

Dopamine and Huntington's disease

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Huntington's disease (HD) is an incurable, inherited, progressive neurodegenerative disorder that is defined by a combination of motor, cognitive and psychiatric features. Pre-clinical and clinical studies have demonstrated an important role for the dopamine (DA) system in HD with dopaminergic dysfunction at the level of both DA release and DA receptors. It is, therefore, not surprising that the drug treatments most commonly used in HD are anti-dopaminergic agents. Their use is based primarily on the belief that the characteristic motor impairments are a result of overactivation of the central dopaminergic pathways. While this is a useful starting place, it is clear that the behavior of the central dopaminergic pathways is not fully understood in this condition and may change as a function of disease stage. In addition, how abnormalities in dopaminergic systems may underlie some of the non-motor features of HD has also been poorly investigated and this is especially important given the greater burden these place on the patients' and families' quality of life. In this review, we discuss what is known about central dopaminergic pathways in HD and how this informs us about the mechanisms of action of the dopaminergic therapies used to treat it. By doing so, we will highlight some of the paradoxes that exist and how solving them may reveal new insights for improved treatment of this currently incurable condition, including the possibility that such drugs may even have effects on disease progression and pathogenesis.

KEYWORDS: dopamine • dopamine receptor • Huntington's disease • motor disorder • striatum

Huntington's disease (HD) is a progressive, autosomal dominant disorder, classically characterized by a triad of deficits including involuntary movements (typically *chorea*), psychiatric symptoms and cognitive decline. The disease has an estimated prevalence rate of 11–14 per 100,000 [1,2], and is caused by a mutation in the *huntingtin* gene (*HTT*), which results in an expansion of cytosine–adenine–guanine (CAG) repeat in exon 1 of this gene. The *HTT* gene encodes the protein HTT and the HD mutation results in an elongated glutamine tract at the N-terminal end of the protein, leading to the production of mutant HTT (mHTT) [3].

Clinically, the natural history of HD can simplistically be divided into a pre-manifest and manifest period. Pre-manifest patients carry the mutant gene, but do not have any overt clinical signs, although may exhibit subtle psychiatric and cognitive deficits. At some point, the patients develop more overt cognitive, psychiatric and motor signs; the last of which is currently needed for a diagnosis of manifest HD to be given even though the

cognitive and affective deficits may be well advanced by this stage [4].

Although the mHTT is ubiquitously expressed in the brain of patients with HD, the primary pathological hallmark of the disease has long been regarded as striatal degeneration. The most affected cells in the striatum are the GABAergic medium spiny neurons (MSNs), which make up about 95% of the striatal neuronal population [5,6]. Their loss results in severe atrophy of the striatum and has been linked to the movement problems associated with HD, as well as some of the cognitive abnormalities seen early in the disease course [5].

However, the exact pathogenesis of HD still remains elusive with many cellular changes being reported along with an emerging number of studies suggesting that the disease has a significant non-cell autonomous component [7]. Nevertheless, it is clear that in HD, toxic mHTT fragments are generated and ultimately contribute to intracellular inclusions, transcriptional dysregulation, impairments in axonal transport [8]. Furthermore, the pathogenesis include the loss of important trophic factors

such as brain-derived neurotrophic factor delivery in corticostriatal pathways [9], abnormalities in autophagy and mitochondrial function [10], inflammation [11] and ultimately widespread cell death [12].

Alterations in neurotransmitter release have also been reported in HD including abnormalities in the dopamine (DA) system [13,14], which has been postulated to play a major role in some of the motor and non-motor deficits of HD [15–19]. Given its major basal ganglia pathology, most drugs used to clinically treat patients with HD have targeted the dopaminergic system and the chorea, thereby making this network an important focus of research in this disorder. It is perhaps surprising that there are so few published studies in this field. The aim of this review is to discuss the role of DA in HD by outlining the evidence of dopaminergic dysfunction from both the patient and animal literature, before describing the symptomatic effects and mechanisms of action of DA-based therapies currently being used to treat HD¹.

The DA system: an overview

The dopaminergic pathways

DA is a major neurotransmitter that plays a critical role in many areas of normal CNS function including movement control, cognition, motivation/reward processing as well as a role in psychiatric behavior [20]. As a result, it is not surprising that dysfunction of central dopaminergic pathways has been linked to many neurological and psychiatric disorders such as HD, Parkinson's disease, drug addiction and schizophrenia [20,21].

The anatomical location of the different groups of dopaminergic neurons (designated A1–A16) ranges from the medulla oblongata in the brain stem, through the midbrain, hypothalamus, diencephalon and olfactory bulb with an additional group, A17, found in the retina.

However, the major dopaminergic pathways are:

- *The nigrostriatal pathway*: A dopaminergic pathway linking the substantia nigra to the dorsal striatum [22]. This pathway is known to have a major function in motor control thereby linked to the chorea of HD, and its loss is central to the pathology of PD. Furthermore, L-dopa used to treat PD acts on this pathway and also accounts for some of the extra side effects of the DA blocking neuroleptic treatments used to treat schizophrenia and related disorders.
- *The mesolimbic pathway*: It includes fibers projecting from the ventral tegmental area of the midbrain to the nucleus accumbens, amygdala and hippocampus. This pathway is involved in regulating reward processing and is linked to certain forms of drug addiction, psychiatric illnesses as well as motivation and may be involved in the apathy seen in HD [23–27].
- *The mesocortical pathway*: It connects the ventral tegmental area with the prefrontal cortex (PFC) and other cortical areas. Abnormalities in this pathway have been linked to schizophrenia [28], and it is also intimately involved in executive function in both healthy volunteers and patients [29]. This latter relationship linking executive function to PFC

DA levels is complex and is best modeled in terms of an inverted U-shaped relationship with an optimal level of DA needed for this cognitive function to be done with greatest efficiency [30,31]. In addition, this pathway also has projections to other cortical regions, albeit to a lesser degree than that seen for the PFC, and this drive some of the paranoia and hallucinations that are seen in PD and rarely in HD.

- *The tuberoinfundibular pathway*: It involves a dopaminergic pathway linking the arcuate nucleus of the hypothalamus to the pituitary gland, and is important in the regulation of hormonal release such as prolactin [32].

DA transmission

DA, upon being released from pre-synaptic terminals, activates a range of specific DA receptors on both the pre-synaptic and post-synaptic neurons [33]. Unbound DA can be recycled back into the pre-synaptic terminal, via the high-affinity DA transporter (DAT), where it is either re-packaged into vesicles by the vesicular monoamine transporter type 2 (VMAT2), or broken down into inactive metabolites by enzymes, such as monoamine oxidase. These transporters are heavily expressed in the striatum but less so in the cortex, where the major process for synaptic DA inactivation is enzymatic degradation through catecholamine-*o*-methyltransferase.

The quantity of DA released is regulated by two modes of firing known as tonic and phasic DA transmission. Tonic DA release occurs spontaneously and can be seen as a baseline activity of DA neurons with low levels of DA being continually released into the synaptic cleft with some escaping into the extrasynaptic space. Tonic firing is too low to activate post-synaptic receptors but has an effect on pre-synaptic DA autoreceptors, thereby autoregulating DA synthesis and release. In contrast, phasic DA release is of higher amplitude and induced by action potentials in the dopaminergic neurons. The large release of DA associated with this firing then stimulates a range of post-synaptic DA receptors (outlined below) as well as being taken up by pre-synaptic DA transporters in cases where they exist or are alternatively broken down by monoamine oxidase and catecholamine-*o*-methyltransferase [34]. This latter release of DA is therefore associated with stimuli that activate the neurons and is thus thought to be the main mode by which the DA system signals change.

The DA receptors

The DA receptors, of which there are many different types (see below) are G protein coupled receptors, widely expressed in the CNS with a range of functions in the normal and diseased brain. They are divided into five subtypes (D1–D5), which are expressed in various overlapping regions of the CNS:

- D1 and D2 receptors (D1R and D2R) are mainly expressed in the striatum, limbic system, thalamus and hypothalamus;
- D3 receptors (D3R) are mostly present in the limbic system;
- D4 receptors (D4R) are weakly expressed in the cortex and limbic system and

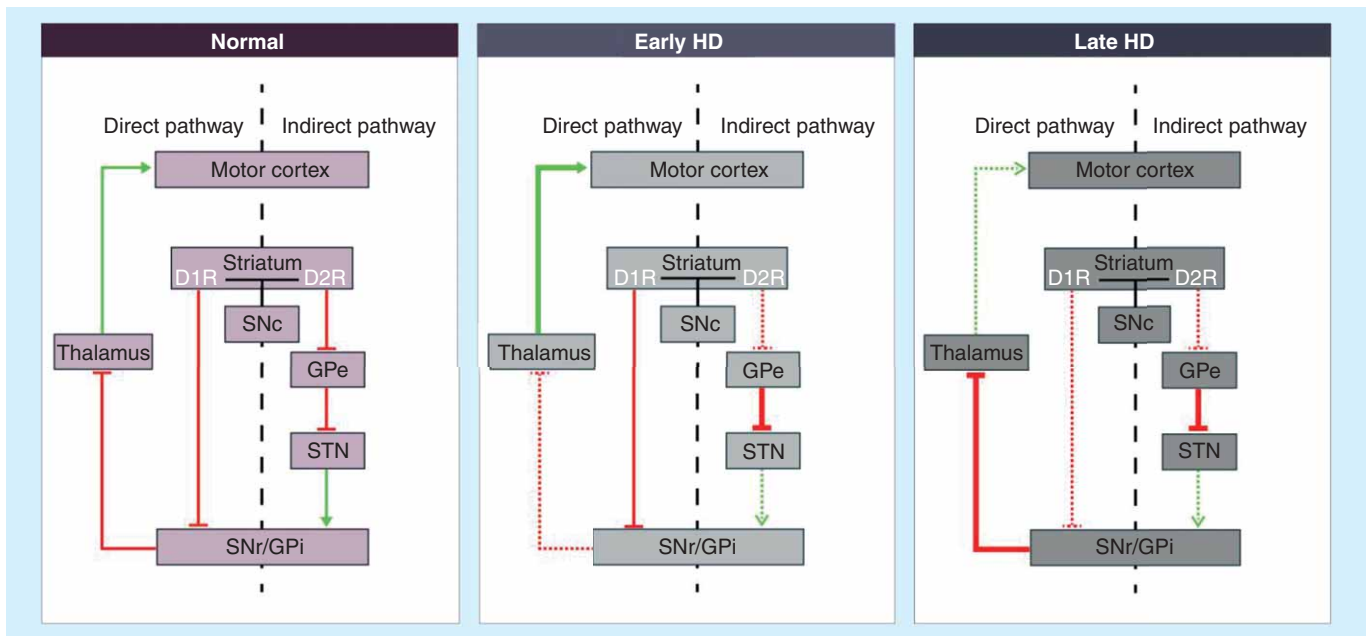


Figure 1. Schematic drawing of the direct and indirect pathways in normal conditions, as well as in early and late Huntington's disease. The direct pathway involves neurons expressing D1Rs and projecting directly to the SNr and to the GPi.

Activation of D1Rs leads to a disinhibition of the motor cortex through glutamatergic signaling (green arrows). Activation of the indirect pathway via D2Rs results in a decrease in motor activation through a GABAergic inhibition (red lines) of the GPe and the STN, which will activate the SNr and to the GPi. In early HD, the decrease in D2R leads to dysfunctions in the indirect pathway, which halts the activation of the SNr and GPi and ultimately generates an overactivation in the motor cortical regions by the thalamus. As the disease progresses to late stages, the reduction in D1Rs, governing the direct pathway, produces an overinhibition of the thalamus which leads in a decrease in the thalamic input to the motor cortical areas.

D1R: Dopamine 1 receptor; D2R: Dopamine 2 receptor; GPe: External globus pallidus; GPi: Internal globus pallidus; SNr: Substantia nigra pars reticulata; STN: Subthalamic nucleus.

- D5 receptors (D5R) are expressed in many regions including the prefrontal cortex, substantia nigra and hypothalamus [20,33].

These five sets of receptors are grouped into two main families, termed D1-like and D2-like. The D1-like receptors contain D1 and D5 receptors, and the D2-like receptors, D2, D3 and D4. The two distinct receptor families were originally defined based primarily on their pharmacological properties as they activate various G proteins and modulate cAMP levels differently – the D1-like family of receptors enhances cAMP release through activation of adenylate cyclase, whereas the D2-like family of receptors inhibits adenylate cyclase, thereby decreasing the level of cAMP.

D1R activation occurs mainly through the binding of DA to post-synaptic receptors, whereas D2Rs and D3Rs are both expressed pre- and postsynaptically and have different mechanisms of action. The binding of DA to D2-like pre-synaptic receptors (mainly D2R and D3R) results in a decrease of DA release while the activation of the same receptors post-synaptically leads to an increase [33].

The DA system in HD

The dopaminergic input to the striatum terminates on two main types of striatal MSNs which form two different efferent

pathways. These two pathways are termed direct and indirect and are defined by their receptor expression and the course of their output projections. Although this segregation of striatal outputs into distinct pathways is debatable, it nevertheless provides a useful framework by which to study the basal ganglia pathways and their role in the control of movement.

- *The direct pathway:* This pathway encompasses MSNs expressing D1Rs and projects directly to the substantia nigra pars reticulata and to the internal part of the globus pallidus. When the direct pathway is activated through D1R, projections from the cortex and thalamus are disinhibited and associated with an increased cortical activation especially in motor areas (FIGURE 1) [35–37].
- *The indirect pathway:* Mainly expressing D2R, this pathway has outputs to various structures including the external section of the globus pallidus and the subthalamic nucleus before projecting to the substantia nigra pars reticulata. This pathway acts in an opposite way to the direct pathway, and when activated, projections are inhibited which results in an attenuation of cortical activity and typically a decrease in motor activation (FIGURE 1) [35–37].

With respect to the MSNs, it is known that the nigral dopaminergic input can also regulate the afferent cortical

glutamatergic input to these neurons. Thus, alterations in dopaminergic input to the striatum will alter widespread networks of cells and their afferent inputs as well as having effects on cortical activation [36] with clinical consequences for movement control and cognition.

Techniques to measure dopaminergic dysfunction in HD

The DA system is amenable to imaging *in vivo* in humans using PET and a range of ligands that target the dopaminergic system [38]. In particular, radiolabeled tracers include ones that can bind to DA receptors, transporters and synthesis. Thus, it is possible to measure the normality of dopaminergic terminals (using F-dopa) as well as D2 receptors (using C-raclopride) and VMAT (using labeled tetrabenazine [TBZ] derivatives), although this is typically only possible in areas where the concentration of these ligands is high such as in the striatum.

In animal research, PET has also been used but it is possible to get more direct measures through more invasive techniques such as microdialysis and fast-scan cyclic voltammetry. This latter technique allows one to measure the release and take up of DA by nerve terminals in the region of study [13,14,39] while with microdialysis, one looks at changes in basal and DA levels over longer periods of time [39,40].

In addition, the expression of DA receptors, and markers of dopaminergic cells can be examined histologically in animal models of disease as well as in human post-mortem material, although this is not straightforward in patients who have been in receipt of drugs that target dopaminergic receptors such as neuroleptics.

Nigral dopaminergic neurons in HD

There is some debate as to the extent of neuropathological changes in the DA system in HD. While the loss of the GABAergic striatal MSNs and resulting atrophy of the striatum is one of the early features of HD, the extent of alterations in the DA system which projects to it are less clear as there have been only a few studies looking at the integrity of this pathway with inconsistent results. Early reports on the state of the substantia nigra in post-mortem HD suggested that the DA neurons were of normal size and number [41,42]. More recently, however, other groups have found a significant decrease in the number and size of DA neurons in the midbrain of post-mortem tissue of HD patients [43,44] as well as differences in the expression of tyrosine hydroxylase (TH) within the nigrostriatal pathway [44–46]. Such a loss of TH might reflect a loss of dopaminergic cells in the brain, but alternatively it may simply relate to a downregulation of expression of the enzyme rather than actual cell death. In order to resolve this, looking for the transporters VMAT and DAT can be helpful as loss of them in conjunction with loss of TH is more likely to reflect actual cell loss, and this seems to be the case in HD [47,48].

Furthermore in HD, the striatal MSNs degenerate in a dorsal to ventral way in a pattern that matches the DA content of this region which is higher in the dorsal, compared with the ventral part. This has led some to propose that the

dopaminergic input may even drive the loss of striatal neurons especially as several studies have found that aberrant DA concentrations can induce neuronal death through increasing the neurotoxic effect of mHTT [49–52].

Therefore, in HD, abnormalities in the integrity of the nigrostriatal dopaminergic system may be responsible not only for some of the symptoms and signs of HD, but may even be involved in the disease process itself. As such, drugs that target this network may work on both aspects of the disease process.

DA receptor abnormalities

Human studies

To date, studies looking at dopaminergic dysfunction in HD patients have mainly focused on the striatum and shown a consistent decrease in striatal D1R, D2R and DAT binding in both pre-manifest [53–55] and manifest patients [56]. Not surprisingly, there is greater loss in the manifest patients (FIGURES 2 & 3) [57] and one study has found that the loss of D2R and D1R binding correlated with total motor Unified Huntington's Disease Rating Scale (UHDRS) and Total Functional Capacity scores [58].

In addition, changes in DA receptor binding in both the caudate and the putamen have also been found to have a strong relationship with executive dysfunction and episodic memory in HD [59]. In fact, in HD, executive dysfunction can be identified up to 15 years prior to diagnosis [60] suggesting that striatal dopaminergic dysfunction may be a very early feature of this disorder.

In line with these PET studies, similar reductions in receptor binding have also been observed using other methods, such as autoradiography on post-mortem tissue. These studies have confirmed that there is a progressive reduction of DA D2R in the striatum as the disease progresses [61].

A few studies have also looked at extra-striatal changes in the DA systems in patients and shown reductions in D2R in the amygdala, cortical areas and the hypothalamus in both pre-manifest and manifest HD patients (FIGURE 2) [54,56,62]. This decrease in receptor binding was correlated with cognitive performance as well as disease duration [53,63].

However, a more recent study using a different radioligand ([¹¹C]FLB 457), known to be more suitable for low-density receptors populations [64], did not find any such changes or correlation.

Together, the human studies suggest that there is a global dopaminergic dysfunction at the level of D2R expression in the striatum and possibly beyond which may contribute to some of the motor and cognitive features of HD and which appear to be present prior to overt motor signs. However, further work is needed to establish this relationship and whether there are really significant changes outside the striatum and if so how this contributes to disease expression.

Animal models

Four of the most commonly used transgenic mice models in HD research have been studied for changes in their

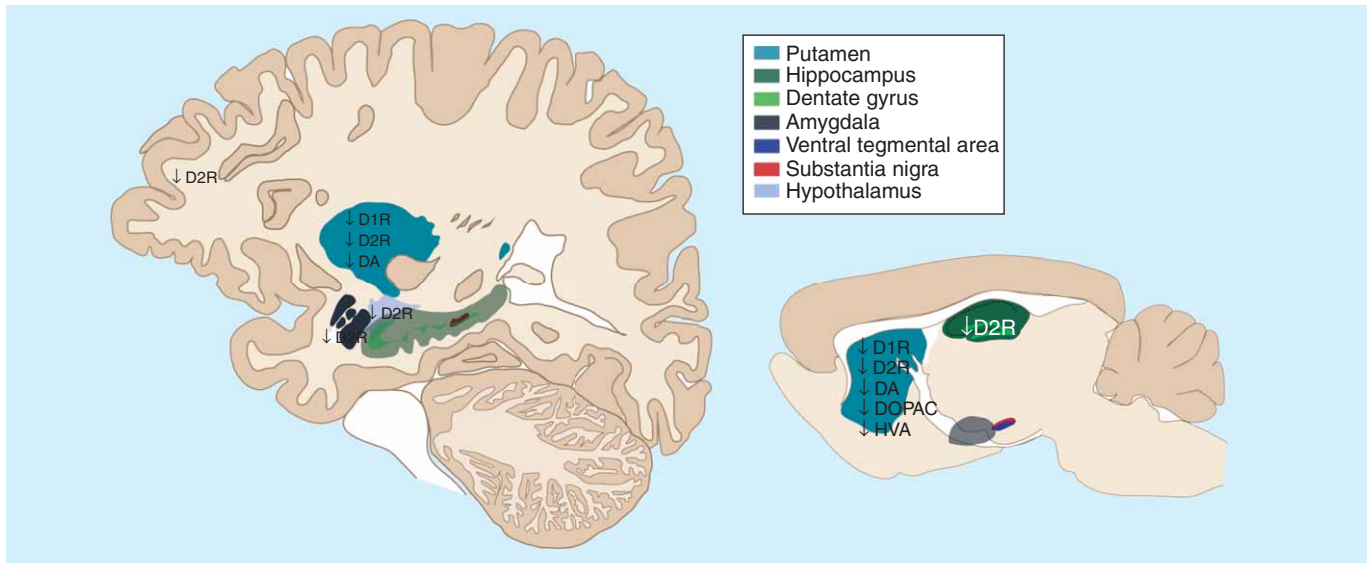


Figure 2. Representation of the dopaminergic deterioration in Huntington's disease (left, in humans; right, in rodent models of HD).

D1R, D2R: Dopamine 1 and 2 receptors; DA: Dopamine; DOPAC: 3,4-Dihydroxyphenylacetic acid; HVA: Homovanillic acid.

dopaminergic networks. These models will be described first and results on DA alterations summarized:

- The R6/2 line, the most commonly used HD mice model, expresses exon 1 of the human HD gene, with approximately 145 CAG repeats. The very high number of repeats leads to the development of early behavioral impairments including weight loss, motor abnormalities and cognitive deficits from 6 weeks of age with the mice typically dying at between 10 and 13 weeks of age. This transgenic model recapitulates some of the HD neuropathology with the presence of HTT-containing aggregates in the striatum and cortex, but while there is significant atrophy of the brain, there is only modest cell death [65–67]. This coupled with the rapid rate of progression in this model of HD limits its relevance to HD in the clinic. No changes in the number or health of the dopaminergic nigral neurons have been reported to date.
- R6/1 mice express exon 1 of the human HD gene with approximately 115 CAG repeats and have a lifespan of approximately 12–14 months, with motor impairments including gait deficits becoming apparent between 16 and 20 weeks of age [65]. With less repeats than the R6/2 mice, the R6/1 line possesses a milder phenotype with a slower progression. At 16 weeks, the volume of the striatum is reduced by approximately 17%, with cellular dysfunction but again little cell death [67,68]. They also have no overt nigral DA cell loss, although the midbrain TH⁺ cells are reduced in size with about 30% of them containing aggregated HTT [40].
- The yeast artificial chromosome 128 (YAC128) mouse model of HD carries the entire human HD gene with 128 CAG repeats. These mice develop hyperkinesia at 3 months, with progressive motor impairments beginning at 6 months of age. Progressive neurodegeneration starts at approximately 9 months followed by hypokinesia at 12 months. These mice

exhibit MSN loss resulting in striatal atrophy [69], and a significant decrease in striatal volume from 10 months of age [70]. No changes in the number and health of the dopaminergic nigral neurons have been reported to date.

- The bacterial artificial chromosome transgenic mouse model of HD contains the full-length human *mHTT* gene (containing 97 mixed CAA-CAG repeats) under the control of endogenous HTT regulatory machinery. They display significant motor incoordination at 6 months of age, and by 10–12 months the brains are visibly smaller, with significant atrophy of the cortex and striatum similar to HD patients but again no real striatal cell loss [70,71]. Again, the integrity and health of the midbrain dopaminergic neurons has not been examined.

The R6/1, R6/2 and YAC128 mice all display a significant reduction in DA receptor expression in the striatum and the cortex, which is not seen in the bacterial artificial chromosome transgenic mouse model of HD mice (FIGURE 2) [70,72]. A study investigating both the mRNA and protein expression of the DA receptors D1 and D2 in R6/2 mice found that these were reduced before clinical signs as early as 4 weeks of age with a further progressive reduction by 8 and 12 weeks [72]. Furthermore in the R6/1 mouse model, DA D2 receptor mRNA expression has also been found to be reduced in the dentate gyrus from 8 weeks of age (FIGURE 2).

These animal models have therefore displayed dopaminergic abnormalities similar to that seen in patients using PET imaging and post-mortem analysis. However, the number of studies have been small and the animal models used possess some limitations. This includes the size of the CAG repeat, the absence of overt cell loss and the speed with which some of the animals develop deficits and die. As such, their relevance to the human condition remains questionable [63,71], although not without value and has been able to provide unique insights as was the

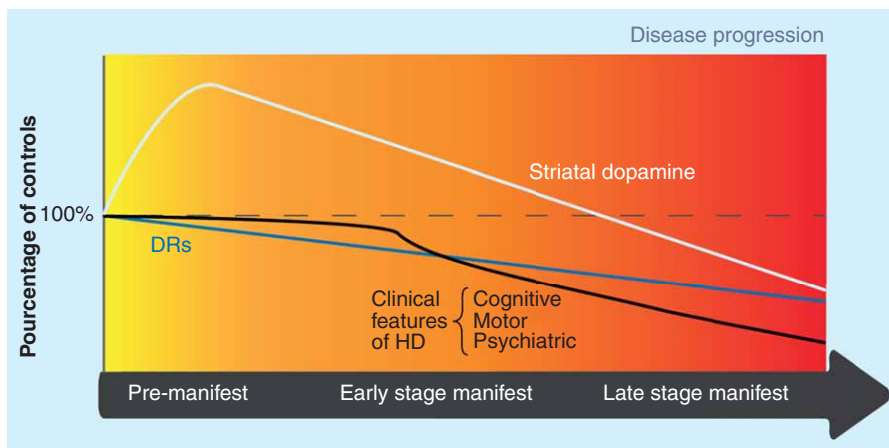


Figure 3. Progression of dopaminergic disturbances in Huntington's disease over a patient's lifespan. Representation of the progression of dopaminergic disturbances (based on the current literature) as the clinical features of HD emerge. Alterations in dopamine receptor expression and dopamine transmission start before clinical manifestations (from the pre-manifest stage of disease). It is hypothesized that there is a biphasic change in DA levels during the transition from the early (increased) to the late (significantly decreased) disease stage, paralleling the transition from a hyperkinetic to a hypokinetic state in HD patients. DA: Dopamine; DRs: Dopamine receptors; HD: Huntington's disease.

case for the original description of the intracellular inclusions [65,73,74].

DA neurotransmission

Alterations in DA transmission have been reported in both HD animal models and patients, and have been linked to some of the motor and non-motor clinical features of the condition.

Human studies

The link between DA and HD first came from the observation of dyskinesias in asymptomatic relatives of HD patients following treatment with L-dopa [18]. Therefore, it was suggested that hypersensitivity or overactivation of DA receptors may be involved in the choreic movements typically seen in most HD patients. This theory has gained credence over the years primarily through the beneficial effects of DA receptor blocking drugs on treating the chorea in HD patients (for discussion see below) as well as post-mortem analysis of DA levels in human's brains and the brains of transgenic HD mice.

Quantification of DA and DA metabolite levels in autopsied HD brains has yielded variable results. Early reports found normal levels in the post-mortem HD striatum [41] but more recent neurochemical studies have reported increased levels of DA in the striatum and substantia nigra of HD human brains independently of any drug treatment [17] in line with a recent study showing increased DA metabolite levels in the CSF of HD patients [75].

Animal models

DA neurotransmission has also been extensively examined in animal models of HD using microdialysis. In contrast to the human studies, extracellular DA levels in the striatum of R6/1

mice has been found to be significantly reduced (74%) when compared with control mice [40], in line with that seen in the striatum of R6/2 mice at 6 weeks of age with DA uptake being unaffected [39]. With time this becomes more prominent such that by 10–11 weeks of age, the extracellular DA concentrations in R6/2 mice is approximately 30% of that seen in normal mice [39,76], and amphetamine-induced release of DA is also significantly diminished [76]. There is a similar 50% reduction in extracellular striatal DA in the YAC128 mice at 10 months of age, with again a diminished response to amphetamine [76]. In addition, DA release, uptake and levels of DA metabolites such as 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid have also been found to be greatly reduced in the striatum of R6/1, R6/2 and YAC128 mice following chemical and electrical challenges which correlates

with their motor impairments and taken together suggests they may be causally linked (FIGURE 2) [13,76,77].

The neurochemical profile of the recently developed transgenic HD rat has also been examined and found to be similar to the transgenic mice – namely DA release as evoked by electrical stimulus was found to be decreased compared with normal rats [14].

In summary, a number of studies both in HD patients and rodent models of the disease have demonstrated alterations in DA receptor expression and DA transmission, which are present before clinical manifestations. These differences are somewhat different between patients and animal models with the former showing an increase in DA turnover and a decrease in D2R expression and the latter having a decrease in both DA release and DA receptors.

The reason for these differences is unclear but could relate to aspects of tissue handling, the method used to measure the integrity of the dopaminergic system and the stage of disease being studied. The most obvious explanation is that in early disease there is a loss of DA receptors and activation leading to increased turnover which is then lost as the disease progresses and the dopaminergic cells themselves are involved in the disease process. However, further work is needed to better understand the relationship between DA release, receptor expression and functionality (both pre- and post-synaptically) and how these all relate to disease stage and clinical features.

Treatments targeting the dopaminergic network in HD

Given the hyperkinetic movements associated with HD and the hypothesis that these clinical signs are related to overstimulation of the DA receptors, pharmacotherapies that modify the activity of the dopaminergic system have been extensively

Table 1. Potential dopaminergic treatments tested in clinical trials.

Drug	Mechanism of action	Clinical findings	Ref.
Vesicular monoamine transporter-type inhibitor			
Tetrabenazine	<ul style="list-style-type: none"> Vesicular monoamine transport-2 inhibitor Depletes pre-synaptic DA levels (serotonin and norepinephrine levels) Blocks post-synaptic DA receptors 	<ul style="list-style-type: none"> 5-point decrease in chorea severity (total maximal chorea score) 	[84–92,131]
DA antagonists			
Haloperidol	<ul style="list-style-type: none"> Antagonizes the DA D2 receptor with high affinity Slow receptor dissociation kinetics 	<ul style="list-style-type: none"> Decrease in chorea 	[95,132,133]
Clozapine	<ul style="list-style-type: none"> Atypical neuroleptic DA receptor antagonist 	<ul style="list-style-type: none"> High doses associated with decreased chorea 	[134]
Olanzapine	<ul style="list-style-type: none"> Serotonin and atypical neuroleptic with some DA (D2) antagonism 	<ul style="list-style-type: none"> Improvement in chorea Help with psychiatric disturbances 	[101–104,135]
Risperidone	<ul style="list-style-type: none"> DA D2 receptor (and also 5-HT2A, α1, α2 and H1 receptors) antagonist 	<ul style="list-style-type: none"> Improvement in psychiatric disturbances and stabilization of motor score (compared with worsening in the control group) 	[106]
Sulpiride	<ul style="list-style-type: none"> Selective DA D2 receptor antagonist 	<ul style="list-style-type: none"> Decreased movements No effect on functional capacity 	[100]
DA agonists			
Aripiprazole	<ul style="list-style-type: none"> Partial agonist acting on DA D2 (and 5-HT1A receptors; also exerts antagonistic effect on 5-HT2A receptors) 	<ul style="list-style-type: none"> Improvement in patient chorea (decreased UHDRS score) Slight improvement in depression level 	[107–109]
Bromocriptine	<ul style="list-style-type: none"> Potent DA D2 receptor agonist (5-HTR receptors agonist and reverse glutamate transporter GLT1) 	<ul style="list-style-type: none"> No therapeutic effect 	[112,113]
Lisuride	<ul style="list-style-type: none"> D2, D3, D4Rs agonist (5-HT1A and 5-HT2A/CR agonist; HT2BR antagonist) 	<ul style="list-style-type: none"> Limited improvement in the abnormal involuntary movements 	[113,114]
Levodopa			
L-Dopa	<ul style="list-style-type: none"> Precursor to DA 	<ul style="list-style-type: none"> Development of choreic movements in subjects at risk for HD Reduction in chorea in some HD patients 	[15,115–117]
DA stabilizer			
Pridopidine	<ul style="list-style-type: none"> DA D2R antagonist Preferentially binds to 'activated' D2 receptors Displays rapid receptor-dissociation kinetics 	<ul style="list-style-type: none"> Improvements in motor function 	[124,125,136]

DA: Dopamine; HD: Huntington's disease; UHDRS: Unified Huntington's Disease Rating Scale.

investigated and used in this disorder (summarized in TABLE 1 & FIGURE 4).

VMAT-type inhibitors

Tetrabenazine (TBZ, Nitoman in Canada; Xenazine in Australasia and Europe) is the only licensed compound for the treatment of chorea in HD patients. It functions by reversibly inhibiting VMAT2, thereby increasing the degradation of monoamines before they can be stored in vesicles and then released into the synapse [78,79]. Pharmacological studies in rats have demonstrated that TBZ depletes DA levels by 40%, serotonin by 44% and norepinephrine by 41%, similar to what was found in post-mortem tissue of HD patients treated with TBZ [80,81]. TBZ has also been shown to specifically inhibit the CNS-expressed VMAT2, but not the peripheral endocrine-

specific VMAT1 [82], thereby limiting the adverse side effects associated with less specific VMAT inhibitors (e.g., hypotension and gastrointestinal problems). In addition, the highest binding density of TBZ is in CNS regions most affected in HD (such as the caudate nucleus, putamen and nucleus accumbens) [83].

The clinical effect of TBZ was first examined 20 years ago in several open-label studies and proved to have beneficial long-term effects on hyperkinetic movement disorders including the chorea of HD [84,85]. More recently, TBZ was the subject of a double-blind placebo-controlled trial, TETRA-HD, run by the Huntington study group. This study of 84 patients reported a significant improvement in choreic movements compared with placebo, although not surprisingly several adverse effects were also reported for the group in receipt of the active agent, in particular, there was some exacerbation of depression

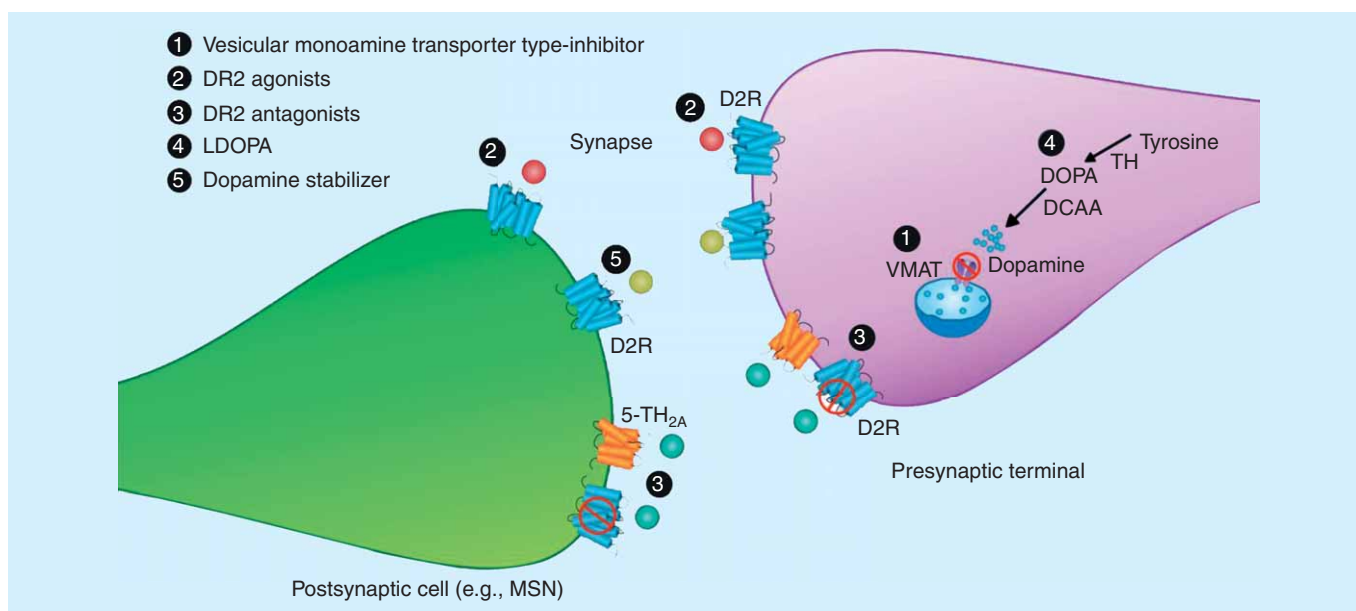


Figure 4. Schematic representation of the dopaminergic therapeutic strategies for Huntington's disease.

D2R: Dopamine 2 receptor; DCAA: Aromatic acid decarboxylase; DOPA: 3,4-Dihydroxyphenylalanine; MSN: Medium spiny neurons; TH: Tyrosine hydroxylase; VMAT: Vesicular monoamine transporter.

and a slight worsening of cognitive abilities [86]. This coupled with a large number of smaller open-label studies [87–93] has shown that with TBZ, there is an improvement in the UHDRS score of treated HD patients and that discontinuation of the therapy leads to re-emergence of the chorea.

While the agent has been trialed for the treatment of chorea, it is often the non-motor symptoms of HD that are known to place a greater burden on the patient's quality of life. Therefore, in light of the side-effect profile of this drug, the benefits of treatment with TBZ and the resulting positive effects on the motor features of HD need to be balanced against its adverse effects on mood and cognition [94].

DA receptor antagonists

Haloperidol is a high-affinity, long-lasting D2R antagonist which has been widely used as a conventional antipsychotic drug and was initially employed as a frontline agent for HD-associated chorea following a favorable blinded study [95]. Furthermore, haloperidol was also shown in *in vitro* and *in vivo* studies to have a protective effect on the pathogenesis induced by mHTT possibly through modulating aspects of the glutamnergic activation [96]. In one study, for example, this D2 receptor antagonist was tested in rats injected with a lentivirus expressing the mHTT to the striatum. Chronic treatment with haloperidol, starting before the development of striatal dysfunction, was found to delay the number of HTT aggregates as well as striatal cell loss when compared with vehicle treatment. While other dopaminergic treatments seem to have predominantly symptomatic effects, this study was the first to show that D2R blockade may actually have disease-modifying effects when given before the onset of neuronal degeneration.

Furthermore, an *in vitro* study also showed that stimulation of D2R, but not D1R, by exogenous DA accelerated the formation of HTT aggregates and increased striatal cell death [97]. Exactly how this comes about at the cellular level remains unclear and requires further investigation.

More recently, other D2R antagonists have been shown to be efficacious in HD and this includes fluphenazine, pimozide and sulpiride [98,99]. So, for example, a small double-blind trial has demonstrated that chronic treatment with sulpiride decreased abnormal movements in HD patients, although no improvement in functional capacity was observed [100].

Other atypical neuroleptics including olanzapine and risperidone have also now been tested in HD patients to treat their chorea. They display a higher affinity for serotonergic receptors, but antagonize both the D2R and additional classes of DA receptors. Olanzapine is currently the most widely prescribed treatment for HD in the UK with approximately 55% of patients taking it to help manage the motor and behavioral features of the disease [101]. It is preferred over other neuroleptics due to its positive effects on weight loss and sleep abnormalities, which are both commonly experienced by patients. In a 6-month, open-label trial of olanzapine, moderate improvements in chorea were reported with significant improvements in measures of depression, anxiety, irritability and obsessive thoughts [102]. These results have been confirmed in follow-up studies [103,104] with similar results seen with risperidone [105,106].

DA receptor antagonists including antipsychotic agents have therefore proved to have some beneficial effects on the chorea of HD patients. However, most studies testing these compounds have been small and open label, which limits the conclusions one can draw from them. Furthermore, many of these

studies have used different outcome measures by which to evaluate the efficacy of the treatment, and then normally only looking at motor effects. To date, there is still a lack of quality evidence supporting the use of these drugs with only a very small number of randomized controlled trials. Nevertheless, this class of agents is widely used for the management of chorea as well as psychiatric disturbances observed in HD [94].

DA receptor agonists

DA agonists activate DA receptors in the absence of the neurotransmitter itself, and have thus been successfully used in conditions of DA loss, such as Parkinson's disease. Given that a characteristic feature of HD is the move from a hyperkinetic to a hypokinetic state and the biphasic change in DA levels during the transition from the early (increased) to the late (significantly decreased) disease stage, treatment with a DA agonist may be useful in advanced HD or juvenile cases, where there is often no chorea but profound bradykinesia.

Aripirazole (AP) is a partial D2R agonist with affinity for the 5-HT1A receptor and an antagonistic effect on 5-HT2A receptors [107]. AP has been tested in HD and, when compared with TBZ, has been shown to have less sedative effects [108]. HD patients treated with AP showed improvements in their motor impairments as evidenced by a decrease in UHDRS scores as well as some reduction in the levels of depression they experienced [108,109].

Other DA agonists, such as bromocriptine and lisuride, have displayed limited therapeutic effects in HD. Bromocriptine is a potent agonist at D2Rs, but does have effects on serotonergic receptors and inhibits the release of glutamate by reversing the glutamate transporter [110]. Despite being of some value in animal models [111], bromocriptine has not been shown to produce any therapeutic action in a double-blind crossover study in HD patients [112,113].

Lisuride has a high affinity for the D2, D3 and D4 receptors and serotonergic 5-HT1A and 5-HT2A/C receptors, while acting as an antagonist on the serotonin 5-HT2B receptor. After initial clinical testing of lisuride suggested the drug had no benefit in HD patients [113], a further study by Frattola *et al.* did report that it may be of some value [114].

L-Dopa

L-Dopa acts as the precursor to DA and has been used for the last half century in Parkinson's disease. In an effort to detect the timing of chorea onset, several studies investigated the effect of DA precursor, L-dopa, in pre-manifest HD patients. Klawans *et al.* found that administration of L-dopa to subjects genetically at risk for this disease led to the development of chorea in some cases [15]. The chorea disappeared on discontinuation of the L-dopa, and none of control subjects manifested such a movement disorder. There have also been reports of HD patients showing improvements in their chorea and gait following chronic treatment with L-dopa [115–117], and this also extends to the more juvenile or rigid forms of HD [118,119].

Dopaminergic stabilizers

Dopidines are a new class of pharmaceutical agents that act by enhancing or counteracting dopaminergic effects in the brain in accordance with the initial level of dopaminergic activity [120], also known as dopaminergic 'stabilizers'. Dopidines can inhibit an overactive DA system or stimulate the system if it is operating at a low level of activity. One such compound, pridopidine, has been trialed in HD patients as it was found pre-clinically to bind preferentially to striatal D2Rs in the 'active' state, and display rapid receptor-dissociation kinetics [120]. These properties enable pridopidine to regulate dopaminergic activity through state-dependent antagonism at the D2R. This pharmacological peculiarity allows for the stabilization of dysregulated psychomotor function through reversing behavioral states which are caused by either hypo- or hyper-dopaminergic transmission [120,121]. Indeed, rodent studies have shown that DA stabilizers can increase locomotor activity in animals with low dopaminergic activity and increase behavior when dopaminergic transmission is high (e.g., following amphetamine), hence the name 'stabilizer' [122]. Clinical trials have showed that pridopidine (≤ 90 mg/day) is both safe and well tolerated in HD patients for up to 1 year [102]. Chronic pridopidine treatment was then tested for its efficacy in two large randomized, double-blind, placebo-controlled trials in HD – the MermaiHD and HART studies. Both studies have shown improvement in the UHDRS total motor score with no side effects. However, the drug did not alter the functional score of the patient, demonstrating that the treatment did not produce a noticeable effect on the patient's activities of daily living [123–125]. Further studies are ongoing to investigate the effect of higher doses to see the extent and degree of benefit that such a therapy can truly offer to patients.

Indeed, it is still unclear why the modulation of D2R with pridopidine does not have the same effect on chorea scores as does treatment with D2R antagonists but may be due to its affinity to other receptors such as σ -1 receptor [126].

Expert commentary

HD has been treated for many years with drugs that target the dopaminergic networks, most notably those that block its effects. While this has now been borne out by a number of trials, the extent to which these drugs work is variable and the exact mechanism is unknown. Pre-clinical and clinical studies have all shown that there is an earlier loss of striatal DA receptors, and thus it seems paradoxical that DA blocking drugs actually works as one would predict that they would make the condition worse. One could argue that this early downregulation of receptors is in fact a response to a relative hyperdopaminergic state with increased DA release and turnover which would also then help explain how the DA blocking agents could work. Alternatively, one could argue that the converse is true, the loss of receptors or their sensitivity may lead to a compensatory increase in DA release and turnover. However, the pre-clinical data in support of this are inconclusive and further work is needed to better understand these early changes in

the dopaminergic pathways in HD as this will enable one to more clearly explain how drugs that either reduce DA release or block DA receptors work so well for the chorea of HD. In addition, it would be useful to look at the effects of these agents on the non-motor aspects of the condition, as there is some suspicion from the published literature that they may worsen this aspect of HD, an area that tends to have more of an impact on quality of life than chorea. In support of this is the emerging literature on the complex effects of DA on cognitive function in the related basal ganglia disorder – Parkinson's disease [127,128]. In this disorder, it is now clear that too much or too little DA can adversely affect cognition, especially executive function, and that this varies as a function of the genetic background of the patients, the drugs they are on and the disease stage. The same may also apply to HD and thus more detailed studies looking at all these aspects of the condition are needed, especially given the extra complication of the psychiatric features and its complex interaction with drug therapies.

In addition, there are some emerging data on the possible disease-modifying effects of DA in models of HD, which suggests that targeting this network may have actions beyond any related to its symptomatic effects on movement control. This relates to the actions of dopaminergic receptors modulating the effects of glutamatergic inputs on some neuronal populations (e.g., MSNs) as well as on other more fundamental aspects of the cell such as autophagy [129]. Indeed, the role that DA plays in other intracellular functions remains unexplored such as any effects it has on mitophagy, free radical production and so on and a better understanding of this may enable the drugs to be used in a different way to that which is currently being done. In particular, it will allow us to explore whether such drugs truly can modulate pathogenic pathways and by doing so have disease-modifying effects. As such, better defining where and how these drugs work *in vitro* and *in vivo*, in better animal models of disease will be vital.

In the coming years, it is likely that the role of DA in the various manifestations of HD will become better understood in patients, as we identify genetic modifiers and develop improved tests and ligands for looking at the functional integrity of the dopaminergic network in patients in life. As such, the role of DA in HD may gain greater prominence and relevance to both basic scientists and clinicians alike, and have an array of actions and benefits that extend beyond that for which it is best known, namely controlling the chorea.

Five-year view

The search for a cure with HD is currently entering a new stage of clinical development as trials using siRNA or antisense oligonucleotides (used for gene silencing) against the mutant protein are about to start. These approaches have the potential to get to the very core of the problem in HD, but until such times as these therapies have proven efficacy and safety, the search for better symptomatic treatments will continue. In this respect, agents targeting the dopaminergic networks will be a high priority given their proven effects in treating many aspects of HD,

most notably the chorea. Indeed, the use of atypical neuroleptics, such as olanzapine, has gained great prominence in the management of this condition by virtue of its ability to not only reduce chorea, but also through their actions on sleep, mood stabilization and weight gain, all problems common in HD.

While such agents are now widely used in routine clinical practice, they are not always well tolerated and in some cases do not work, and are currently only seen as being symptomatic in their effects and then largely in the motor domain. Thus, there is an urgent need to know what effects they have on other aspects of the disease as well as on quality of life and functional independence. As the tests used to assess patients with HD improve, so hopefully will the data addressing this issue. Furthermore, there will be a need to better understand the nature of the dopaminergic abnormalities in HD as a function of brain region (e.g., striatal vs extrastriatal) and disease (early vs late) stage. This will allow one to use drugs that act on the dopaminergic system in a more judicious way as well as enabling drugs that have stabilizing actions at the DA synapse to be used with greater confidence.

Of late, there is emerging evidence that these agents may also work to slow down the disease process itself; consequently, a better understanding of how dopaminergic manipulation relates to the cellular pathology of HD is likely to be an area of fruitful research. This sits well with a move toward large-scale drug screening pre-clinically with agents that already have an FDA/EMA license for clinical use, thus leading to the idea of rebranding or repurposing of agents for HD that are already in clinical use for other indications. Thus, it is imagined in the coming years that many drugs with a license, which work on the dopaminergic system, will be trialed in HD as being possibly disease modifying, although exactly how one measures such an effect remains a moot issue [130].

Therefore, there is no doubt that over the next 5 years we will learn more about the dopaminergic networks in HD both in pre-manifest and manifest patients as more focused studies using imaging and post-mortem approaches are undertaken. These studies will need to be complemented by animal and *in vitro* studies given the complexities of studying patients and the issues of confounding drug therapies on any findings especially with regard to the dopaminergic systems of the brain. While this area of HD neurochemistry is being better defined, the use of DA blocking agents will continue in the routine management of patients. However, it is hoped that more effort will be put into discovering how such agents change all aspects of HD not just the motor abnormalities and even whether they are disease modifying. This will require a new round of trials with more intensively studied patients over longer periods of time, and may even extend to newer agents working on the dopaminergic synapse. As such, it is likely that this field will remain an area of intense research and therapeutic potential for the foreseeable future.

¹In this review, papers were selected on PubMed using the following keywords: 'Huntington's disease' or 'HD' and 'Dopamine', 'Dopaminergic', 'Dopaminergic treatments'. Only papers in English were selected.

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Key issues

- Alterations in the dopaminergic system have been reported in Huntington's disease (HD) and associated with both motor and cognitive features of the condition.
- There are many techniques to measure dopamine (DA) levels and turnover along with DA receptor expression in animal models of HD. However, in humans, techniques are limited to PET scanning and more sophisticated and dynamic techniques are needed.
- DA receptors are reduced both in patients and animal models of HD and this has been found early in the disease course (often ahead of overt manifest disease) and correlated in some studies with some aspects of executive dysfunction. However, exactly how DA abnormalities map on to the cognitive problems of HD is unclear.
- DA levels seem to follow a biphasic pattern with increased levels in the early stages and decreased concentrations in the later stages of the disease progression.
- Treatments targeting the dopaminergic system have been tested in animals models and patients with HD and found to have effects primarily on chorea and other motor symptoms, although this largely is a result of seeing HD as being a movement disorder rather than a complex neuropsychiatric condition.
- A new type of drug stabilizing the dopaminergic synapse is now being trialed with some success.
- Treatments depleting or blocking DA receptors may also have disease-modifying effects, although this is currently unproven.
- The future development of more selective DA receptor drugs may not only help better treat HD, but may also have disease-modifying effects.

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