A Comprehensive Review on Neuropsychiatric Manifestations and Molecular Pathogenesis of Huntington's Disease

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Abstract
Huntington's Disease is an autosomal dominant hereditary neurodegenerative disease with a toxic gain of function caused by a single gene mutation and the functional loss of wild-type huntingtin (wtHTT). HD is usually characterized by progressive dyskinesia, cognitive impairment, and neuropsychological problems. Herein, we review the systemic manifestation of HD in peripheral tissues, and the impact of systemic signaling on HD pathogenesis. Selective neuronal loss in the striatum and brain, which results in progressive motor dysfunction, cognitive deterioration, and behavioural abnormalities, is the pathological hallmark of HD. We assess this evidence and discuss how the intracellular pathogenic threshold in manifest disease might be better determined. Knowing the cellular pathogenic threshold would be informative for both understanding the mechanism in HD and deploying treatments. As yet there are still no disease-modifying treatments available, but an intensive international research effort is underway with many clinical trials currently ongoing. In this chapter, we will first cover the etiology and pathogenesis of HD and then discuss the clinical aspects of the disease and the latest developments in HD therapeutics research. Our Review covers the pathogenesis of Huntington's disease's-relevant therapeutic targets and the translation of this work to clinical trials. We highlight relevant areas of progress and principles, questions, and challenges ahead in trying to develop and test such treatments in patients, particularly before functional impairment happens when neuronal dysfunction and other neurobiological abnormalities are most likely to be still reversible.

Keywords: Huntington's disease, Neuropsychiatric manifestations, CAG, Molecular pathogenesis, Autophagy.

1. Introduction:

Huntington's disease is an inherited neurodegenerative condition that is autosomal dominant and characterized by severe motor dysfunction, mental problems, and cognitive impairment [1]. The two most noticeable neurological characteristics are chorea and dystonia. Nearly all HD patients have cognitive deficits and mental problems. The strain on caregivers is increased while these clinical manifestations are frequently more difficult to manage than mobility disorders. Numerous harmful behaviors are treatable, and they can improve the quality of life for both patients and their caregivers [2–3].

A progressive neurodegenerative ailment, Huntington's disease (HD) often manifests as a triad of motor, cognitive, and mental symptoms around midlife. In 1872, Dr. George Huntington made the first mention of both motor dysfunction and the neuropsychological aspects of sexual inhibition and self-awareness [4]. The frequency of HD, a monogenic condition, is around 1 in 7,500 people in the overall population [5].

The caudate putamen's medium spiny neurons are the main target of neurodegeneration, which deteriorate in a dorsomedial to ventrolateral axis, while the interneurons in the area are generally unaffected [5]. On the other hand, patients with late-onset HD may not have any symptoms until the seventh or eighth decade of their lives. The condition lasts around 15-20 years from diagnosis to death due to the disease's gradual progression. It's vital to understand how diseases sneakily evolve. Years before the typical physical symptoms and warning signs are well enough to manifest to support a clinical diagnosis of HD, structural and physiological brain changes as well as mild cognitive, psychological, and motor changes may start. [6-10].

Since HD affects people all over the world, it is challenging to estimate the exact prevalence and frequency of the condition. Geographic clustering occurs for any highly hereditary illness, therefore epidemiological studies that only sample a small region may underestimate or overestimate the total frequency.

Venezuela has one of the biggest prevalences of HD, with 700/100,000 persons residing in towns close to Lake Maracaibo. Genetic linkage investigations in this community were what uncovered the HD-causing genetic mutation [11–12]. Regardless of the fact that the HD gene was discovered more than 20 years ago, only symptomatic treatments are now available for HD and there is no effective disease-modifying medication. Given that HD is a monogenic condition with a well-characterized gene, there is a tremendous chance to find disease-modifying treatments. [13].

1.1 Aetiology of Huntington’s disease:

The aberrant production of the Huntingtin protein (HTT), which is particularly prone to misfold and accumulate and causes axonal and synaptic dysfunction, results in neuronal death in HD. This build-up of the mutant Huntingtin protein that is misfolded (mHTT) may interfere with the protein's ability to move inside cells or prevent the proteasome from degrading it, both of which might result in autophagy [14].

1.2 CAG instability and repeat size: The huntingtin coding gene (IT15) on chromosome 4 contains an enlarged Cytosine-Adenine-Guanine (CAG) repeat (36), which

leads to the development of mutant huntingtin protein (mHTT), which has an aberrant amount of glutamine repeats (polyQ) in its N terminus. HD is autosomal dominantly inherited. [15].

The gene responsible for the huntingtin protein has an enlarged trinucleotide CAG repeat, which results in HD (Htt). Longer repetitions can hasten the start of the disease, whereas the existence of more than 40 CAG repeats results in the mutant huntingtin protein (mHTT), which leads to the disease within a normal lifespan [16]. HD often develops in midlife and progresses over the next 15 to 20 years. However, early in the course of the illness [17], non-motor elements of the condition frequently manifest. The dysfunction in the striatum, which serves as the neurobiological substrate for such disease's motor symptoms, cannot simply account for the emergence of these traits. Universally expressed and essential for embryonic development is the normal HTT. The exact method by which mHTT causes neuronal cell toxicity has not been determined, however, it may include a number of mechanisms including excitotoxicity, aberrant protein aggregation, transcriptional dysregulation, protein-protein interaction issues, and mitochondrial malfunction. [18-19].

1.3 Age of the Person Having HD:

The majority of investigations revealed there was no connection between the parent's age and the level of illness transferred to the child. [20-21].

1.4 Gender of the Affected Person:

It has been shown that when a male is afflicted, the likelihood of expansion happening is higher, but some studies have found no difference between paternal and maternal transmission. Maternal transmission averages between 0.36 and 0.4 units, whereas paternal transmission averages between 1 and 9 units. [22-24].

1.5 Other Factors Associated with HD:

Patients who use cigarettes and alcohol were shown to be more likely to experience HD progression, according to a small number of studies. [25-26].

2. HTT Gene and Huntingtin:

The huntingtin (HTT) gene, which is positioned at the 4p16.3 locus on the short arm of chromosome 4, is the cause of HD [27]. On 75 disease-carrying families, the Huntington's Disease Collaborative Research Group utilized haplotype assessment of linkage disequilibrium [27]. The 5′ coding regions of the new gene IT15 were discovered to possess an unstable trinucleotide (CAG) repeat. The HTT protein translated this repetition into an extended polyglutamine (polyQ) tract. The body's cells universally express huntingtin, with brain levels being greater than those found in peripheral tissues [27-28].

It has been demonstrated using in situ hybridization that HTT mRNA is expressed throughout the rat brain, with levels of expression being higher in areas with greater densities of neurons, like the cerebellum and also the dentate gyrus of the hippocampus [29]. Additionally, this study discovered that neurons expressed more than glial cells did. These results were verified in human post-mortem tissue. [28-29].

In addition to neural and non-neural murine tissue, Trottier et al. discovered HTT expressed in lymphoblast and fibroblast cell lines after the creation of monoclonal antibodies specific for human huntingtin (350 Kda) [30]. With modest amounts in the heart, liver, and lungs, the result is displayed the greatest HTT expression in the peripheral. HTT was present in the kidney, spleen, and gut at low but measurable levels. The cerebral cortex and cerebellum have the greatest levels of HTT.

Human post-mortem tissue stained strongly with HTT puncta throughout the brain using immune histochemistry. The substantia nigra pars compacta, layers IV and VI of the cortex, as well as the Purkinje cells of a cerebellum all displayed the greatest staining levels. Sparse staining in the striatum, pallidum, and fiber tracts suggests that the distribution of HD neuropathology is not associated with the distribution of HTT protein. HTT is mostly found in the cytoplasm of the cell, where it is mainly found in the perikarya, axons, dendrites, and axon terminals. Only around 5% of HTT is ever found in the nucleus. [31].

3. Neuropsychic manifestation:

HD is a neurodegenerative condition that causes gradual brain atrophy. The caudate nucleus & putamen are included in the neostriatum, which is the primary and first site of disease. The striatum is thought to be particularly susceptible to the harmful effect of the mutant huntingtin protein, which results from the CAG repeat mutation. Over the course of the illness, more generalized brain atrophy is observed, suggesting a loss of anatomical and functional connections between the striatum and other regions of the brain. The basal ganglia's function in cognition may be understood using the model that HD has supplied.

Along with bradykinesia, which is the slowing down of movement, and dystonia, which causes the limbs to twist slowly, HD patients also have stiff limbs similar to those with Parkinson's disease. These many motor characteristics may co-occur, but with varying predominance in various people. Notably, significant bradykinesia is more frequently linked to juvenile HD than chorea. [32]

3.1 Neuropsychological Features:

The areas of memory, emotion processing, executive functioning, and social cognition are where HD shows the most significant improvements.

3.2 Psychomotor Slowing:

Psychomotor slowness is the first alteration and the greatest indicator of illness progression. The most frequent instances of slowing are during timed activities like Stroop, Digit symbol replacement, and Trail creation. In the "pre-manifest" [33] phases of HD, cognitive slowness has been proven to be a major predictor of daily functioning ability. Contrary to popular belief, the easier psychomotor task of word reading on the Stroop test serves as a more sensitive indicator of change rather than the more difficult Interference component. In daily life, psychomotor slowness has a significant practical influence. For instance, it has been discovered to be a strong predictor of quitting driving**.** [34].

3.3 Executive Skills:

Executive impairments in HD include issues with sequencing, planning, and organizing as well as set-shifting and cognitive flexibility. Although its use has decreased recently, the Wisconsin Card Sorting test was often utilized in early research to measure cognitive flexibility [35]. Verbal fluency tests frequently reveal decreased performance in HD patients. Low scores are likely caused by cognitive slowness as well as executive issues in strategic search. Multitasking is a frequent practical challenge seen in HD. Neuropsychological research supports the existence of attentional issues. However, it is important to note that dual-task difficulties in HD extend to activities that in healthy people would be regarded as very low attention-demanding, like bimanual motor tapping and moving while doing a cognitive task. These findings suggest that individuals with HD need to pay closer attention to actions that are purportedly "automatic." [36].

3.4 Memory

Memory issues are frequently reported in HD, and both the affected individual and their loved ones may become aware of them. Studies on memory have revealed that free recall is proportionately worse than the recognition memory and ability to connect, that HD has much more passive study methods than controls, that source memory, and prospective memory are problematic, and that retention is only somewhat preserved from instant to delayed recall. According to the profile of memory disturbances, executive function plays a significant role in memory failures, which is consistent with the disruption of striatal-frontal connections. [37]. Along with issues with declarative memory, or the conscious retention of previously presented information, patients with HD also struggle with memory consolidation (i.e., skill and habit learning). Tasks requiring motor skills, serial response time, and sequential learning have all been shown to be challenging. The findings of difficulty in the concurrent execution of very low-level, "automatic" activities are consistent with procedural memory issues. Understanding the function of the basal ganglia in the recall has mostly been based on research on HD. [38].

3.5 Other Cognitive Domains:

The mentioned domains are the most significant when it comes to describing the neuropsychological profile in HD. Apraxia, agnosia, and frank aphasia are not present in HD patients [38]. However, the motor dysfunction makes speech production gradually less understandable, they may struggle with sophisticated syntax, and deficits in language tasks may develop as a result of other cognitive issues. People with HD struggle with complex constructional, perceptual integration, and high-level perceptual discrimination tasks in the visuospatial domain. When doing activities that require mental rotation or information processing, as well as timed visual search, patients with HD exhibit spatial difficulties. Prior to the start of clinical symptoms, there has been evidence of slowed visual search and poor mental rotation. Practically speaking, psychomotor slowness is a significant predictor of quitting driving, although perceptual and spatial issues in HD have not been specifically established as indicators of difficulty in tasks like driving. Executive function issues and cognitive impairment have a negative impact on daily activities, independence, and the quality of life for persons with HD, and caregivers have regarding these issues as having the largest impact [39].

4. Molecular pathogenesis of Huntington's disease (HD):

4.1 Principles of Pathogenesis:

The repeating units at about 50 consecutive glutamines (polyQ) of Htt are the major cause of Huntington's disease [40]. The pathophysiology of this illness can have a number of important characteristics. The first potential cause is a Htt mutation, which has the propensity to impair the production of appropriate conformations and -sheet structures. However, this is not the primary cause of the disease's start. There are several more causes, such as the fact that tissues and cells of people with Huntington's disease have malfunctioning mechanisms for handling aberrant proteins. Also, toxic N-terminal fragments can result from the Htt gene being truncated. Through altering the structure of proteins, the Htt gene's post-translational alteration can also cause toxicity [41]. The gain of functionality concept of the Htt gene has impacted most efforts to explain the pathophysiology of this illness. Determining the pathways by which the polyQ tract promotes neurodegeneration has also been investigated [42]. The post-translational N-terminal proteolysis of the protein's huntingtin by the caspases, endoproteases, and calpains is what causes this polyglutamine aggregation. The shortened N terminal protein's mutant polyglutamine tract is accessible to the neighbouring substrates and is therefore extremely aggressive. [43].

Normal alleles have between 27 and 35 CAG repeats, whereas intermediate alleles have less than 27 repeats. Less penetrance HD will develop in CAG repeats 36–39. HD will fully penetrate in those who have 40 or even more CAG repeats. Additionally, it has been found that the sooner the disease manifests and the more severe it is, the higher the CAG expansion [44-45].

Table 1: CAG repeats used in genetic testing

	CAG repeats
Normal chromosomes Individuals with these alleles will not develop HD.	⩽ 26 CAG repeats (less than or equal to 26 CAG repeats)
Intermediate alleles These are associated with a normal phenotype, but unstable alleles are prone to changes during reproduction and new mutations for HD can arise from intermediate alleles, particularly with paternal transmission.	27 to 35
Zone of reduced penetrance / increased risk range The majority of people will manifest HD within their expected lifetime, but potentially with slower disease progression, less severity and at a later age. Some individuals with these CAG numbers might not develop HD. There is a risk that offspring will develop HD.	36 to 39
HD All individuals with these HD alleles will eventually develop symptoms of HD, should they live long enough.	⩾ 40 CAG repeats (greater than or equal to 40 CAG repeats)

Juvenile HD A variant that typically manifests in teenage years and is associated with paternal inheritance. Behavioural symptoms and learning difficulties are often the first signs. Motor symptoms may resemble parkinsonism, and epileptic fits often occur.	>60

4.2 Molecular pathogenesis:

Numerous pathways are involved in the malfunction and death of neurons caused by mutant huntingtin. These include the exon 1 mHTT fragment's direct impacts, the protein's propensity to aggregate abnormally, and its impact on cells' proteostasis, axonal transport, transcription, translation, mitochondrial dysfunction, and synaptic function [46–47].

The striatum's median spiny neurons (MSNs) are especially susceptible to mHTT's actions. Striatal pathology progresses in two phases, with the first phase marked by the loss of MSNs in the indirect pathway, which causes a hyperkinetic phenotype, and the second phase marked by the loss of MSNs in the direct pathway, which causes a hypokinetic phenotype. [48].

Dopamine D2 receptors, which are expressed by indirect but not direct MSNs and are linked to HD pathophysiology [49], may play a role in the selective susceptibility of indirect route MSNs. The depletion of brain-derived neurotrophic factor, glutamate excitotoxicity from cortico-striatal projections, and toxic effects of repeat-associated non-ATG translation proteins are some further theories. [50].

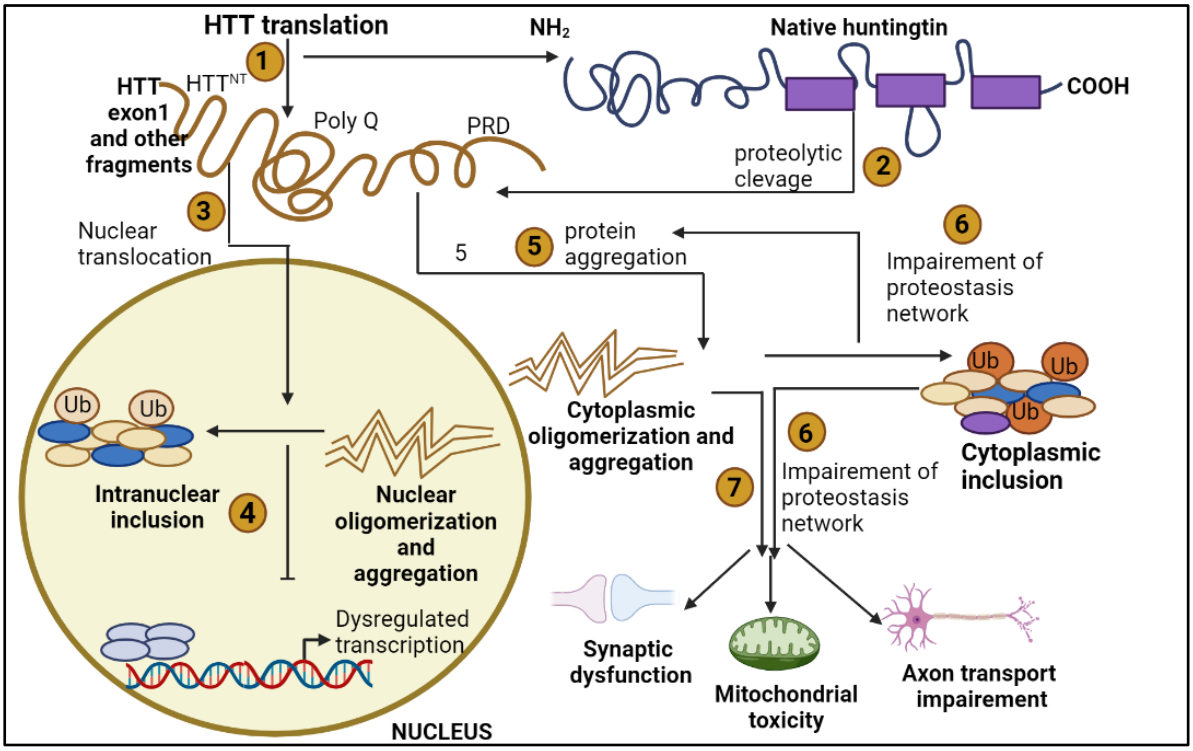

Figure 1: Pathogenetic cellular mechanisms in Huntington's disease

(1) The amino-terminal HTT exon 1 fragment and the full-length huntingtin protein are both produced during the translation of HTT (the result of aberrant splicing). In these proteins, the degree of somatic instability determines how long the polyglutamine (polyQ) tract is. (2)

Proteolytic cleavage of full-length native huntingtin results in the production of extra protein fragments. The nucleus is invaded by protein fragments. (4) Fragments are kept in the nucleus by self-association, oligomerization, and aggregation, which results in the development of inclusions. This process results in transcriptional dysregulation by sequestering other proteins and by additional as-yet-undescribed processes. (5) In the cytoplasm, huntingtin fragments oligomerize and collect. (6) The disease-related dysfunction of the proteostasis system, which also results in general cellular dysfunction, exacerbates the aggregation of huntingtin. (7) Additional general cellular defects brought on by the abnormal forms of huntingtin include synaptic dysfunction, mitochondrial toxicity, and a reduced rate of axonal transport. Proline-rich domain; ubiquitin; and PRD reproduced from with thanks to [49-50].

5. Mechanisms of cell death and therapeutics targets:

5.1 Mutant Huntingtin aggregation:

Although the HD gene was identified about 15 years ago [15], more research is still needed to fully understand how mHtt interacts with the several biochemical pathways that seem to be involved in neuronal death in HD. It has been suggested that transglutaminase activity mediates mHtt aggregation [51]. There is a tonne of data that transglutaminase is expressed in HD [52–54] and that transglutaminase plays a role in HD etiology. Interestingly, the ubiquitin-proteosome system degrades proteins with polyglutamine expansions, like mHtt, in a specific environment (UPS) [55]. The mutant protein may contain polyglutamine regions that the proteasome might not be able to break, according to recent research [55]. There is ongoing discussion regarding whether inclusions constituted by the accumulated N-terminal truncation of mHtt lead to neuronal cell death through modifications to nuclear transport or Genetic material arrangements affecting transcription, similar to other degenerative diseases wherein the protein aggregates are a defining characteristic of the disease. Aggregation may play a protective function, according to recent studies. [56]. Enhanced survival of neurons that included mHtt aggregates has been demonstrated [57] using an automated microscopy approach to measure the time period in which neurons expressing mHtt perish. It is obvious that other pathogenic pathways are active in HD concurrently with mHtt aggregation, regardless of whether this process is protective or harmful.

5.2 Oxidative stress and mitochondrial dysfunction

There is strong evidence that HD has elevated oxidative stress and mitochondrial dysfunction [58]. Prior to tissue loss, both humans and transgenic rodent HD brain exhibited a general decrease in striatal glucose consumption [59–60] as well as a decrease in the activity of numerous mitochondrial complexes [61-62]. The rise in lactate levels is associated with the Repeats size in the brain and striatum [63]. Human and transgenic rodent HD brain and serum also exhibit higher levels of oxidative stress biomarkers, such as DNA oxidative alterations and strand breaks [64-66] as well as deletions in mitochondrial DNA. [67]. Recent data imply that mHtt directly engages mitochondria in HD [68]. Because of this interaction, the calcium buffering function of the mitochondria is altered, which results in mitochondrial malfunction. Additionally, mHtt is said to suppress PGC-1, a peroxisome proliferator-activated receptor co-activator [69]. PGC-1 plays a key role in the mitochondrial regulation of ATP and is a

transcriptional co-activator that controls a variety of genes and metabolic processes that defend against reactive oxygen species [70]. In HD mice, decreased PGC-1 levels cause striatal neurodegeneration, aberrant motor behaviour, and an increase in oxidative stress sensitivity. Importantly, the degenerative phenotype of R6/2 animals was markedly alleviated by the introduction of lentiviral-mediated PGC-1 expression into the striatum.

5.3 Transcriptional dysregulation

The modification of gene transcription is a significant component of HD disease pathogenesis [71]. Numerous pieces of evidence point to a direct connection in between mHtt protein and transcriptional, even though the precise molecular cause of transcriptional dysregulation is unclear [72-73]. It is believed that mHtt alters gene expression as shown in both murine and human HD by the sequestration of transcriptional regulators into mHtt aggregates [74-76]. It's significant that transcriptional changes linked to mHtt arise before symptoms, indicating that this dysregulation isn't an epiphenomenon. As a result, there is now substantial evidence that histone hypoacetylation and hypermethylation in HD are connected to transcriptional dysregulation [77–78]. Substantial hypoacetylation of histone H4 has been shown experimentally in murine models [79–81], whereas HD patients and HD mice show hypermethylation of histone H3[81-82].

5.4 Apoptosis

It is likely that mHtt-induced pro-apoptotic signaling cascades contribute to striatal neurodegeneration. Apoptotic-induced cell death is caused by signaling cascades that simultaneously activate genes that cause cell suicide and numerous proteases that break down proteins necessary for neuronal survival [74]. The cysteine proteases called as caspases are the main participants in the apoptotic cascade. At least three effector caspases and four initiator caspases, including caspase-3, -6, and -7, are present. [75]. It has been demonstrated that expanded polyglutamine lengths successively stimulate the initiator caspases [75]. There is mounting evidence that the pathophysiology of neurodegenerative disorders involves apoptosis-mediated cell death. The release of cytochrome C into the cytoplasm by mitochondria, which activates caspase-9 and causes the stimulation of downstream executioner caspases, is one significant step in the apoptotic cascade [76]. Pharmacologic suppression of proteins implicated in different stages of the signaling cascade might be a potentially useful therapeutic approach to treat HD given the apoptotic activity in HD.

5.5 Excitotoxicity

In HD, the striatal neurodegeneration seen is thought to be a result of excessive glutamatergic input. Similarities between striatal damage seen in rat & primate models of HD and kainic, glutamic, as well as quinolinic acid lesions provide evidence for the excitotoxic theory [87–88]. The significance of abnormal glutamate excitotoxicity in HD pathophysiology is further supported by elevations in striatal glutamate throughout the brains of HD patients [89] and changes in presynaptic receptor subtypes in the R6/2 mouse model of HD. Albin, Greenamyer, and Beal proposed the idea of gradual excitotoxicity in HD as an alternate excitotoxic theory, wherein regular levels of glutamate might cause neuronal malfunction and

death in the context of that rising amounts of excitatory amino acid residues are not heightened in HD[91-92].

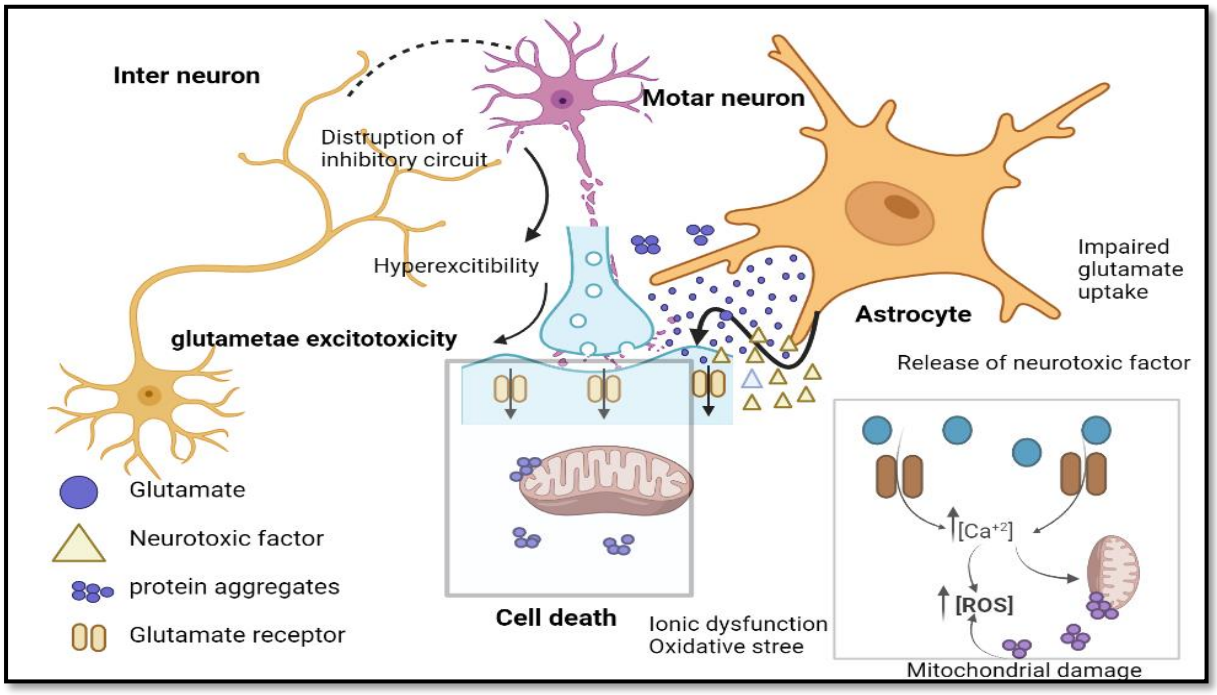

Figure 2: Pathogenic pathway of excitotoxicity

Given the many processes underlying the neuropathology of HD, a therapeutic approach at any one or more readily available locations should be effective in treating HD. Targeting numerous pathogenic processes may provide the greatest ability to treat or stop the course of HD illness, which is important. Although some HD patients have had success, new treatment studies in mouse models of HD provide preclinical proof-of-principle and justification for clinical trials in human HD [92].

Table 2: Pathogenic cascades involved in Huntington's disease.

Pathogenic Mechanism	Action of mHtt	Resulting Abnormalities	References
Excitotoxicity	• Altered transcription of the GluN2B subunit of NMDARs • Impaired interaction with PSD95 • Increased cytosolic Ca2+ concentration	• Abnormal sensitivity and distribution of NMDARs, favoring extra synaptic NMDARs • Activation of calpains and calcineurin, leading to apoptosis	[93-94]

Mitochondrial dysfunction	• Direct interaction with Mfn2 • Increased mitochondrial Drp1 translocation • Reduced complex II, III, and IV activity • Direct interaction with mitochondrial proteins • Sequestration of GAPDH and HAP1into mHtt aggregates • Binding to the IP3R on the ER	• Impaired mitochondrial fusion • increased mitochondrial fission • Altered cellular energy supply • Mitochondrial depolarization, opening of the MPTP, release of pro-apoptotic factors • Impaired mitochondrial trafficking • Ca2+ release from ER stores, increases in cytosolic Ca2+ concentration, loss of dendritic spines	[95-96]
Oxidative stress	• mHtt-induced mitochondrial dysfunction increases ROS production, leading to oxidative damage to proteins, lipids, and DNA	• Mitochondrial calcium overload, opening of the MPT • BER, OGG1 activity triggering further expansion of the CAG repeats in the HTT gene	[97-98]
Transcriptional dysregulation	• Impaired transcription of CREB, PGC-1α • Nuclear translocation of REST	• Impaired synthesis of endogenous antioxidants • Repression of BDNF gene transcription	[99-100]

	• Increased transcriptional activity of p53	• Upregulation of pro-apoptotic factors, such as BAX, PUMA	
Dysfunction of glial cells	• Downregulates the expression of astrocytic Kir4.1 channel • Binds to nMYRF in oligodendrocytes	• Alteration of astrocytic membrane potential and sensitivity to neuro-mediators • Myelination deficits	[101-102]
Neuroinflammation	• Promotes the expression of pro-inflammatory cytokines	• Microglial M1 polarization • activation of the JAK/STAT and MAPK pathways	[103]

6. The ubiquitin-proteasome system, autophagy, and the aggregation of mutant Htt:

The most flexible way for cells to dispose of and recycle waste is through the lysosome-mediated downregulation called as macro-autophagy. Macro-autophagy has the ability to destroy a variety of payloads, including aggregated proteins, organelles, and bulk cytosol, using both selective & non-selective methods.

Htt has recently been linked to research in mice and Drosophila that shows it is important for selective autophagy. First discovered by Zeitlin and colleagues, the deletion of the polyQ stretch even now in typical Htt appeared to elevate the potential for autophagy in neurons [104]. Additionally, they reported that Htt function loss resulted in protein accumulation in the CNS of mice and drosophilas, which was consistent with a different study that showed that Htt or its interactor, HAP1, depletion impaired the retrograde transport of autophagosomes that included non-degraded selective cargo and resulted in accumulation [105].

By facilitating cargo identification and autophagy initiation both in fly and mammalian cells and facilitating the binding among p62 and the autophagy-initiating kinase, ULK1[106], Htt serves as a scaffold for selective autophagy, indicating that a loss of autophagy regulation may contribute to HD pathogenesis [107].Htt's participation in autophagy may not come as a surprise given that it has already been shown that it participates in endocytosis and the trafficking of payloads from mitochondria to other vesicle communities [108], including autophagosomes. But it's still unclear how much the polyQ mutation affects patients' Htt function in this way [109].

It is possible that Htt plays a role in autophagy. However, it is yet unclear how much the polyQ mutation affects patients' Htt functioning in this area. The usual adult onset repeating length is 44, however, the mutation lengths frequently utilized in experimental paradigms greatly

surpass this number, and the effects of these shorter repeating lengths have received minimal research. Furthermore, although rodents & cells with transgenic overexpression of mutants Htt with more than 100 polyQ or homozygous knock-in animals with longer polyQ do not show obvious changes in autophagic activity, and aggregate clearance by autophagy is still possible [110].

Another possible treatment target for HD is mHtt degradation. Organelle & protein turnover seems to be a crucial aspect that supports health and function in normal neurons.

Protein denaturation or misfolding errors may be caused by altered proteolysis. The ubiquitin-proteosomal pathway and also the lysosomal pathway are two separate pathways that mediate proteolysis in neurons. It is necessary to tag proteins for degradation before they may be subjected to UPS-mediated degradation. Generally speaking, transiently expressed proteins are degraded by the UPS [111]. It's crucial to note that proteins intended for proteosomal destruction must first properly unfold in order to pass through the proteosome's small aperture [90]. Additionally, a process known as autophagy uses the lysosomal route to degrade proteins and organelles in large quantities [112]. Through this process, cells' degradative components are encased in double-membrane-bound vesicles known as autophagosomes, which join lysosomes. Hydrolytic lysosomal enzymes break down the contents once they have fused. Autophagy is a process that is governed by protein kinases, notably the well-known mammalian target for rapamycin (mTOR) [113]. The mechanisms governing autophagy are not fully understood. Protein synthesis is associated with phosphorylated mTOR, while the dephosphorylation of mTOR triggers autophagy. Glucose levels have also been connected to mTOR-mediated autophagy, with elevated glucose activating autophagy and increasing mHtt clearance through lower mTOR phosphorylation. However, it should be noted that autophagy may be activated without the involvement of mTOR by the activation of insulin receptor substrate-2 [114]. This significantly lowers mHtt accumulation in vitro and thus is dependent on Beclin1 and hVps34-mediated proper autophagosome formation.

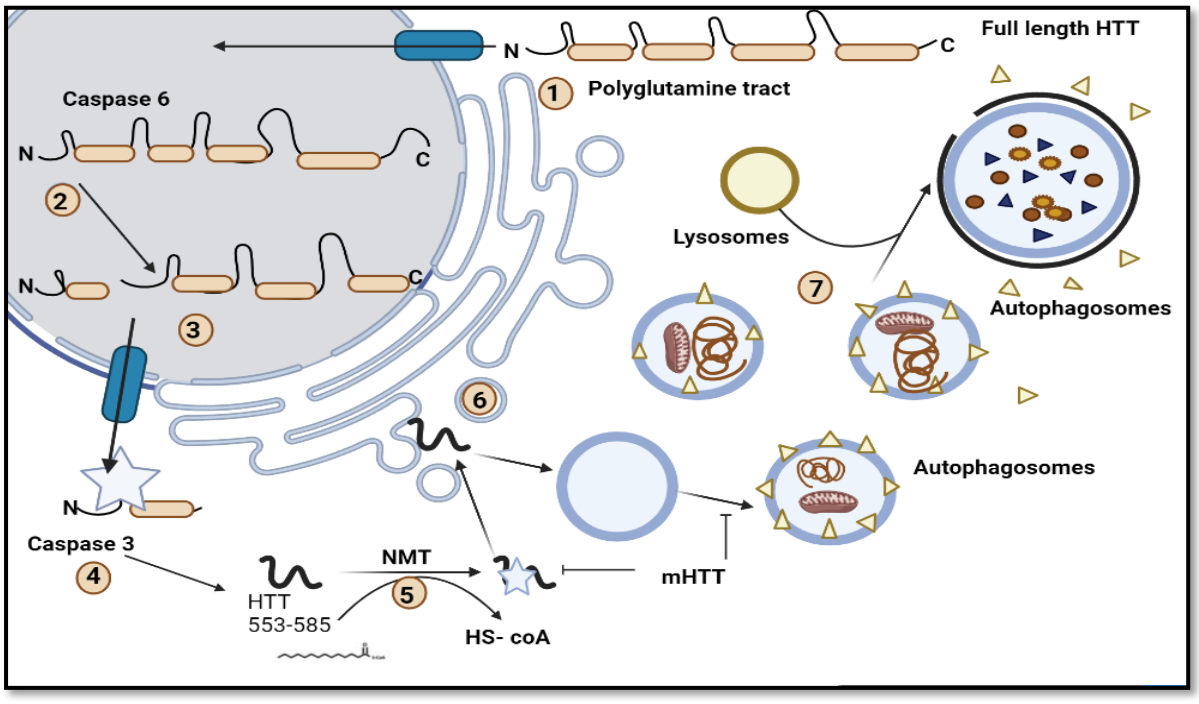

Figure 3: Autophagy in Huntington's diseases

7. Management of Huntington's disease:

7.1 Symptomatic therapies for HD

Through anti-glutamatergic, anti-dopaminergic, and GABAergic pathways, the majority of symptomatic therapy for HD targets motor symptoms such as chorea, dystonia, myoclonus, and tics [115]. The American Academy of Neurology published recommendations in 2012 endorsing the use of the anticholinergic drugs riluzole, amantadine, and tetrabenazine to treat chorea. The only FDA-approved drugs in the United States for the treatment of chorea in HD are TBZ and the recently released deutetrabenazine. The vesicular monoamine transporter 2 (VMAT-2) in the CNS is reversibly inhibited by TBZ. Because VMAT-2 transports serotonin, dopamine, and norepinephrine from the cytoplasm into presynaptic vesicles, its blockage causes these monoamines to break down too soon [116].

7.2 Pharmacological Therapies

The second-generation tetracycline antibiotic minocycline has been shown to have neuroinflammatory action. In various animal models of CNS illnesses, including Parkinson's disease, HD, amyotrophic lateral sclerosis, multiple sclerosis, spinal cord injury, and traumatic brain injury, it has been demonstrated to delay disease onset while being neuroprotective [117]. HD has more recently begun to examine laquinomod, a disease-modifying medication for the management of relapsing-remitting multiple sclerosis. Laquinomod is a tiny molecule that has an excellent safety profile and may be administered orally. It has both immunomodulatory & neuroprotective properties, while its specific mechanism is yet unknown. In YAC128 mice (transgenic animals expressing the human HTT including a 128CAG repeat expansion and hence an improved behaviour), laquinomod has been found to restore striatal and cortical neurodegeneration and to enhance cognitive function. [118]. Laquinomod improved functional outcomes and neuroprotection by reducing NF-kB activation in both the peripheral and central nervous systems and by lowering the quantities of released pro-inflammatory substances. The neurotrophic factor brain-derived neurotrophic factor (BDNF), whose expression and release are decreased in HD, has also been found to be upregulated by laquinomod [119].

7.3 Cell-based therapies:

The basic objective of cell-based therapies is to restore the processes that lead to disease onset and progression. This is done by replacing damaged or dead cells and by taking use of the trophic effects that specific cell types may have after being injected into an injured area. [120-121]. Various cell types, such as foetal cells and tissues, progenitor cells, or primary stem cells derived from various organs of an adult organism, can be used in these therapeutic procedures [122-123] The current situation of HD-specific cell-based therapy is covered in this review. Some of these treatments are still in the early stages of development and require preclinical research on animals to be completed before regulatory organizations would permit their usage in clinical studies (involving humans). However, as will be addressed later, only a small number of investigations have already entered clinical trials [124-125].

For many years, fundamental research has made use of human foetal tissue (hFT). By transplanting hFT into HD patients' damaged central nervous systems (CNS), clinical research using hFT seeks to repair the structure of the brain and neural circuitries. In general, hFT

transplantation into the brains of HD patients is seen to be a safe procedure [126]. However, one research found that two more HD patients required surgical drainage, and three of the seven HD patients who received bilateral stereotactic transplantation experienced subdural hemorrhages [126-127].

Table 3: Recent status of Huntington's disease (HD) drug therapy

Drug/Reagent	Primary Target (Mechanism of Action)	Status and Principal Result	reference
Drugs against excitotoxicity			
Riluzole	Glutamate release inhibitor	Does not show efficacy in human trails	**[128]**
Tetrabenazine (TBZ)	Dopamine pathway (Vesicular monoamine transporter 2 inhibitor)	Approved by food and drug administration (FDA) for the treatment of chorea in HD	**[129]**
Targeting Caspase and huntingtin (HTT) proteolysis			
Minocycline	Caspase-dependent and independent neurodegenerative pathway	Inhibits caspase-1 and -3 mRNA upregulation, and decreases inducible nitric oxide synthetase activity	**[130]**
Targeting HTT aggregation and clearance			
Rapamycin	Aggregation mammalian target of rapamycin(mTOR) inhibitor	Showed efficacy in a rodent model	**[131]**
Targeting mitochondrial dysfunction			
Creatine	Mitochondrial dysfunction	Attained futility in human trial	**[132]**
Eicosapentaenoic acid (EPA)	Mitochondria dysfunction	A mixed scenario of positive and negative trial	**[133]**
Targeting transcriptional dysregulation			
Sodium phenylbutyrate	Transcriptional deregulation histone deacetylase inhibitor	Showed efficacy in a rodent model	**[134]**
Suberoylanilide hydroxamic acid	Transcriptional deregulation histone deacetylase inhibitor	Showed efficacy in a rodent model	**[135]**
Targeting mutant huntingtin (mHTT)			
RNA interference and	Blocks transcription of mHTT	Showed efficacy in a rodent model	**[136]**

antisense oligonucleotide (ASO)			
Other therapeutics			
Ubiquilin	Reduces mHTT aggregation	Showed efficacy in a rodent model	**[137]**
Chaperonins	Decrease mHTT aggregation	Showed efficacy in a rodent model	**[137]**

Conclusion:

Even after the huntingtin gene was identified more than 20 years ago, a treatment for the disease is still difficult to find. Therefore, further study is needed to pinpoint innovative therapeutic targets that might slow or stop the progression of the disease. Promising HD treatment strategies include those methods which are based on anti-inflammatory and immunomodulatory methods. Understanding the particular immune/inflammatory processes that contribute to HD development is crucial. Though, Stem cells may be an alternative to immuno-based pharmacological therapy due to their potential immunomodulatory and/or anti-inflammatory properties. Although the number of people entering clinical trials shows the expanding scientific and medical community's attempts to find a disease-modifying therapy or cure for this debilitating neurological ailment, some guidelines are necessary.

Additionally, elements like the quantity of CAG repeats should be taken into account as they have a significant impact on clinical trial outcomes. The next step is the creation of more sophisticated assessments that are sensitive to HD's longitudinal cognitive alterations and choosing acceptable cognitive outcomes.

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Conflict of Interest

The authors declared that there is no conflict of interest

Source of interest

None

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