in ppENK expression to glutamate (GLU) activity, MK-801, which prevents signaling through NMDAR, prevents HAL-induced increases in ppENK in the striatum [50].

2.3 Neurodegenerative Changes

Excessive GLU transmission leads to excitotoxicity and localized neuron damage or neurodegeneration. Activity-dependent plastic changes, increased immediate early gene (IEG) expression and increased excitatory synapses in chronically HAL-treated rats as described above, supports the idea of excessive GLU transmission in localized brain regions. Striatal excitotoxicity has been proposed

to underlie VCM development in rats [64][49] and has been suggested to be due to overactive cortical glutamatergic input, although apoptosis of striatal and nigral neurons has also been implicated [65]. Consistent with this possibility, increased levels of striatal glutamate have been described in rats chronically treated with HAL [66]. Excitotoxic degeneration of GABAergic neurons outside the striatum, specifically from the SN/globus pallidus (GP) to thalamus have also been described [67]. Specific mechanisms underlying HAL-induced increased GLU release are not known, but one hypothesis is that HAL binds to a butyrophenone regulatory site on NMDA receptors to increase GLU currents.

A second possible neurodegenerative mechanism is that HAL, a small, lipophilic molecule, induces indirect excitotoxicity by disrupting mitochondrial cellular energy metabolism by interfering with the electron transport chain [68][64]. Free radicals from increased DA turnover have also been proposed as a cause of oxidative stress in TD [49]. Consistent with this mechanism, the neuroprotective agent, GM1 ganglioside prevent the development of VCMs and D2 receptor upregulation after chronic HAL treatment [35]. The antioxidant vitamin E has also been shown to suppress HAL-induced VCMs and degeneration [69][49]. In further support of oxidative stress mechanisms, brain damage and aging are two known risk factors for TD, and are two conditions which increase susceptibility to oxidative stress [70][71][72][73]

3. FUNCTIONAL CHANGES

While the structural changes described above are robust, they do not provide information about functional alterations induced by typical APDs in these structures and in connected brain areas. Several studies have sought to determine mechanisms underlying APD-induced adverse effects. Neuronal activity and metabolism can be assessed using the complementary techniques of 2-deoxyglucose (2-DG) uptake and IEG activation. 2-DG uptake reflects the overall metabolism of neurons and reflects cumulative activity primarily at presynaptic terminals [74][75] whereas immediate early genes reflect a genomic response to calcium influx at the cell body [76].

3.1 2-Deoxyglucose (2-DG) Uptake

Autoradiography studies detecting 2-DG uptake have been conducted after acute and chronic HAL treatment to examine changes in patterns in neuronal activity. Labeled (C^{14}, H^{3}) 2-DG competes with glucose for uptake into neurons, where it is only partially metabolized and label therefore accumulates within the cell. Amount of label is then quantified as an index of activity of nerve cells, in particular of synaptic activity [77][78][79][80].

The majority of 2-DG studies have been conducted in rats, after a single acute HAL treatment (0.5 or 1mg/kg). In these studies, sacrifice occurs approximately 2 hours after HAL, at the time corresponding to peak cataleptic response, a common marker of HAL-induced acute extrapyramidal symptoms (EPS). However, this behavior is not universally measured and it is difficult to extrapolate the relevance of observed changes in 2-DG uptake to possible mechanisms underlying TD. Acute HAL treatment has been found to predominantly decrease 2-DG uptake throughout the basal ganglia and thalamus. Specifically, in a study of 43 brain areas, HAL was associated with decreased 2-DG uptake in the SN, GP and subthalamic nucleus (STN) [81]. This study has been extended and confirmed by Pizzolato [82-83] who found decreases in the CPu and SN, and by Cochran *et al.* [75](Cochran, McKerchar *et al.* 2002) who reported significant LCGU decreases in the dorsolateral caudate putamen (dlCPu), primary motor cortex (M1) and GP, although the effects were less pronounced in the latter study. In a separate study, a region-specific decrease in 2-DG uptake has been reported in the substantia nigra pars reticulata (SNr) but not in the substantia nigra pars compacta (SNc) [84]. There are two factors that limit the applicability of these studies to the pathology of TD. First, as noted, HAL was administered acutely, rather than chronically. Second, treatment with clozapine (which is not associated with acute EPS or chronic orofacial dyskinesias in animal models) was found to have a similar profile of 2-DG uptake in the GP and SN [84], M1 and GP [75][85]. In fact, in studies designed to compare the two drugs, the dlCPu stands as an area that is uniquely affected by acute treatment with HAL, but not clozapine treatment [75, 85]; This finding is significant, as it corroborates several IEG studies reporting that activity changes in the dlCPu correlate with antipsychotic-induced EPS [86-87][88].

Another consistent finding of 2-DG studies has been increased LCGU in the lateral habenula (LHb) [82-83][84]. This has also been reported after acute administration of D2 but not D1 DA receptor antagonists [89], and after lesions of the nigrostriatal system [90][91]. The LHb receives projections from both the STN and SNr, and the increased metabolic activity in this area is hypothesized to reflect derangements of nigrostriatal DA transmission and are consistent with the observed HAL-induced LCGU decrease in the SNr. HAL also reportedly decreases 2-DG uptake in the raphe [92][85] , and while this area does not express D2 receptors, it does receive more extensive glutamatergic innervation from the STN than previously thought [93]. The observed 2-DG changes in the raphe may reflect a disinhibition due to decreased STN activity (Fig. **1**). The effects of acute HAL treatment on 2-DG uptake were found to be age-dependent in the rat, with HAL-induced decreases in LCGU being most pronounced in 33 month old rats [83]. Along with the known age-dependent alterations in DA metabolism [82], this finding may provide insight into the mechanism of increased susceptibility to TD with age.

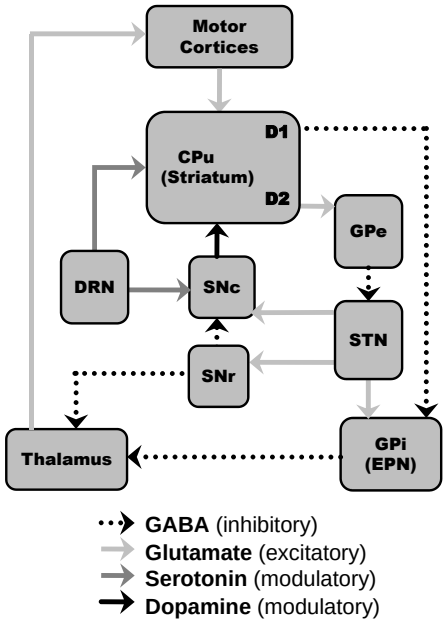

Fig. (1). Schematic representation of key basal ganglia connections. A simplified diagram of the basal ganglia circuitry depicting key neuronal connections is shown. Neurons which express D1 receptors and project to the GPi (EPN) give rise to the direct striatal ouput pathway, whereas D2-expressing neurons project to the GPe on to the STN and GPi and give rise to the indirect pathway. While the mechanisms underlying the pathology of TD are incompletely understood, we speculate that chronic dopamine D2 antagonism results in hyper-sensitivity of the indirect basal ganglia output pathway. Over-activity of glutamatergic projections from the STN to the SNc is thought to lead to excitotoxic damage to dopaminergic neurons of the SNc. Moreover, increased activity of glutamatergic projections from the STN to SNr would increase inhibition of SNc mediated by the SNr. Both of these changes would reduce dopamine outflow from the SNc to CPu, which further increases activity of the indirect pathway.

A caveat in interpreting these findings is the distinction between acute and chronic effects of HAL. In two studies directly comparing acute (1mg/kg), and chronic (0.5 or 1.0 mg/kg/day, for 21 days) HAL treatment on 2-DG uptake, an adaptation to HAL has been reported, with fewer regions being effected and the magnitude of decreased 2-DG uptake being reduced after 21 days of HAL treatment [92][85]. Interestingly, in both studies the STN was the only basal-ganglia or movement associated area that showed decreased 2-DG uptake in the chronic preparation [92][85]. A single study with chronically (several years) HAL-treated Cebus monkeys also reported decreased 2-DG-uptake in the medial GP and increased uptake in the ventroanterior/ ventrolateral (VA/VL) complex of the thalamus [80]. The authors suggested that chronic HAL decreases inhibition of the VA/VL due to underactivity of its inputs from the SN and GP, and that the underactivity of the SN and GP may be the result of underactive subthalamopallidal pathway. An alternative explanation that may reconcile the reduced STN 2-DG uptake and decreased glutamic acid decarboxylase (GAD, the GABA-synthesizing enzyme) in the STN with the observed decreased medial GP (mGP) activity is that the STN adapts to the long-term excitatory effects of HAL treatment on the indirect pathway. When given chronically, fast STN firing induced by HAL leads to excitotoxicity, in effect inducing a functional lesion in the projection site, the mGP [94][95]. Unlike findings in rodent studies, the findings reported in Cebus monkeys were limited to those expressing orofacial dyskinesias, which may make findings more applicable to TD pathology, rather than to unrelated, non-dyskinetic effects of chronic therapy with classical APDs.

3.2 Immediate Early Genes (IEGs)

Immediate early genes are transcribed in response to calcium influx that occurs upon neuronal activation. Measuring expression of these genes thus provides an indirect measure of neuronal activity. Because of the high expression of D2 receptors and the putative involvement of these receptors in orofacial dyskinesias, the striatum has been the focus of many IEG studies.

D2 antagonists, including typical APDs, potently induce immediate early gene expression in the striatum. This effect is observed with multiple IEGs [96][97][98] and is most pronounced in the dlCPu [99][100][98]. These effects of HAL are exclusively due to D2 antagonism, since they are blocked by co-administration of the D2 agonist quinelorane, which has no effect by itself. Also, the effects are less prominent with non-specific DA agonists and are not seen with D1 agonists. This suggests that D1 and D2 exert opposing influences on IEG expression in the CPu, with D2 activation tonically inhibiting IEG expression [88][101].

Signaling through D2 is negatively coupled to adenylyl cyclase via $G_{\alpha i}$, suppressing activity of D2-expressing neurons, which is relieved by HAL. Since functional adenosine and glutamate transmission are necessary for the maximal effects of HAL on IEG induction [88], it is possible that this disinhibition arising from D2 blockade unmasks the influence of $G_{\alpha s}$-coupled inputs and NMDA activation, which are mediated by adenosine and glutamate respectively. Furthermore, MK-801 prevents effects of HAL on IEGs [99][101][102], implicating glutamatergic transmission in HAL-induced IEG activation.

Caution must be used in interpreting the aforementioned IEG studies. First, the majority of IEG studies are based on an acute dose of HAL treatment, although similar results have been reported with chronic treatment, with induction of IEGs in CPu as well as STN and several motor regions of the thalamus being reported [103] [104][98]. Second, although striatal IEG expression has been related to acute HAL-induced EPS, the relation to TD is unclear [105][87][106]. Finally, the functional consequences of IEG expression are not clear, but are known to regulate several synaptic plasticity-related proteins [107] and neurotransmitter receptors [108][109][110].

4. ALTERATIONS IN NEUROTRANSMITTER SYSTEMS

4.1 GABA

In addition to the glutamatergic hypotheses discussed above, excitotoxic glutamatergic transmission has also been investigated as a potential substrate for TD [49]. Following chronic HAL treatment, excitotoxicity has been observed in GABAergic neurons from SN/GP to the thalamus and in GABAergic MSNs in the striatum, as described above [67]. Specifically, ppENK-expressing striatal MSNs, which also express D2 receptors, may be particularly susceptible to oxidative stress resulting from HAL treatment [63].

GABA-gated chloride channel binding is slightly elevated in the vlCPu and decreased in the GP after chronic HAL treatment in rats expressing high levels of VCMs [22]. However, the latter decrease was also observed in HAL-treated rats expressing low levels of VCMs, suggesting that pallidal changes alone cannot account for the development of VCMs [22]. By contrast, increased GABA-binding may reflect a compensatory up-regulation in response to decreased numbers of GABAergic neurons in the CPu. These findings, along with reports that chronic HAL treatment in non-human primates reduces the GABA-synthesizing enzyme GAD in the SN, GP and STN [111], has lead to the GABA insufficiency hypothesis. This hypothesis suggests that decreased inhibitory GABA-mediated transmission in the basal ganglia may underlie TD [49][20]. This GABA insufficiency may be the result of excitotoxic damage to GABAergic neurons and may exacerbate GLU-mediated excitotoxicity.

4.2 Dopamine

HAL-induced excitotoxic damage has been reported in dopaminergic neurons of the SN [49], and DA turnover was decreased in CPu and SN in monkeys with TD [112]. It has been suggested that the nigrostriatal DA system becomes more sensitive to DA as a consequence of chronic D2 antagonism [113][24], which is manifest as an up-regulation of D2, but not D1 receptors [114][115][24]. In fact, slightly decreased D1 binding has been reported in the CPu of chronically HAL-treated rats, although this finding was found to not correlate with VCM expression [116]. D2 receptors are located post-synaptically throughout the basal ganglia and also exist as somatodendritic inhibitory autoreceptors. Chronic HAL-induced upregulation of these autoreceptors could account for the observed decrease in number of spontaneously active SNc neurons after haloperidol treatment *in vivo* [117]. *In vivo* D2 receptor occupancy has been linked to VCM emergence in HAL-treated rats [118][119-120]. However, while a certain level of D2 occupancy may be necessary for inducing VCMs, high D2 occupancy does not correlate with VCM severity [13] and does not appear to be sufficient in and of itself to induce the VCM syndrome [121].

4.3 Serotonin

Serotonin (5-HT) has been implicated in TD pathology by the lower incidence of TD seen with atypical antipsychotics, which has been ascribed to their 5-HT2 antagonism. Dopaminergic inputs to the striatum regulate 5-HT receptor gene expression, and 5-HT2 receptors modulate DA transmission in the basal ganglia via 5-HT2 receptors on somatodendritic surface of DA neurons [122][123][124]. Chronic HAL treatment leads to inhibited striatal 5-HT2C mRNA expression, which is thought to be mediated by interference with D2 receptor signaling [125][126]http://www.sciencedirect.com.myaccess.library.utoronto.ca/science/article/pii/S0166432811000519 - bib0155. However, Wolf et al. showed an adaptive increase in 5-HT2C coupling to G-proteins as a result of repeated HAL administration, which was limited to the striatum [127]. It is not clear how this increase in coupling is mediated, but it is thought to involve post-translational modifications of the 5-HT2C receptor [127]. In the striatum, 5-

HT2C receptors are located on medium spiny interneurons, which regulate information outflow to the STN and GPe [128]. Intrastriatal infusion of the 5-HT2A/2C agonist mCPP induces orofacial dyskinetic movements [129]. 5-HT2C receptors are also located on GABA interneurons in the SNr which project to the pars compacta [129]. This provides a potential mechanism whereby 5-HT2C receptors could mediate inhibition of DA cellular activity in the SNc, which is the main source of DA projections to the striatum [130]. Antagonism of these 5-HT2C receptors, for example by atypical antipsychotics, would thus increase DA release to the striatum, compensating for a possible DA deficiency as suggested by Gunne and Jorgensen. In agreement with this mechanism, antagonism of 5-HT2C receptors [131][126] and administration of atypical antipsychotics such as clozapine suppresses HAL-induced VCMs [132][133]. Moreover, 5-HT2 antagonism prevents HAL-induced IEG induction in the CPu [134-135] and up-regulation of D2 receptors [136].

4.4 Acetylcholine

Specific interactions between DA, GABA and ACh in the dlCPu have been implicated in HAL-induced dyskinesias [137][55]. Striatal cholinergic neurons represent approximately 1% of striatal neurons, but provide rich innervation to this structure [138]. Striatal ACh release is tonically inhibited by DA activation of D2 receptors [139][140], and HAL treatment increases ACh release [137]. Chronic HAL treatment leads to reduced numbers of choline acetyl transferase (ChAT)-positive neurons in the striatum [55], increased synaptic protein expression in these neurons [47] and increased sensitivity of ACh receptors [114]. However, this latter finding has not been replicated in all studies, and may depend on ligand specificity and receptor subtype [141][142]. Moreover, ACh-mimetics exacerbate HAL-induced EPS, whereas anticholinergics such as scopolamine suppress HAL-induced VCMs [143][144][137]. These observations support the idea that chronic HAL leads to a slight loss of cholinergic cells which in turn leads to a compensatory increase in sensitivity of striatal cholinergic receptors, supporting the idea that altered ACh transmission may also be involved in the dyskinetic effects of HAL [55].

CONCLUSION

Neuroimaging studies in pre-clinical models have provided a number of non mutually-exclusive hypotheses and neurocorrelates of antipsychotic-induced TD. Advanced age is the most significant risk factor for TD. Aged rats are more susceptible to oxidative stress and excitotoxicity, and exhibit decreased brain TH, rate of DA synthesis and concentration of DA and its metabolites [145][146] and age-related decrease in D2 receptors [147][148]. Excitotoxic degeneration in the SNr after chronic HAL was only observed in aged rats [49]. In addition to its role in excitotoxicity, GLU transmission has been linked to IEG activation and changes in striatal neurochemistry by the observation that MK-801 abolishes changes and may have effects on interacting neurotransmitter systems. Specifically, GABA inhibition increases excitatory tone in the basal ganglia, amplifying HAL effects on GLU and other neurotransmitter systems. This would lead to widespread functional changes throughout the basal ganglia and/or other HAL-affected brain areas that may underlie the persistent nature of APD-induced dyskinesias. While the HAL-treated rodent and non-human primate share several important features with TD observed in human patients [19][20], neuropathology induced by HAL treatment must be interpreted with caution. Specifically, it is yet to be determined which HAL-induced changes in brain structure and function of are causally related to TD, and which are simply a byproduct of chronic APD therapy and not related to motor symptoms. Elucidating the mechanisms underlying the TD pathology partly through the use of animal models will lead to the development of safer APDs or more effective therapies for TD.

LIST OF ABBREVIATIONS

2-DG	=	2-deoxyglucose
5-HT	=	Serotonin
ACh	=	Acetylcholine
APD	=	Antipsychotic drug
ChAT	=	Choline acetyltransferase
CPu	=	Caudate putamen
DA	=	Dopamine
dlCPu	=	Dorsolateral caudate putamen
EPN	=	Entopeduncular nucleus
EPS	=	Extrapyramidal symptoms
GABA	=	Gamma-aminobutyric acid
GAD	=	Glutamic acid decarboxylase
GLU	=	Glutamate
GP	=	Globus pallidus
GPe	=	External globus pallidus
GPi	=	Internal globus pallidus
HAL	=	Haloperidol
IEG	=	Immediate early gene
LCGU	=	Local cerebral glucose utilization
LHb	=	Lateral habenula
MSN	=	Medium spiny neurons
NMDA	=	N-methyl-d-aspartate
ppENK	=	Pre-proenkephalin
RT-PCR	=	Real time polymerase chain reaction
SN	=	Substantia nigra
SNc	=	Substantia nigra pars compacta
SNr	=	Substantia nigra pars reticulata
STN	=	Subthalamic nucleus
TD	=	Tardive dyskinesia
VA/VL	=	Ventroanterior/ventrolateral thalamus
VCMs	=	Vacuous chewing movements
vlCPu	=	Ventrolateral caudate-putamen

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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