Ind. J. Pharm. Edu. Res., 2026; 60(2):494-510.
https://www.ijper.org

Review Article

Animal Models and Pathogenesis on Neurodegenerative Disorders (Huntington's Disease): An Updated Review

Diksha Diwakar[1], Shahbaz Khan[2,*], Shivani lodha[3], Deepika Pal[4], Dinesh Kumar[5], Devesh Kumar[6], Alka Lohani[7]

[1]Sahu Onkar Saran School of Pharmacy, Faculty of Pharmacy, IFTM University, Lodhipur-Rajpoot, Moradabad, Uttar Pradesh, INDIA.
[2]Pharmacy Academy, IFTM University, Lodhipur-Rajput, Moradabad, Uttar Pradesh, INDIA.
[3]Faculty of Pharmacy Veer Madho Singh Bhandari, Uttarkhand Technical University, Dehradun, Uttarakhand, INDIA.
[4]Krishna Pharmacy College, Bijnor, Uttar Pradesh, INDIA.
[5]School of Pharmaceutical Sciences, Faculty of Pharmacy, IFTM University, Lodhipur-Rajpoot, Moradabad, Uttar Pradesh, INDIA.
[6]Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh, INDIA.
[7]Amity Institute of Pharmacy, Amity University, Uttar Pradesh, Noida, INDIA.

ABSTRACT

Background and Objectives: Huntington's Disease (HD) is a rare neurodegenerative disorder marked by abnormal body movements, behavioral and psychiatric issues, and dementia. This inherited genetic disorder leads to cognitive dysfunction and abnormal movements known as chorea. The condition was first accurately described by George Huntington, an Ohio physician, in 1872. HD is a dominantly inherited illness that causes progressive neurodegeneration in the striatum and other brain regions, particularly the cerebral cortex. This fatal condition is caused by an abnormally expanded and unstable cytosine-adenine-guanine repeat in the gene encoding the huntingtin protein. **Materials and Methods:** This review was conducted through a systematic and comprehensive literature search focused on animal models and pathophysiological mechanisms involved in HD. **Results:** Various hypotheses have been proposed to explain the pathogenic pathways of mutant huntingtin-induced neuronal dysfunction and cell death, but none provide a definitive explanation, making it an ongoing area of study. HD encompassing such as molecular genetics, selective neuronal susceptibility, excitotoxicity, mitochondrial dysfunction, apoptosis, and transcriptional dysregulation. Recent studies have highlighted the role of oxidative stress in HD development. Although no specific medication can prevent disease progression, there are drugs available to help reduce chorea symptoms. Animal models are crucial for evaluating potential treatments, with various models available that mimic some or many symptoms of HD. **Conclusion:** The biology of neurodegenerative disorders is better understood because of animal models. These models replicate the histological lesions, primary symptoms, and various facets of a particular disease. Furthermore, genetic or transgenic animal models have received a lot of attention in recent years. As research advances, refining these models will be crucial for developing effective therapeutic strategies that bridge the gap between preclinical findings and clinical outcomes in humans.

Keywords: Huntington's disease, Neurodegenerative disorder, Cognitive disorder, Motor disorder.

Correspondence:
Dr. Shahbaz Khan
Associate Professor, Pharmacy Academy, IFTM University, Lodhipur Rajput, Delhi Road, Moradabad-244102, Uttar Pradesh, INDIA.
Email: shahbazkhanmaju123@gmail.com

Received: 02-09-2025;
Revised: 17-10-2025;
Accepted: 24-12-2025.

INTRODUCTION

Huntington's Disease (HD) is a progressive and fatal neurodegenerative disorder marked by severe motor dysfunction, cognitive decline, and psychiatric disturbances.[1] Caused by a CAG trinucleotide repeat expansion in the Huntingtin (HTT) gene, HD leads to the production of a Mutant Huntingtin Protein (mHTT) that disrupts cellular processes and drives neuronal degeneration, primarily within the striatum and cortex.[2] One of the hallmark motor symptoms of HD is chorea, characterized by involuntary, abrupt and irregular movements that can affect the face, limbs and trunk, often impairing coordination and functional ability (Figure 1). Despite considerable advances in understanding the genetic underpinnings of HD, the precise mechanisms driving neurodegeneration and the absence of effective disease-modifying treatments underscore the complexity of the disorder.

Animal models have played a pivotal role in advancing the understanding of the pathogenesis of HD, serving as invaluable tools for investigating the molecular and cellular mechanisms at play. Various models, including rodent as well as non-mammalian organisms such as *Caenorhabditis elegans* and *Drosophila melanogaster*, have been instrumental in recapitulating key

DOI: 10.5530/ijper.20262132

features of HD.[3,4] These models enable researchers to study the impact of mutant HTT expression on neuronal function, neuroinflammation, cellular toxicity, and disease progression, providing critical insights into the multifaceted nature of the disorder.These models also allow for the identification of conserved cellular and molecular pathways involved in neurodegeneration, providing a foundation for discovering potential therapeutic targets.

Despite the wealth of information gained from animal models, challenges remain in translating findings from these models to human clinical settings. Each model system has its limitations, as they may fail to fully recapitulate the complexity of HD's pathological and clinical manifestations in humans. This review provides an updated examination of animal models used in HD research, focusing on their contributions to our understanding of HD pathogenesis, and highlighting their potential in preclinical drug discovery and therapeutic development.

Incidence Studies

According to estimatation, the annual incidence of HD in western countries ranges between 4.7 to 6.9 new cases per million. However, it is not clear whether this incidence is rising concurrently with prevalence, which may also be increasing relative to premolecular research.[5,6] The prevalence of HD in western population range from 10.6 to 13.7 cases per 100,00 individuals. While the prevalence HD range from 1 to 7 cases per million in Japan, Taiwan, and Hong Kong, it is lower in black communities in South Africa than in white or mixed populations. In populations with high prevalence, average CAG (Cytosine, Adenine, Guanine) repeat lengths are longer. Only case studies or regional clinical evaluations provide epidemiological data from population in Africa and Asia; the global incidence and prevalence of HD are still unknown. According to report of high prevalence, the most well-known of which is the Maracaibo area of Venezuela, where a single founder has been linked to hundreds of related individuals.[7]

Clinical Justification

Psychiatric, cognitive and motor abnormalities are common symptoms and indicators of HD. Other less well-known but often debilitating effects of HD include inadvertent weight loss, changes to sleep and circadian rhythms, and problems with the autonomic nerve system. Early in the illness, there may be minor coordination problems, a few involuntary movements, difficulty solving puzzles, and a low or agitated mood. Chorea usually becomes more noticeable during the intermediate phase, and increasing dysarthria and dysphagia make it difficult to perform voluntary motor movements.

Cognitive signs and symptoms

Cognitive impairment is a secondary indicator of HD, which can appear well before the onset of motor signs and can be minor in the later stages of the illness. When patients make poor decisions, complex problems arise, and they don't respond as the environment or they used to. Under normal conditions, cognitive and physical behaviours are planned and goal-directed. While semantic memory (long term memory) can be partially preserved, memory can actually deteriorate (Figure 2).[8]

Motor signs and symptoms

First, the distal extremities (fingers and toes) as well as the tiny face muscles are frequently used for movement. Every person has a unique combination of hypokinesia (motor impairment; slow or no movements) and chorea. It is extremely difficult to differentiate between ataxic and choreatic walking. Additionally, pyramidal signs, also known as the Babinski sign, exist. Motor disturbances have a gradually increasing impact on daily tasks. Both hyperkinesia and hypokinesia cause challenges in standing and walking, frequently resulting in an ataxic gait and a high rate of falls. Further, it becomes increasingly difficult to perform daily tasks like getting out of bed, bathing, dressing, house cleaning and eating (Figure 2).[9]

Psychiatric sign/symptoms

Psychological symptoms are present in the early stage, usually before motor symptoms appear. The percentage of people revealing mental signs ranges from 33% to 76%, depending on the research method used. Depression is the most common indication in HD. It may cause weight loss, lethargy and apathy. There are some feelings like guilt, anxiety and low self-esteem. Anxiety is also common (34-61%) and it can sometimes be linked to concerns about the onset or trajectory of the illness. Early on, hypersexuality can seriously harm a relationship. Later phases are characterized by hyposexuality (Figure 2).[10]

Development of HD

The preclinical and clinical stages of HD development each corresponds to high-risk times in the patient's life. Three phases typically define the clinical course, each of which represents a decrease in self-sufficiency and a rise in the requirement for medical attention. Before the clinical stage with obvious symptoms: premanifest gene positive stage and transition phase, during which there is growing doubt regarding symptom presentation. When the situation returns to normal, these symptoms may temporarily disappear. In the past, a motor symptom was always the primary symptom. If the non-motor symptoms are not clearly defined, a diagnosis can be extremely difficult. Various patients recall a regular shift in their behavior and productivity at work in the past. These symptoms may have been the first indication of HD, as our understanding of the genetic makeup and progression of the condition has grown.[11,12]

Aetiology

The uncontrolled growth of trinucleotide repeat region within the coding region of a gene of unclear functions on chromosome 4's short arm is the cause of HD. The homologous protein HTT converts the CAG repeat into a poly-glutamine stretch. This places HD firmly within the context of a group of eight other heritable neurodegenerative illnesses known as poly-glutamine disorders, which are also defined by mutant proteins containing aberrant poly-glutamine regions.[13] The discovery of the HD mutation in 1993 marked a major turning point in the field of molecular medicine and served as the initial event in current HD research.[14] Apart from HD, these conditions also include six types of spinocerebellar ataxia and X-linked spinal and bulbar muscular atrophy (kennedy's disease). HD incidence and prevalence are not well-established globally; the few epidemiological data from populations in Africa and Asia are derived from case studies or regional clinical evaluations (Table 1).[15,16]

Pathobiology of HD

HTT is a large protein with a molecular weight of about 348 kDa and roughly 3,144 amino acids.[54] It is essential for transcriptional control, intracellular transport, and neuronal homeostasis. An N-terminal polyglutamine (polyQ) tract, HEAT repeat domains, and a less well-defined C-terminal region are among the discrete structural components of the HTT protein. The HTT gene on chromosome 4 encodes the polyQ tract, located between amino acids 18 and 44. The polyQ region is encoded by ≤35 CAG repeats in normal HTT, which preserves the stability and functionality of the protein. HD, on the other hand, results in a mutant HTT protein (mHTT) with an extended polyQ tract when the CAG repeat grows to ≥36 repetitions. The disease fully manifests when there are 40 or more expansions. By disrupting the normal conformation of the HTT protein, the enlarged polyQ region encourages misfolding, aggregation, and proteolytic cleavage, which produces hazardous fragments.[55-58] These abnormal pieces disrupt transcription, protein homeostasis, and mitochondrial activity, among other biological functions. Pathological events in HD are depicted in Figure 3, which also highlights the molecular mechanisms of the disease and potential treatment targets. The primary cause of the production of toxic aggregates is the mutant mHTT protein. The hallmark of HD is the loss of striatal neuronal function, which is a result of these aggregates impairing cellular processes, especially in neurons. The figure illustrates molecular-level strategies for reducing the impact of mHTT. Zinc Finger Proteins, antisense oligonucleotides, and RNA interference are examples of DNA- and RNA-based strategies that target mHTT in order to reduce its pathogenic impact. Furthermore, the goal of Histone Deacetylase (HDAC) inhibitors and the inhibition of Histone Acetyltransferase (HAT) enzymes is to to correct transcriptional dysregulation and aberrant acetylation caused by altered post-translational modifications of mHTT, including phosphorylation and acetylation.[59]

The N-terminal calpain cleavage site is located at residue 536, resulting in the creation of an intermediate product that is an N-terminal HTT fragment with a mass of 72 kDa.[60] This protease play a vital part in the formation of intranuclear inclusions because it produces smaller N-terminal HTT fragments than caspases.[61]

Clinical features

The three types of HD symptoms include progressive motor, cognitive and psychiatric and behavioral changes. The term "motor dysfunction" refer to the combination of involuntary movements (dystonia, rigidity, chorea) and impaired voluntary movements (dysarthria, dysphagia, akinesia, difficulties coordinating motions). Though symptoms can appear at any age, from infancy to old age, they are most commonly reported between the ages of 35 and 50. The average time to death is 15-20 years after the onset of symptoms however, some people die earlier due to falls or suicide, while others live for 30-40 years.

Cognitive disorder

The subcortical pattern of cognitive dysfunction can be seen years before symptoms appear. It is characterized by reduced emotional processing of identity, speed of processing, visual information processing, and executive function.[62] Early impairments affect short-term memory, skill acquisition, multitasking, and concentration. In keeping with earlier smaller studies, a new large-scale prospective observational study of premanifest individuals revealed reductions in a number of metrics, including verbal fluency, working memory and attention.[63] Cognitive decline eventually leads to dementia after a prolonged period. HD dementia varies from Alzheimer's dementia in that it is mostly subcortical, with executive dysfunction, delayed thought processes, attention and sequencing issues, and other issues.[64] Despite the clear manifestation of cognitive and motor symptoms to others, people with HD frequently exhibit a startling lack of insight into their own symptoms.[65]

Motor disorder

In HD-related motor dysfunction, two major components can be distinguished. The first consists of chorea, or uncontrollable movements. The second includes stiffness, bradykinesia, and incoordination, which influence voluntary movement.[66] Dystonia is a common condition marked by sustained postures or twisting movements. Bradykinesia, which is characterized by slowness and decreased scaling of movement, is common among HD patients. It manifests as short steps, fewer arm swings, reduced facial expression, and fewer spontaneous gestures..[67] Additionally, dysphagia, or difficulty swallowing, increases the risks of falls, severe injuries, weight loss, and aspiration, which can further complicate the condition.[68]

Psychiatric disorder

HD is linked to a wide range of mental symptoms, including psychosis, obsessive compulsive behavior, irritability, melancholy, anxiety, and apathy. In the premanifest stage, mental disturbances are also common, occurring several years before symptoms appear, despite the high prevalence of various disorders.[69] Apathy (loss of interest or emotion) is equally prevalent, but more difficult to address. The cognitive rigidity and perseverance characteristic of frontal lobe diseases may be reflected in compulsive behaviors in HD, which most likely stem from striatal dysfunction.[70] Unlike antidepressants and antipsychotics, which are used to treat depression, anxiety, and irritability, there are few effective therapies for apathy.

Management/treatment

Despite the fact that the pathogenesis of the disease is still unidentified. Currently, HD has no known cure. Nonetheless, numerous treatment options are available to address symptoms and signs in an effort to enhance quality of life. The primary forms of treatment include supportive care and medication. There is no significant role for surgical management. Numerous drugs and interventions, such as dopamine antagonists, acetylcholinesterase inhibitors, benzodiazepines, lithium, glutamate antagonists, and deep brain stimulation, have been tested for their ability to reduce chorea. These interventions typically target hyperkinetic movement disorders, such as dystonia, myoclonus, and chorea, that are associated with HD. Cognitive interventions, behavioral regimens, and adjunctive therapy may also be important and should be taken into account. The detrimental effects of the drug on psychiatric disorders associated with HD, such as depression, irritability, mania, or apathy, must be considered.[71]

New therapies under investigation

Pharmacological agents under investigation include those that aim to inhibit apoptosis, HTT aggregation, excitotoxicity, as well as HTT proteolysis, phosphorylation, and oxidative damage. Sodium butyrate, minocycline, memantine, and a phosphodiesterase 10a inhibitor are among the treatments that have advanced to clinical trials after showing promise in preclinical animal studies. Preclinical animal studies have demonstrated that gene silencing to address the cause of HD is safe. The effectiveness of intravenous infusion of mesenchymal stem cells is being investigated. However, cell transplantation has yielded inconsistent outcomes and raised safety concerns.[72]

Animal models of HD

HD play a vital role for understanding its pathophysiology and developing treatments. Common models include transgene mouse, such as R6/2 and YAC128, which carry the human mutant HTT gene and exhibit motor, cognitive, and neuropathological

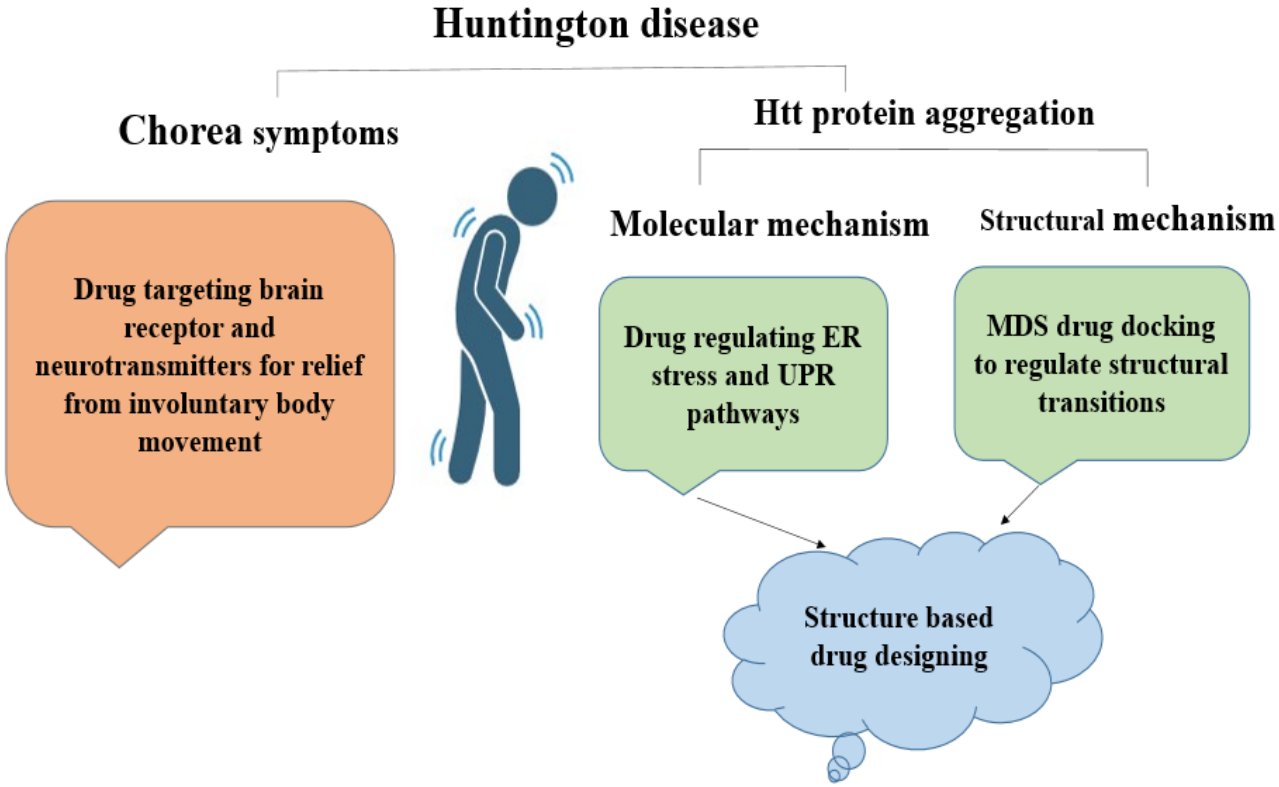

Figure 1: Concepts for research on structural and molecular pathways provide a potential approach to structure-based medication design.

Table 1: Aetiology of HD.

Country	Region	Prevalence (per 100,000)	Year studied	References
Europe				
Russia	Volgograd and Volzhsky	0.6	2000s	17
Iceland	--	1.0	2007	18
Finland	--	2.12	2010	19
Greece	--	3.95	2008	20
Croatia	Rijeka	4.5	1981	21
Germany	Franconia	4.7	1987	22
France	Haute Vienne	4.8	1970s	23
--	Nord and pas-de-Calais	5.0	1980s	24
Slovenia	--	5.2	2006	25
Sweden	--	4.5	1974	25
--	--	5.6	1985	26
Netherlands	--	6.5	1999	27
Norway	--	5.8	1950	28
--	--	6.7	1940	29
--	--	6.9	1930	28
Spain	Valencia	5.38	1992	29
--	Salamanca	8.4	1980s	30
Italy	Molise	10.85	2010s	31
Malta	--	11.8	1994	32
United Kingdom	Northern Ireland	6.4	1991	33
--	Northern Ireland	10.4	2001	34
--	--	11.2	1990	35
--	--	12.3	2010	35
Asia				
China	Hong kong	0.37	1997	36,37
--	Taiwan	0.42	2007	38
Japan	San-in	0.65	1997	39
--	Western Japan	0.72	1997	39
Oceania				
New South wales	--	6.3	1996	40
Tasmania	--	12.1	1990	41
Africa				
--	--	0.01	1970s	42
--	--	0.5-1	1980s	43
Kilimanjaro	--	7	1970s	44
America				
Venezuela	Nationwide excluding Zulia	0.5	2006	45
Mexico	Mexico city	4.0	2008	46
United States of America	Michigan	5.0	1940	47
--	South Carolina	5.0	1980	48

Country	Region	Prevalence (per 100,000)	Year studied	References
Europe				
--	Maryland	5.15	1980s	49
--	Minnesota	6.3	1989	50
Canada	Quebec	3.4	1963	51
--	Saskatchewan and Manitoba	8.4	1975	52
--	British Columbia	13.7	2012	53

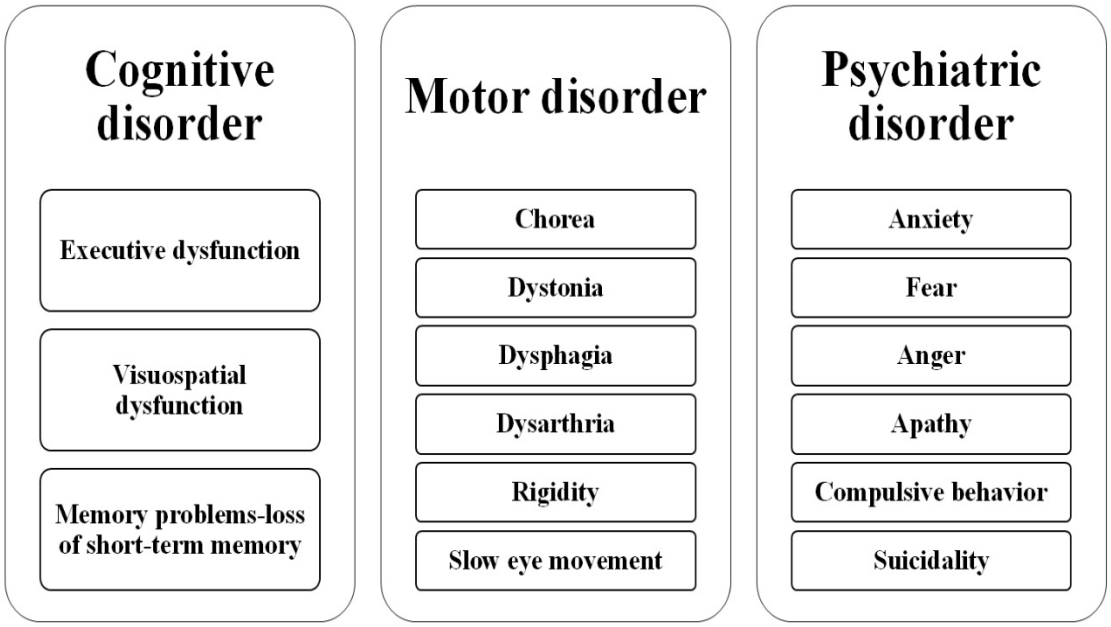

Figure 2: Some of the sign and symptoms of HD.

symptoms similar to HD. Knock-in mouse models, like HdhQ111, have the prolonged CAG repeat inserted into the endogenous mouse gene, showing progressive symptoms. Rat models and transgenic monkey models offer insights due to their longer lifespans and closer physiological similarities to humans. Additionally, simpler organisms like *Drosophila melanogaster* and *Caenorhabditis elegans* are used for genetic studies and drug screening. Despite their limitations, these models collectively enhance our understanding and aid in developing therapeutic strategies. An overview of animal models used to study of HD is depicted in Figure 4.

Models of Toxin

Models of energy metabolism deficit

Several clinical and preclinical studies have found significant evidence of decreased glucose consumption in the brain, particularly in the basal ganglia. Many animal models, such as malonate acid and 3-NP, have been developed to mimic the metabolic changes observed in HD during experiments (Table 2).

Malonate acid

Malonate is a different process for a selective modulator of succinate dehydrogenase. When given intrastriatally to animals, it causes neuronal degeneration and motor deficits similar to HD. Malonate, like 3-NP, causes age-dependent striatal damage that N-methyl-D-aspartate receptor (NMDA) antagonists can significantly reduce. Malonate-induced neurotoxicity is supported by other indirect data.[73,74] In mice exposed to malonate-induced toxicity, creatine and cyclocreatine provide neuroprotection by changing the production of hydroxyl radicals.[75] Malonate increased salicylate conversion to 2,3- and 2,5-dihydroxybenzoic acid, which is a measure of hydroxyl radical production. This effect is more pronounced in mice that lack glutathione peroxidase, a free radical scavenger. Strong evidence to show that NO-mediated oxidative damage plays a role in the pathways leading to cell death following energy disturbance caused by malonate and 3-NP. The mechanism by which these mitochondrial poisons cause cell death is related to that noticed in HD. The action of an oxidative phosphorylation enzyme compelx that is known to be decreased in the disease. Thus, the reduction of oxidative damage plays a

crucial part in the cell-death cascade that mhtt in HD patients started and serves as an execution step (Figure 5).[76]

3-Nitropropionic acid (3-NPA)

The mitochondrial enzyme succinate dehydrogenase is permanently inhibited by a toxin known as 3-NP.[77,78] Chinese newborns who ate sugarcane infested with arthrinium provided the first indication of 3-NP effects in the brain.[79] The 3-NP model is best suited for the observation of HD due to reproduction of mitochondrial failure. Enzyme deficiencies in brain cells cause decreased glucose metabolism, which lowers ATP generation.[79-81] The brains of HD patients contain decreased the amount of many enzymes that regulate the electron transport chain and the tricarboxylic acid cycle.

ROS are abnormally formed in response to disruptions in mitochondrial action. Electron outflow from the mitochondria and the generation of the ROS including superoxide radical (O_2 −•), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH −•) can occur when the enzymes in the electron transport chain are inhibited. ROS are known to harm genetic information and cellular membranes, as indicated by an increase in the DNA damage marker 8-hydroxydeoxyguanosine (8-OHdG).[82] 3-NPA damages mitochondria by inhibiting the enzyme succinate dehydrogenase. 3-NPA is able to enter the bloodstream and be given systemically to nonhuman primates, mice, and rats. Rat strains differ significantly in how they respond to the 3-NPA toxin.[83]

Although Fischer rats are the most vulnerable, it is challenging to conduct experiments with this species because of their notable diversity in their reaction. Lewis rats have persistent lesions and behavioral abnormalities even though they are less vulnerable to 3-NPA when given the right dosage. It may mimic both hyperkinetic and hypokinetic indications of HD, depending on when the delivery occurs. Rats given two different dosages of 3-NPA often have hyperkinetic symptoms similar to those seen in the early to middle phase. Nonhuman primates develop limb dystonia and choreaform movements when less amount of 3-NPA are give over the course of three to six weeks.[84]

Models of Excitotoxins

The administration of excitatory agonists into the brain to rats and mice resulted in the establishment of one of the earliest experimental models of HD. It raises the Ca^{2+} content within the cells. Enzymes such as endonucleases, phospholipases, and proteases that are triggered by Ca^{2+} speed up the death of neurons and the disintegration of other cell components. Pathophysiological alterations in intracellular ion concentrations, pH, protein phosphorylation, mitochondrial activity, energy consumption, and motility are caused by an excessive ligand interaction with GluR subtypes.

Quinolinic Acid (QA)

The excretion of QA in rats urine fed a meal rich in tryptophan was first reported in descriptions of QA, one of the two byproducts of tryptophan metabolism through kynurenine pathway

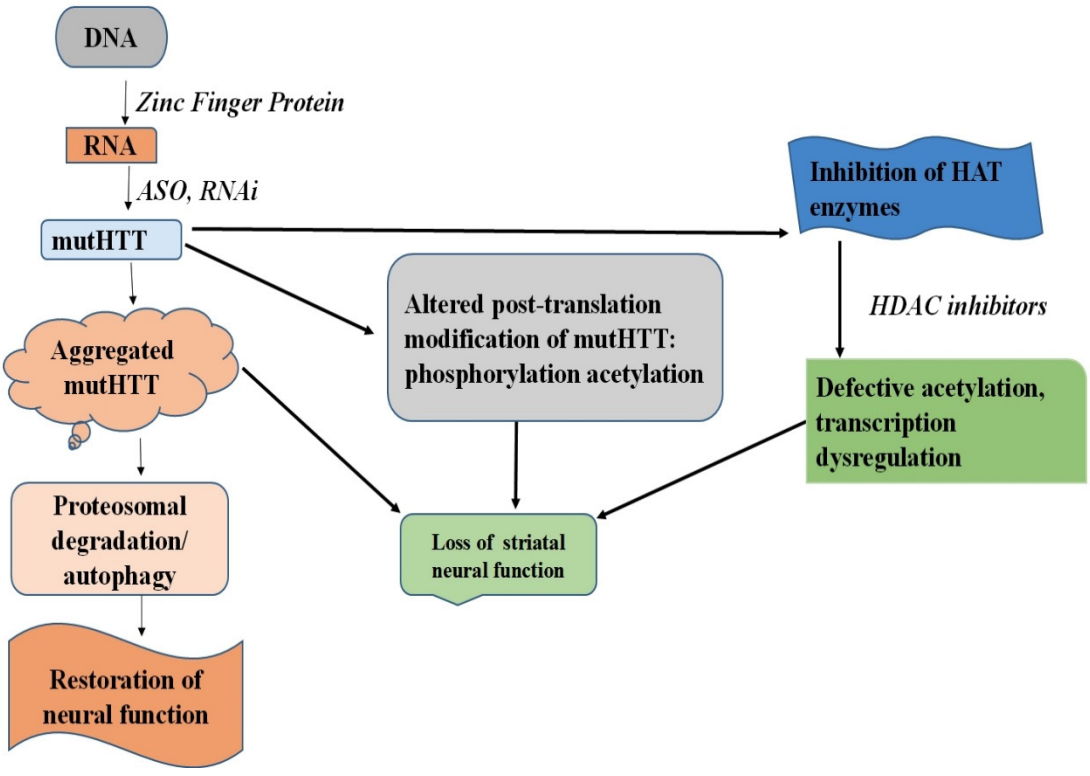

Figure 3: Pathological Events in HD.

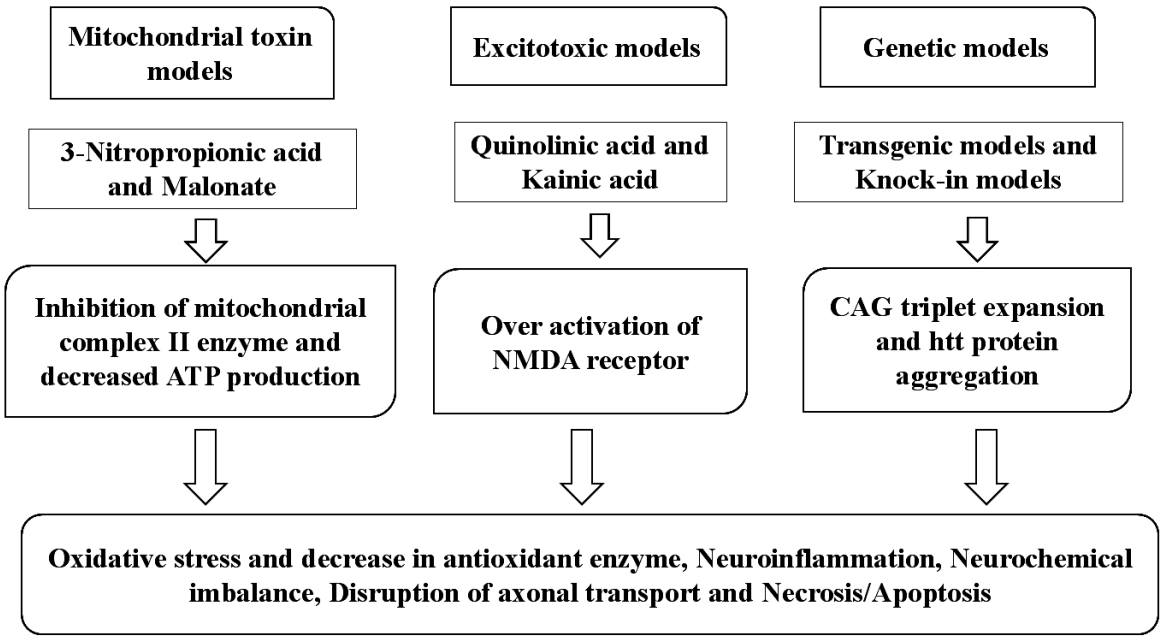

Figure 4: An overview of animal models used to study of HD.

(Figure 6).[85] Results showed that eating tryptophan enhanced the presence of QA and that it was a common element in the urine of different animals.[86] Tryptophan is taken up by dendritic cells, astrocytes, macrophages and microglia in the brain, where it is converted to kynurenine.[87] When 3-hydroxyanthranilic acid oxygenase is present, kynurenine is transformed to QA by a series of enzymatic processes. Investigations of brains of HD survivors showed that the part of the brain, the striatum-the most prone to neurons in the HD brain-exhibited the greatest rise in 3-hydroxyanthranilic acid oxygenase levels.[88] According to these results, the HD striatum experiences a dangerously high conversion of kynurenine to QA, which might be a contributing factor in the disease's neuronal death.[89] QA is administered experimentally straight into the stratum as it is unable to directly across the Blood-Brain Barrier (BBB).[90]

In rats, mice and primates, it resembles the pattern of striatal neurodegeneration found in HD.[91-93] The impairments seen in the early stages of HD are typically replicated by QA lesions, but not in the later stages. Mice with unilateral QA portion show parallel spinning activity when given the dopamine agonist apomorphine.[94] Imbalance of dopamine between the lesioned and undamaged hemispheres is the cause of the rotational behavior. The direction of rotation for rats with QA lesions is ipsilateral to the lesioned hemisphere as shown. Rats with unilateral lesions dangling by their tails choose to move in the direction of the affected hemisphere, indicating dysfunction in the contralateral striatum.[95] Rats with contralateral forelimb lesions have difficulty utilizing their unilateral lesions.[96] These rats favor using their ipsilateral forelimb when exploring and caring for their offspring.[97] Cognitive tests such as the Morris water maze, the T-maze, and the radial arm water maze are challenging for rats with QA lesions.[98,99]

Rats with QA lesions have a similar deficit, indicating that optimal cognitive performance on these tasks depends on the striatum's intact condition. In fact, transplanting fetal striatum can correct T-maze abnormalities induced by bilateral QA striatal lesions, according to a pioneering work by Isacson and colleagues.[100] This implies that lesions confined to the striatum can simulate particular cognitive characteristics associated with HD, which vary from impairments resulting from degradation of cortical circuitry. QA as a model for HD has the advantage of being easy to adapt to more complex species, including nonhuman primates.[101] When apomorphine is administered, unilateral lesions limited to the posterior putamen produces dystonia and dyskinesias. An interesting paradigm for future investigation is the development of chorea-like symptoms 48 hrs after bilateral posterior putamen injuries in nonhuman monkeys. Furthermore, the QA model also affects cognitive capacities. The monkeys with QA lesions are able to do the task with correct motor abilities; but, instead of locating and identifying the entrance of the box, they mistakenly cling to the temptation to reach immediately for the prize.[102] Several features of pathology seen in the QA model and the HD brain are shared by both.

Rats given QA treatment show that, like HD patients, the substantia nigra's neurotransmitters, γ-Aminobutyric acid (GABA) receptors and $GABA_A$, are elevated.[103] Further cause for the drug's common procedure in HD investigation is the possibility that QA generates cell death that resembles the neuronal demise process seen in HD brains.[104,105] Even though the exact mechanism of

cell death in HD is unknown, a hypothesis suggests it involves gradual, glutamate-induced excitotoxicity. HD brain decreased the adenosine triphosphate synthesis and significantly impairs the Na^{+-} K^{+} ATPase pump, that maintains electrical inclines across cell membranes through action potentials. Consequently, the membrane remains chronically depolarized after action potentials, causing the ejection of Mg^{2+} that typically inhibits NMDA receptors. When QA is administered to the striatum, an area rich in NMDA receptors, leading to increased Ca^{2+} influx, reduced production of ATP as well as excitotoxic cell death, mirroring features of neurodegeneration seen in HD. This mechanism is similar to how QA induces neurodegeneration in animal models of HD (Figure 7).

Kainic Acid

The Kainic Acid (KA) model of HD involves the administration of kainic acid, an agonist of kainate receptors, to induce excitotoxicity and neurodegeneration. By overstimulating these glutamate receptors, KA increases intracellular calcium levels, oxidative stress, and neuronal damage, selectively affecting regions such as the striatum, hippocampus and cortex-areas commonly impacted in HD (Figure 7). This model produces motor deficits, seizures, and behavioral changes that mimic HD symptoms, making it useful for studying the mechanisms of excitotoxicity and neuronal death.

While the KA model provides valuable insights into the pathways involved in HD-related neurodegeneration and aids in evaluating potential neuroprotective treatments, it represents an acute form of neurodegeneration and lacks the genetic and progressive nature of HD. Therefore, it is often used alongside other models to offer a more comprehensive understanding of the disease.[106]

Transgenic Models

The striatum is composed of met-enkephalin-immunopositive cells and NeuN-labeled neuronal nuclei, regardless of age. However, dopamine and cyclic adenosine monophosphate (cAMP)-regulated phosphoprotein (DARPP-32) staining in the striatum are diminished in R6/1 mice beginning at 5 months of age, suggesting cellular dysfunction. In the absence of cell death, striatal shrinking may also be observed (Table 3).

R6/1

The R6/1 mice were generated in the same manner as the R6/2 animals, except that their 116 repetitions resulted in a very mild behavioral phenotype. Similar to R6/2 mice, the human htt supporter drives the production of mutant HTT gene in every cell in the body. But only 31% of the endogenous mouse gene's levels of production are achieved (as opposed to 75% in the R6/2 line). Regardless of age, the striatum contains NeuN labeled cells and met-enkephalin-immunopositive cells. However, dopamine and cyclic adenosine monophosphate (cAMP)-regulated phosphoprotein (DARPP-32) staining in the striatum are diminished in R6/1 mice beginning at 5 months of age, suggesting cellular dysfunction. In the absence of cell death, striatal shrinking may also be observed. After 22 weeks, the mice's body weight reaches a plateau and then starts to decrease.[108] The animals also exhibit unusual strides, a lowered level of anxiousness, and a hindlimb clasping behavior, according to an analysis of their footprints. Since the R6/1 model is not as widely used as the R6/2 model, there are fewer specialists in this model.

R6/2

R6/2 is widely used transgenic mice model for HD. By introducing a 1.9-kB segment from the human HTT gene's 5 terminus into rat genome, bates and colleagues' ground breaking work produced this transgenic mouse strain.[109] This section contains just exon-1 of the human HTT gene and states around 144 Cytosine-adenine-guanine (CAG) repeats. The transmuted gene in mice expresses itself at a level of 75% of the wild-type gene in every cell. People who show early symptoms of HD are consistent with the high amount of recurrences into the R6/2 model. It has a fairly

Table 2: Animal toxin models.

Animals models	Species	Routes of administration	Cells affected	Motor/Cognitive symptoms
3-Nitropropionic acid (3-NP)	Rat (all except Fischer)[83]	Injections administered systemically, intrastriatally, or intraputamenally	GABAergic aspiny interneurons and medium spiny neurons, primarily affecting the lateral striatal[107]	Increase in muscular activity and decrease in muscular activity. Rats radial arm water maze test results in deficiencies in working and reference memory, while nonhuman primates' adaptation to open-field apparatus is also compromised[84]
Quinolinic Acid (QA)	Rat (Sprague-Dawley and Fischer)[90]	Intrastriatal injections, intraputamenal injections[91]	Increased levels of enkephalin, substance P, calbindin, parvabumin, and spiny interneurons[104]	Apomorphine-induced dystonia, dyskinesia, and hyperkinesia, higher dosages causing spontaneous dyskinesia. Poor memory recall, procedural memory deficiencies, and visuospatial deficits[96,98]

destructive behavioral trait. Some R6/2 mouse have been seen to exhibit signs before 4 weeks, despite the fact that symptoms typically appear between 9 and 11 weeks. Animals typically die between 10 and 13 weeks of age, and very few survive into 14 weeks. Early R6/2 mouse investigations found just a few htt-having presence in brain, but no other evident disease.[110]

However, recent research by stack and colleagues investigated the time-based changes in the brain volume, striatum volume, and striatum neuronal counts of R6/2 mouse.[111] The weight and volume of the brain start to decrease with time, starting on perinatal days i.e.30 and 60 days, according to study findings. Furthermore, around the ninety-day mark of life, there was a notable decline and atrophy of striatal neurons. Grip power, body weight, rotarod performance, and dystonia were all linked to pathological changes. Pre-proenkephalin messenger RNA (mRNA1), an enkephalin marker, started to sharply decline in the striatum at week 6, although pre-protachykinin messenger RNA (mRNA), a substance P marker, remained constant at all ages. Before reaching the striatum,inclusions originate in the cortex and hippocampus,with CA1 preeceding CA3. Research has shown that R6/2 brain has "dark neurons" that mimic the features of HD brain of humans, despite the fact that the precise process of cell loss in this brain is unclear.[112] A kind of cell death that is not necrotic or apoptotic has been identified in the cerebellum,striatum and cingulate cortex. Striatal anatomical abnormalities in R6/2 animals are similar to adult-onset HD, even though their 144 CAG repeats are comparable to those of juvenile HD patients. R6/2 mouse have many domain impairments in both motor and intellectual function. Motor symptoms comprise chorea-like movements, resting tremor, limb dystonia, involuntary and repeated grooming motions, and when hanging by stail. The mice in the rotarod test show a progressive decline starting at 40 days of age, and by 12 weeks, they are unable to maintain their balance for even 10 sec.[113] After 20 days, in an open-field test of behavior also locomotion, R6/2 animals demonstrates higher investigative activity than wild-type rat. There are also cognitive abnormalities in the R6/2 mouse.[114] Morris water maze (MWM) reveals spatial understanding deficits in HD models as quickly as 3.5 weeks, before the beginning of overt motor symptoms. By 7 to 8 weeks, these deficits are exacerbated, with older animals unable to understand the task, just because of decreased level of swim.

Additionally, HD model mice perform poorly on modification of T-maze exercise, struggling to another entrance into opposing arms, likely due to a tendency to persist in responding to the first stimulus, a behavior similar to that observed in HD volunteer. The spatial nature of MWM deficits, reliant on hippocampal function,

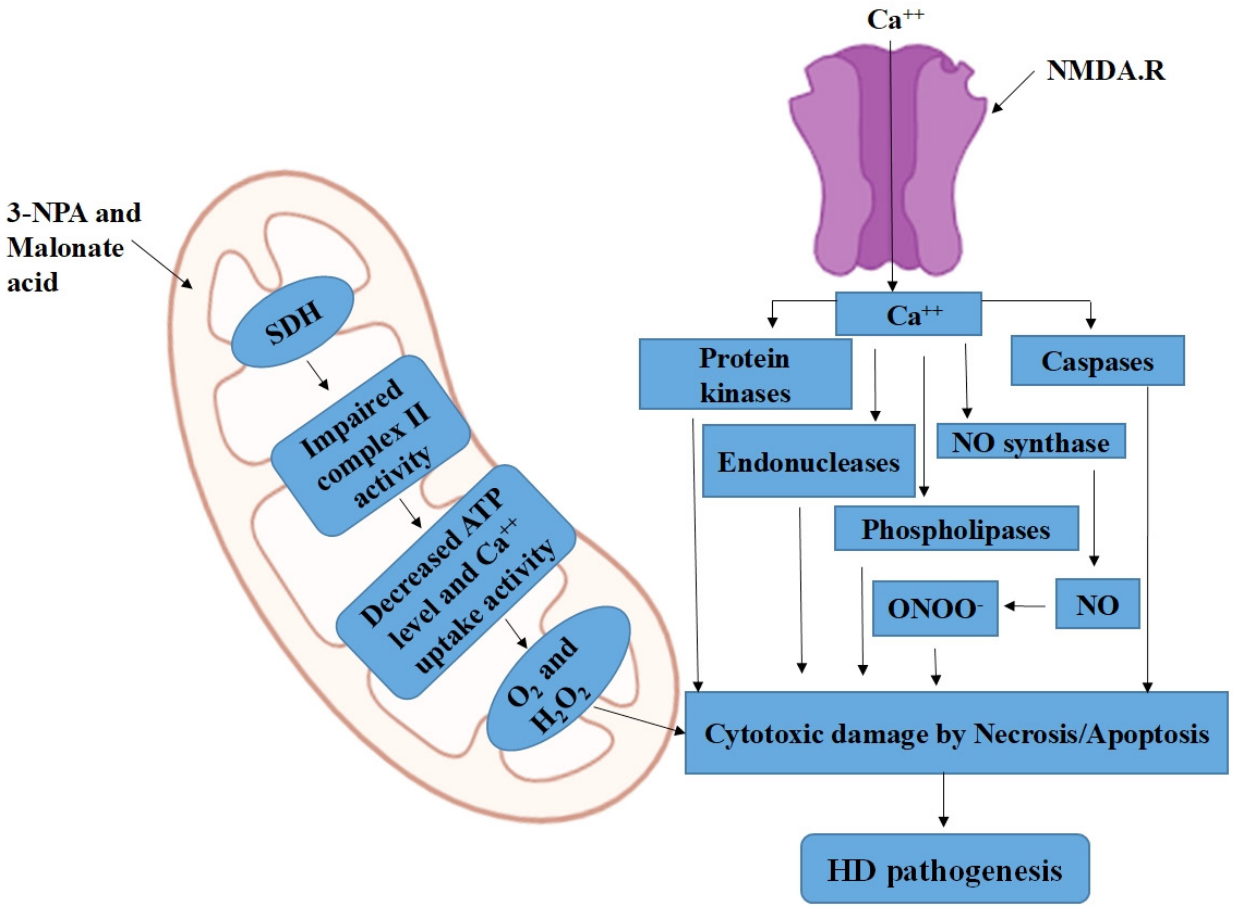

Figure 5: The mode of action of Malonic acid and 3-NPA.

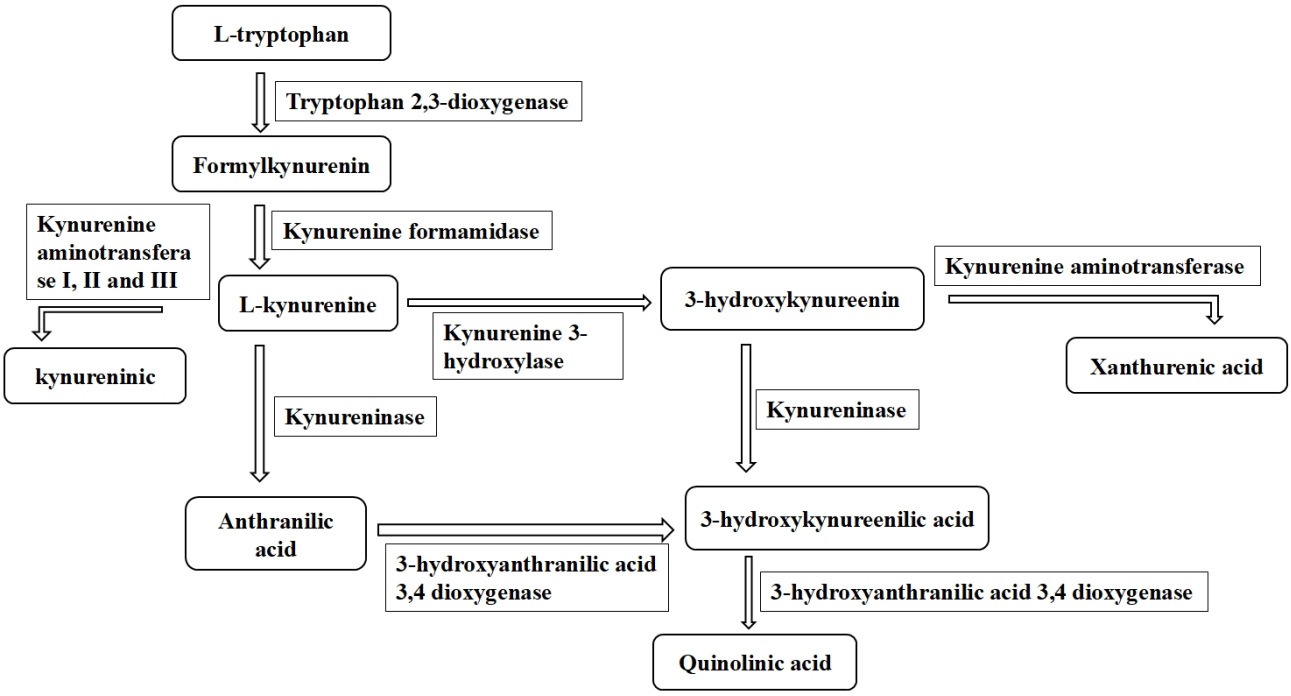

Figure 6: Kynurenine pathway.

may stem from htt aggregate accumulation in the hippocampus. Similarly, HD patients shows difficulties in adoptable stage of the Wisconsin Card Sorting Task, reflecting challenges replacing previously learned strategies, a process dependent on intact frontostriatal circuitry. Both tasks highlight impairments in cognitive flexibility and learning due to HD pathology.[115] Therefore, it's possible that impairments in the T-maze are more directly linked to abnormalities seen in HD.

N171-82Q

The N-terminal 171 amino acids of the volunteer HTT gene were inserted into the rat genome to create the N171-82Q transgenic mouse model, which was created by Borchelt and colleagues.[54] This model may be more suited to simulating adult-onset HD as symptoms manifest later in life due to its lower polyglutamine repeats than those of the R6 mice. On the other hand, we see that line 81 of this mouse model has a reduced lifetime of five to six months. In their first two and a half months of existence, these creatures appear to be acting perfectly normally. The abnormal gait, hypokinesia, clasping of the forelimsb and hindlimb, and resting tremor are all present in animals with the behavioral syndrome.[116] When the tested for work and position recall in the circular arm water maze at 14 weeks of age, the N171-82Q rat express the impairments of their cognitive function.[117] However, multiple HTT presences in the hippocampus may be the source of this cognitive decline, as opposed to the frontostriatal circuitry as suggested by previous studies. These rats ensure the not demonstration of hyperkinetic behaviors like the R6/2 model does. Researchers have observed 20% reduce in striatal cell volume and 25% loss of neurons in the striatum of N171-82 HD rat at 16 weeks of age.[116] The brain, hippocampus, and striatum of N171-82Q rat exhibit mutant HTT-positive presences at 16 to 20 weeks of age. The longer time course of symptoms in this paradigm compared to R6/2 mouse, along with the delayed inception of behavioral signs and striatal neurodegeneration, make it a striking model for the learning of presymptomatic treatment.

Yeast Artificial Chromosome (YAC)

YAC transgenic mice were produced by Hayden and colleagues by the use of a YAC vector system to express the whole human htt gene under the control of the human htt promoter.[118] 72 or 128 CAG repeats can be found in YAC mouse strains. The number of neurons decreases in both strains, mainly in the lateral striatum.[119] The YAC 72 mice's body weight at 12 months is 50% less than that of their wild-type littermates. They also have abnormal walking, ataxia, conspicuous circling behavior, and clasping of the hindlimbs. YAC 128 mice begin to show signs of hypokinesia at 6 months of age, while their hyperkinetic behavior on an open-field test and a progressive decline on the rotarod test begin at 3 months of age.

In the YAC 72 and 128 models, there is more nuclear HTT staining. In research on cognitive impairment in the YAC 128 model, a basic linear swimming chamber and the swimming T-maze test conducted at 8.5 months of age have been utilized.[115] Procedural learning effectiveness is measured by how fast the mouse turns and swims toward the platform. At 8 months of age, YAC 128 mice show significant deficits in this task: they fail to turn promptly and take significantly longer than wild-type mice

to recognize and reach the platform. Another cognitive test is swimming in a T-maze. The T-shaped platform in the chamber's right arm is where the mice are initially trained to swim. The animals will eventually need to locate the platform when it is moved to the left arm. Wild-type mice first rejoin the right arm before swiftly swimming to the left arm when they are unable to locate the platform. After a rather high number of trials, the YAC 128 mice either swim toward the right arm or return to the start arm, despite the platform being relocated to the left arm. Their inability to finish this work indicates a shortcoming like to that of a human: instead of coming up with a novel approach, they keep applying what they have previously learned.

Knock-in mouse model

The CAG140 knock-in mouse, developed by Scott Zeitlin's lab, expresses 140 CAG repetitions.[121] An open-field test at one month of age reveals mild hypoactivity in CAG140 mice, but by twelve months, overt motor dysfunction is evident as the mice exhibit a reduction in stride length. When compared to wildtype mice, CAG140 knock-in mice also exhibit much more rearing activity using both forelimbs at one month of age; however, this behavior starts to significantly drop at four months. In the neuropil as well as the nucleus, these aggregates occur. The amount of lost neural cells in these mice has not yet been measured. Detloff and colleagues established the CAG150 mouse model, which is perhaps the most promising of the knock-in animals.[122] Beginning around 4 months of age, these mice exhibit a clasping phenotype, hypoactivity, and increasing impairments on the rotarod. After 25 weeks of age, they are also noticeably smaller than their littermates of the wild kind. At 14 months, their striatal gliosis and nuclear aggregates in the striatum are much higher than those of their wild-type littermates.[123] Despite the brain's total lack of apoptotic TUNEL staining, electron imaging showed dark bodies around cytoplasmic vacuoles, a sign of cellular abnormality. The pathology shown in CAG150 knock-ins was found to be more severe than that of CAG140 knock-ins. This suggests that pathology more representative of the disease observed in people may be produced in future models with even more CAG repeats (Table 4).

Non-mammalian animal models

Caenorhabditis elegans in Huntington research

Non-mammalian animal models like *Caenorhabditis elegans* (*C. elegans*) and *Drosophila melanogaster* have proven valuable in Huntington's Disease (HD) research due to their simpler genetics, rapid life cycles, and the conservation of many cellular and molecular pathways involved in neurodegeneration.

Caenorhabditis elegans: Because of its transparent body, well-mapped brain circuitry, and simplicity of genetic manipulation, the nematode C. elegans is frequently employed in research on neurodegenerative diseases, including HD. In order to simulate the protein aggregation and neurotoxicity observed in human HD, researchers frequently insert mutant

Table 3: Animal transgenic models.

Animals	Species	Cells affected	Motor/Cognitive symptoms
R6/1	Transgenic mouse	5 M: A reduction in DarPP-32 in the striatum starting from the age of five months. Reduction in striatal volume and cellular inclusions' presence[120]	22 wk: Body weights plateau after which they begin to decline, Decreased anxiety on open-field test
R/2	Transgenic mouse	90 d: Considerable atrophy and loss of neurons in the striatum[111]	40 d: The Rotarod test improves. 9 weeks: weight loss, narcolepsy, clasping behavior, chorea-like motions, resting tremor, stereotypies, and spontaneous shuddering movements, 20 d: An increase in the open-field test's interested behavior. 60 d: Decreased exploratory activity during the test in the wide field. 3.5 weeks: T-maze and Morris water maze deficiencies
N171-82Q	Transgenic mouse	25% of striatal neurons are lost in week 16. 20% shrinking of cells. additions to the cortex, hippocampus, and striatum [116]	11Wk Loss of weight, clasping behavior, and rotarod deficiency, Deficiencies in working memory and the text of reference for the radial arm water maze
YAC	Transgenic mouse	12 M: Cell loss ranges from 18% to 40%, with the lateral stratum bearing the brunt of the loss. HTT staining of the nucleus rose. 18 M: Included in the strain of YAC 128[118]	3 M: an open-field test demonstrating hyperkinesia. In an open-field test, 6 M: hypokinesia. 12 M: 50% reduction in body weight from littermates of wild type. pronounced spinning of the hindlimbs, ataxia, impairments of gait, and behavior. rotarod test results show a progressive degeneration, T-maze deficiencies

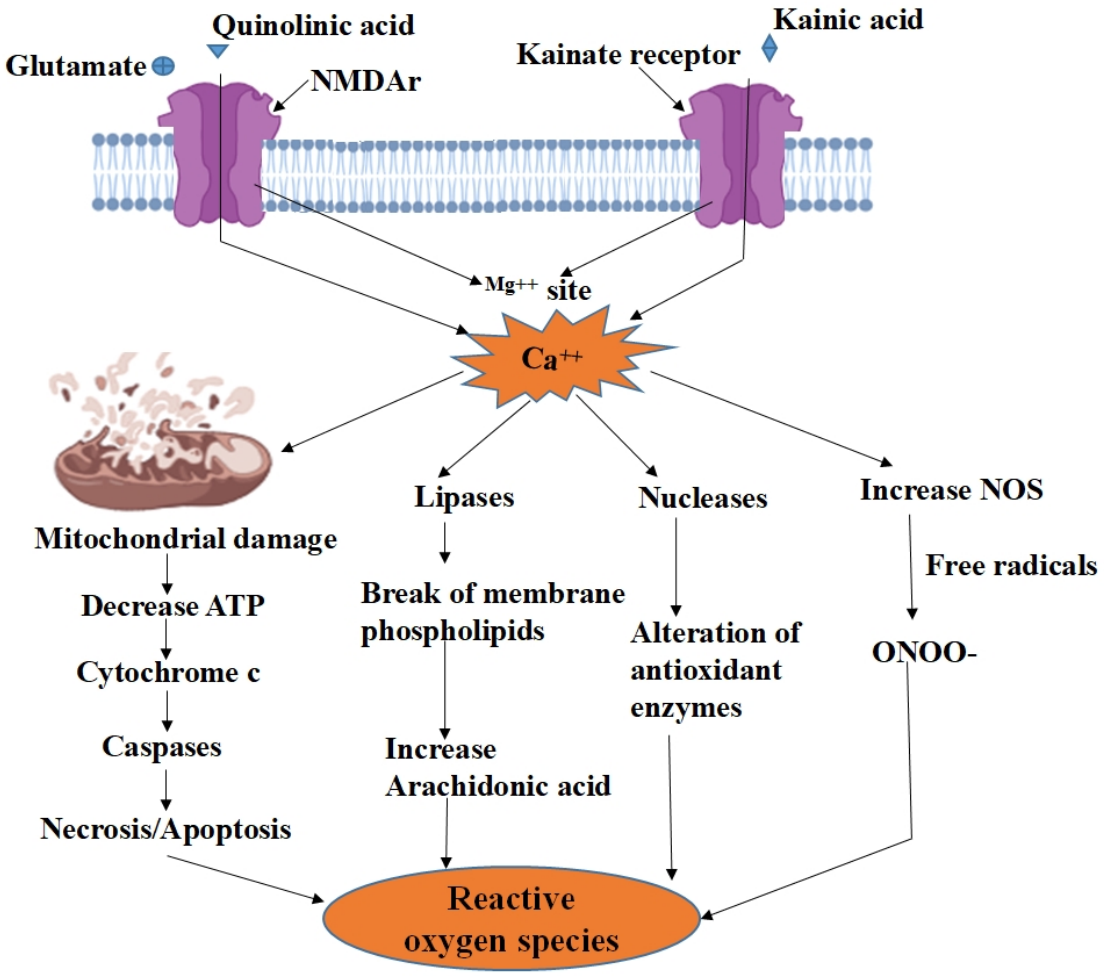

Figure 7: Mode of action of Kainic acid and Quinolinic acid.

HTT genes with enlarged CAG repeats.[124] By using these models, *C. elegans* has shed light on the processes that underlie dementia, including oxidative stress, mitochondrial failure, and disturbed protein homeostasis. Furthermore, this model's simplicity makes high-throughput drug screening easier, enabling researchers to find substances that can lessen HD symptoms or reduce the disease's progression.

Drosophila melanogaster

The fruit fly Another important model in HD research is *Drosophila melanogaster*.[125] Drosophila models can more accurately replicate some features of HD disease seen in mammals, such as motor impairments, progressive neurodegeneration, and decreased lifespan, because of its highly conserved genome and more sophisticated neural system. Transgenic Drosophila that express mutant human HTT proteins exhibit neurodegeneration and progressive motor symptoms, providing a similarity to the pathology of HD in humans. The identification of cellular processes impacted by HD, such as defective autophagy, synaptic dysfunction, and disturbed cellular signaling pathways, has been made possible in large part by these models. Drosophila is a great model for finding modifier genes that can be used as possible therapeutic targets because of its quick gene manipulation capabilities.

Therapeutic approaches in genetic models

Researchers may be able to better understand the fundamental biological principles of HD pathology by using genetic models, which also make it possible to examine the impact of possible treatments in animal models that additional closely resemble the phenotype and genotype of the human illness. Currently, coenzyme Q10 is undergoing clinical studies following its efficacious usage in Model of transgenic mouse R6/2. Excessive dosages of coenzyme Q10 avoided weight reduce, better grip strength and rotarod deficits, and extended longevity in a dose-response research conducted on R6/2 mice.[126] In the R6/2 model, coenzyme Q10 tests enhance its positive effects when combined with the anti-inflammatory drug minocycline and the antioxidant vitamin E.[127,128]

A recent evaluation of neuroprotective strategies in genomic rat models of HD found that Adeno-Associated Virus (AAV) Gene Delivery of glial cell line-derived Neurotrophic Factor (GDNF) can mitigate motor impairments and neuropathological effects

Table 4: Animal knock-in models.

Species	Cells Affected	Motor/Cognitive Symptoms
HdhQ92 mouse[124]	No striatal degeneration.	Absence of obvious signs
2q HdhQ111 mouse[125]	No striatal degeneration.	24M: Abnormal movement, Absence of obvious signs
CAG140 mouse[121]	2 M: Inclusions of neurons and nuclei in the hippocampus, cerebellum, cortex, and striatum	1M: Rearing behavior employing both forelimbs and open-field test locomotion is increased in comparison to the 4 month decrease in wild-type mice. Absence of obvious signs
CAG150 mouse[122,123]	2M: Striatal gliosis significantly increased in comparison to littermates of the wild type. There is a rise in EM48 positive nuclear aggregates in the stratum. Decomposition of myelin	4M: onset of clasping behavior, hypoactivity, increasing deficits on the rotarod, and abnormalities in gait. Absence of obvious signs

in the N171-82Q transgenic rat model. This approach suggests that GDNF has significant potential in correcting some of the functional and structural deficits associated with the disease.[117] The differential findings between these two investigations may be clarified by the extra aggressive behavioral phenotype observed in the R6/2 model as well as the administration of the AAV-GDNF in the presymptomatic stage of the disease in N171-82Q rat. A novel and intriguing technique for HD treatment is (RNA interference) RNAi. The mechanism of action involves binding to corresponding messenger RNA (mRNA) sequences and inhibiting their production through the routine of Small Interfering RNA (siRNA), Short Hairpin RNA (shRNA) or microRNA (miRNA) segments. Using this medication specifically for HD can decrease the appearance of mutant HTT and the pathogenic processes that follow its generation.

By using this method with the N171-82Q transgenic rat model, it was possible to use viral delivery of shRNA that was directed against a sequence in exon 2 of the mutant htt gene to prevent the formation of mutant HTT positive inclusions in transduced cells and to reduce the amount of mutant HTT protein in the injected striatum by 50-55%.[129] Additionally, an increase in existence time and the rescue of motor impairments (clasping, rotarod, and open-field tests) were observed by this study. Giving shRNA to transgenic mice with HD190QG (htt-EGFP fusion mice) decreased the number of HTT positive presences in the striatum in postsymptomatic animals, according to recent promising research. This shows that the treatment could be helpful in mitigating the effects of some elements of HD pathogenesis.

Thinking about for animal use in experimental

HD is an extremely crippling illness. Through genetic engineering or the use of certain neurotoxins like QA or 3-NP, animal models can mimic human symptoms. The most typical signs of the neurotoxin-induced illness are weight loss, tremors or convulsions, eventual paralysis, recumbency, and frequently even death. Weekly weight checks and careful daily observation are essential components of animal care in these models. In order to minimize any suffering resulting from the disease's presentation, animals who exhibit pain should be given analgesics as needed. When required, the approach should involve appropriate therapy in addition to discussions with veterinary experts. If an animal loses the ability to feed itself, gavage may be necessary. When moribund animals are exposed to toxins, either right once or over time in genetic models, euthanasia can be required.

CONCLUSION

A neurodegenerative condition called HD is characterized by increasing motor impairment, emotional instability, and dementia caused by the striatal degradation of GABAergic MSNs. There is no treatment to stop HD from progressing, and several medications can relieve symptoms. The demand for creative, efficient therapy is pressing. To investigate the pathogenic process and test potential drugs for this uncommon disease, many animal models might be employed. Each model focuses on certain pathogenic characteristics of the illness, including as excitotoxicity, selective neurodegeneration, and mitochondrial inhibition. Genomic rodent models of HD that produce either announcing transgenic genes that prompt the defective HTT protein or involve knocking in a mutated gene that replaces part or all of the mouse gene. These are the "gold-standard models" of HD, yet none of the models available today can be considered the best because they all exhibit overt frontostriatal cognitive impairments and do not exhibit significant degeneration.

The selection of a specific model is contingent upon the research topic, as is the case with all animal models utilized in investigations. Toxin-based models may remain useful, but the majority of experimental hypotheses-particularly those involving therapeutic interventions-need to be successful in genetic models, the selection of which is dependent upon the nature of the experiment being studied. Based on the expected mechanism of action of the test drug's cation, a particular model can be chosen to cause the illness. Clinical investigations have started to offer more quantitative measurements of illness onset and development in order to prepare for upcoming clinical trials.

Hopes for the quick discovery of potent treatments are raised by recent advancements in the clinical and foundational scientific domains.

ABBREVIATIONS

3-NP: 3-Nitropropionic Acid; **HD:** Huntington's Disease; **HTT:** Huntingtin Protein; **Htt:** Huntingtin Gene; **HDAC:** Histone Deacetylase; **HAT:** Histone Acetyltransferase; **BBB:** Blood-Brain Barrier; **KA:** Kainic Acid; **MA:** Malonic Acid; **MSNs:** Medium Spiny Neurons; **NMDA:** N-Methyl-D-Aspartate; **QA:** Quinolinic Acid; **TEs:** Transposable Elements.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

An autosomal dominant neurological disease that eventually results in death, Huntington disease (HD) is defined by a progressive deterioration in motor, behavioral, and cognitive abilities.s

As of right now, chorea is the only treatment for HD and medication is frequently effective in treating psychiatric problems. Improved knowledge of the pathophysiology of HD and more advanced clinical studies utilizing novel biomarkers.

Researching biomarkers and potential treatments for other neurodegenerative illnesses may benefit from using HD model.

Huntington's disease (HD) is a rare, dominantly inherited neurodegenerative disorder characterized by progressive cognitive decline, psychiatric disturbances, and involuntary movements known as chorea. The disease results from an expanded cytosine-adenine-guanine repeat in the huntingtin gene, leading to neuronal dysfunction and degeneration, primarily in the striatum and cerebral cortex.

Animal models play a pivotal role in understanding HD pathophysiology and testing potential therapies. These models replicate key histological and symptomatic aspects of HD, although they do not fully capture the complexity of the human disease. Recent advancements in genetic and transgenic models have improved disease representation, making them vital tools for bridging preclinical research with clinical applications. Future refinements in animal modeling will be critical for developing more effective therapeutic strategies against HD.

This review aims to provide an updated overview of HD pathogenesis and the role of animal models in understanding disease mechanisms and evaluating potential therapeutic strategies. It explores key molecular and cellular pathways implicated in HD progression, highlights the limitations and advantages of existing animal models, and discusses their relevance in bridging the gap between preclinical research and clinical applications.

REFERENCES

1. Mehanna R, Jankovic J. Systemic Symptoms in Huntington's Disease: A Comprehensive Review. Mov Disord Clin Pract. 2024;11(5):453-64.
2. Tong H, Yang T, Xu S, Li X, Liu L, Zhou G, *et al.* Huntington's disease: complex pathogenesis and therapeutic strategies. Int J Mol Sci. 2024; 29;25(7):3845.
3. Rana N, Kapil L, Singh C, Singh A. Modeling Huntington's disease: An insight on *in vitro* and *in vivo* models. Behav Brain Res. 2024;29; 459:114757.
4. Itkin T, Unger K, Barak Y, Yovel A, Stekolshchik L, Ego L, *et al.* Exploiting the Unique Biology of *Caenorhabditis elegans* to Launch Neurodegeneration Studies in Space. Astrobiology. 2024;24(6):579-89.
5. Ramos-Arroyo M, Moreno S, Valiente A. Incidence and mutation rates of Huntington's disease in Spain: experience of 9 years of direct genetic testing. J Neurol Neurosurg Psychiatry. 2005;76(3):337.
6. Pringsheim T, Wiltshire K, Day L, Dykeman J, Steeves T, Jette N. The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis. Mov Disord. 2012;27(9):1083-91.
7. NS W. Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. Proc Natl Acad Sci USA. 2004;101:3498-503.
8. Harper PS, Jones L. Huntington's disease: genetic and molecular studies. Oxford Monogr Med Genet. 2002;45:113-58.
9. Van Duijn E, Kingma EM, Van Der Mast RC. Psychopathology in verified Huntington's disease gene carriers. J Neuropsychiatry Clin Neurosci. 2007;19(4):441-8.
10. Wheelock VL, Tempkin T, Marder K, Nance M, Myers RH, Zhao H, *et al.*, Group HS. Predictors of nursing home placement in Huntington disease. Neurology. 2003;60(6):998-1001.
11. Witjes-Ane MNW, Vegter-Van der Vlis M, Van Vugt JPP, Lanser JBK, Hermans J, Zwinderman AH, *et al.* Cognitive and motor functioning in gene carriers for Huntington's disease: a baseline study. J Neuropsychiatry Clin Neurosci. 2003;15(1):7-16.
12. Paulsen JS, Langbehn DR, Stout JC, Aylward E, Ross CA, Nance M, *et al.* Detection of Huntington's disease decades before diagnosis: the Predict-HD study. J Neurol Neurosurg Psychiatry. 2008;79(8):874-80.
13. Orr HT, Zoghbi HY. Trinucleotide repeat disorders. Annu Rev Neurosci. 2007;30:575-621.
14. Bates GP. The molecular genetics of Huntington disease-a history. Nat Rev Genet. 2005;6(10):766-73.
15. Korolchuk V, Imarisio S, Carmichael J, Chen CW, Saiki S, Rose C, *et al.* Huntington's disease: from pathology and genetics to potential therapies. Biochem J. 2008.
16. Vonsattel JPG. Huntington disease models and human neuropathology: similarities and differences. Acta Neuropathol. 2008;115:55-69.
17. Kirilenko NB, Fedotov VP, Baryshnikova NV, Dadali EL, Polyakov AV. Nozological spectrum of hereditary diseases of the nervous system in the cities of Volgograd and Volzhsky. Russ J Genet. 2004;40:1036-40.
18. Sveinsson O, Halldórsson S, Olafsson E. An unusually low prevalence of Huntington's disease in Iceland. Eur Neurol. 2012;68(1):48-51.
19. Sipila JOT, Hietala M, Siitonen A, Päivärinta M, Majamaa K. Epidemiology of Huntington's disease in Finland. Parkinsonism Relat Disord. 2015;21(1):46-9.
20. Panas M, Karadima G, Vassos E, Kalfakis N, Kladi A, Christodoulou K, *et al.* Huntington's disease in Greece: the experience of 14 years. Clin Genet. 2011;80(6):586-90.
21. Sepcic J, Antonelli L, Šepić-Grahovac D, Materljari E. Epidemiology of Huntington's disease in Rijeka district, Yugoslavia. Neuroepidemiology. 1989;8(2):105-8.
22. Przuntek H, Steigerwald A. Epidemiologic study of Huntington disease in the catchment area of the Würzburg University Neurologic Clinic with special reference to the Lower Franconia district. Nervenarzt. 1987;58(7):424-7.
23. Leger JM, Ronauil R, Vallat JN. Huntington's chorea in Limousin: statistical and clinical study. Rev Med Limoges. 1974;5:147-53.
24. Petit H, Salomez JL. Huntington's disease. Contribution of clinical and epidemiological data to genetic counseling. J Genet Hum. 1985;33(2):91-102.
25. Peterlin B, Kobal J, Teran N, Flisar D, Lovrečić L. Epidemiology of Huntington's disease in Slovenia. Acta Neurol Scand. 2009;119(6):371-5.
26. Al-Jader LN, Harper PS, Krawczak M, Palmer SR. The frequency of inherited disorders database: prevalence of Huntington disease. Public Health Genomics. 2002;4(3):148-57.
27. Maat-Kievit A, Helderman-van den Enden P, Losekoot M, de Knijff P, Belfroid R, Vegter-van der Vlis M, *et al.* Using a roster and haplotyping is useful in risk assessment for persons with intermediate and reduced penetrance alleles in Huntington disease. Am J Med Genet. 2001;105(8):737-44.
28. Saugstad L, Odegard O. Huntington's chorea in Norway. Psychol Med. 1986;16(1):39-48.
29. Burguera JA, Solis P, Salazar A. Estimate of the prevalence of Huntington disease in the Valencia region using the capture-recapture method. Rev Neurol. 1997;25(148):1845-7.

30. Ruiz JJ, Ortin A, Cacho J, Alburquerque J. Corea de Huntington: estudio epidemiológico en la provincia de Salamanca. Arch Neurobiol. 1985;48:302-3.
31. Squitieri F, Griguoli A, Capelli G, Porcellini A, D'alessio B. Epidemiology of Huntington disease: first post-HTT gene analysis of prevalence in Italy. Clin Genet. 2016;89(3):367-70.
32. Gassivaro Gallo P, Buhagiar M, Cuschieri A, Viviani F. Huntington's chorea (HD) in Malta: Epidemiology and origins. 1999.
33. Morrison PJ, Johnston WP, Nevin NC. The epidemiology of Huntington's disease in Northern Ireland. J Med Genet. 1995;32(7):524-30.
34. Morrison PJ. Accurate prevalence and uptake of testing for Huntington's disease. Lancet Neurol. 2010;9(12):1147.
35. Evans SJW, Douglas I, Rawlins MD, Wexler NS, Tabrizi SJ, Smeeth L. Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. J Neurol Neurosurg Psychiatry. 2013.
36. Chang CM, Yu YL, Fong KY, Wong MT, Chan YW, Ng TH, *et al.* Huntington's disease in Hong Kong Chinese: epidemiology and clinical picture. Clin Exp Neurol. 1994;31:43-51.
37. Leung CM, Chan YW, Chang CM, Yu YL, Chen CN. Huntington's disease in Chinese: a hypothesis of its origin. J Neurol Neurosurg Psychiatry. 1992;55(8):681-4.
38. Chen YY, Lai CH. Nationwide population-based epidemiologic study of Huntington's disease in Taiwan. Neuroepidemiology. 2010;35(4):250-4.
39. Adachi Y, Nakashima K. Population genetic study of Huntington's disease--prevalence and founder's effect in the San-in area, western Japan. Nihon Rinsho. 1999;57(4):900-4.
40. McCusker EA, Casse RF, Graham SJ, Wllllams DB, Lazarus R. Prevalence of Huntington disease in New South Wales in 1996. Med J Aust. 2000;173(4):187-90.
41. Pridmore SA. The prevalence of Huntington's disease in Tasmania. Med J Aust. 1990;153(3):133-4.
42. Hayden MacGregor, JM and Beighton, PH MR. The prevalence of Huntington's chorea in South Africa. South African Med J. 1980;58(5):193-6.
43. Scrimgeour EM, Pfumojena JW. Huntington disease in black Zimbabwean families living near the Mozambique border. Am J Med Genet. 1992;44(6):762-6.
44. Scrimgeour EM. Huntington's disease in Tanzania. J Med Genet. 1981;18(3):200-3.
45. Paradisi I, Hernández A, Arias S. Huntington disease mutation in Venezuela: age of onset, haplotype analyses and geographic aggregation. J Hum Genet. 2008;53(2):127-35.
46. Alonso ME, Ochoa A, Boll M, Sosa AL, Yescas P, López M, *et al.* Clinical and genetic characteristics of Mexican Huntington's disease patients. Mov Disord. 2009;24(13):2012-5.
47. Reed TE, Chandler JH. Huntington's chorea in Michigan. I. Demography and genetics. Am J Hum Genet. 1958;10(2):201.
48. Wright HH, Still CN, Abramson RK. Huntington's disease in black kindreds in South Carolina. Arch Neurol. 1981;38(7):412-4.
49. Folstein SE, Chase GA, Wahl WE, McDonnell AM, Folstein MF. Huntington disease in Maryland: clinical aspects of racial variation. Am J Hum Genet. 1987;41(2):168.
50. Kokmen E, Ozekmekci FS, Beard CM, O'Brien PC, Kurland LT. Incidence and prevalence of Huntington's disease in Olmsted County, Minnesota (1950 through 1989). Arch Neurol. 1994;51(7):696-8.
51. Barbeau A, Coiteux C, JG T, Fullum G. Huntington's chorea in French Canadians. Preliminary study. Union Med Can. 1964;93:1178-82.
52. Shokeir MHK. Investigations on Huntington's disease in the Canadian Prairies: I. Prevalence. Clin Genet. 1975;7(4):345-8.
53. Wexler A. Stigma, history, and Huntington's disease. Lancet. 2010;376(9734):18-9.
54. Moldovean SN, Chiş V. Molecular dynamics simulations applied to structural and dynamical transitions of the huntingtin protein: a review. ACS chemical neuroscience. 2019; 16;11(2):105-20.
55. Iennaco R, Formenti G, Trovesi C, Rossi RL, Zuccato C, Lischetti T, *et al.* The evolutionary history of the polyQ tract in huntingtin sheds light on its functional pro-neural activities. Cell Death and Differentiation. 2022;29(2):293-305.
56. Beckerman M, Beckerman M. Huntington's disease and other unstable repeat disorders. Fundamentals of Neurodegeneration and Protein Misfolding Disorders. 2015: 301-32.
57. Luo S, Vacher C, Davies JE, Rubinsztein DC. Cdk5 phosphorylation of huntingtin reduces its cleavage by caspases: implications for mutant huntingtin toxicity. J Cell Biol. 2005;169(4):647-56.
58. Pengo M, Squitieri F. Beyond CAG Repeats: The Multifaceted Role of Genetics in Huntington Disease. Genes. 2024;19;15(6):807.
59. Huang WJ, Chen WW, Zhang X. Huntington's disease: Molecular basis of pathology and status of current therapeutic approaches. Experimental and therapeutic medicine. 2016;12(4):1951-6.
60. Gafni J, Ellerby LM. Calpain activation in Huntington's disease. J Neurosci. 2002;22(12):4842-9.
61. Lunkes A, Lindenberg KS, Ben-Häiem L, Weber C, Devys D, Landwehrmeyer GB, *et al.* Proteases acting on mutant huntingtin generate cleaved products that differentially build up cytoplasmic and nuclear inclusions. Mol Cell. 2002;10(2):259-69.
62. Papoutsi M, Labuschagne I, Tabrizi SJ, Stout JC. The cognitive burden in Huntington's disease: pathology, phenotype, and mechanisms of compensation. Mov Disord. 2014;29(5):673-83.
63. Balaban ÖD, Atbaşoğlu CE. Neuropsychiatric Aspects of Huntington's Disease. Psikiyatride Guncel Yaklasimlar. 2022;14(1):98-112.
64. Rohrer D, Salmon DP, Wixted JT, Paulsen JS. The disparate effects of Alzheimer's disease and Huntington's disease on semantic memory. Neuropsychology. 1999;13(3):381.
65. Hoth KF, Paulsen JS, Moser DJ, Tranel D, Clark LA, Bechara A. Patients with Huntington's disease have impaired awareness of cognitive, emotional, and functional abilities. J Clin Exp Neuropsychol. 2007;29(4):365-76.
66. Rosenblatt A, Liang KY, Zhou H, Abbott MH, Gourley LM, Margolis RL, *et al.* The association of CAG repeat length with clinical progression in Huntington disease. Neurology. 2006;66(7):1016-20.
67. Feigin A, Kieburtz K, Bordwell K, Como P, Steinberg K, Sotack J, *et al.* Functional decline in Huntington's disease. Mov Disord Off J Mov Disord Soc. 1995;10(2):211-4.
68. Bachoud-Levi AC, Ferreira J, Massart R, Youssov K, Rosser A, Busse M, *et al.* International guidelines for the treatment of Huntington's disease. Frontiers in neurology. 2019;10:710.
69. Tabrizi SJ, Langbehn DR, Leavitt BR, Roos RAC, Durr A, Craufurd D, *et al.* Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurol. 2009;8(9):791-801.
70. Zadegan SA, Kupcha L, Patino J, Rocha NP, Teixeira AL, Stimming EF. Obsessive-compulsive and perseverative behaviors in Huntington's disease. Behav Brain Res. 2024;26; 458:114767.
71. Ajitkumar A, De Jesus O. Huntington disease. InStatPearls [Internet] 2023. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/sites/books/NBK559166/
72. Caron NS, Wright GEB, Hayden MR. Huntington Disease. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. University of Washington, Seattle; Seattle (WA):1998.
73. Sanberg PR, Calderon SF, Giordano M, Tew JM, Norman AB. The quinolinic acid model of Huntington's disease: locomotor abnormalities. Exp Neurol. 1989;105(1):45-53.
74. Kaye J, Reisine T, Finkbeiner S. Huntington's disease mouse models: unraveling the pathology caused by CAG repeat expansion. Faculty reviews. 2021;21;10:77.
75. Perez-De La Cruz V, Santamaria A. Integrative hypothesis for Huntington's disease: a brief review of experimental evidence. Physiol Res. 2007;56(5):513-26.
76. Alston TA, Mela L, Bright HJ. 3-Nitropropionate, the toxic substance of Indigofera, is a suicide inactivator of succinate dehydrogenase. Proc Natl Acad Sci. 1977;74(9):3767-71.
77. Coles CJ, Edmondson DE, Singer TP. Inactivation of succinate dehydrogenase by 3-nitropropionate. J Biol Chem. 1979;254(12):5161-7.
78. Ming L. Moldy sugarcane poisoning—a case report with a brief review. J Toxicol Clin Toxicol. 1995;33(4):363-7.
79. Browne SE, Bowling AC, Macgarvey U, Baik MJ, Berger SC, Muquit MMK, *et al.* Oxidative damage and metabolic dysfunction in Huntington's disease: selective vulnerability of the basal ganglia. Ann Neurol Off J Am Neurol Assoc Child Neurol Soc. 1997;41(5):646-53.
80. Gu M, Gash MT, Mann VM, Javoy-Agid F, Cooper JM, Schapira AH V. Mitochondrial defect in Huntington's disease caudate nucleus. Ann Neurol Off J Am Neurol Assoc Child Neurol Soc. 1996;39(3):385-9.
81. Browne SE, Bowling AC, Macgarvey U, Baik MJ, Berger SC, Muquit MMK, *et al.* Oxidative damage and metabolic dysfunction in Huntington's disease: selective vulnerability of the basal ganglia. Ann Neurol Off J Am Neurol Assoc Child Neurol Soc. 1997;41(5):646-53.
82. Ouary S, Bizat N, Altairac S, Menetrat H, Mittoux V, Conde F, *et al.* Major strain differences in response to chronic systemic administration of the mitochondrial toxin 3-nitropropionic acid in rats: implications for neuroprotection studies. Neuroscience. 2000;97(3):521-30.
83. Palfi S, Ferrante RJ, Brouillet E, Beal MF, Dolan R, Guyot MC, *et al.* Chronic 3-nitropropionic acid treatment in baboons replicates the cognitive and motor deficits of Huntington's disease. J Neurosci. 1996;16(9):3019-25.
84. Singal SA, Briggs AP, Sydenstricker VP, Littlejohn JM. The effect of tryptophane on the urinary excretion of nicotinic acid in rats. J Biol Chem. 1946;166:573-9.
85. Henderson LM, Hirsch HM. Quinolinic acid metabolism. 1. Urinary excretion by the rat following tryptophan and 3-hydroxyanthranilic acid administration. J Biol Chem. 1949;181:667-75.
86. Ruddick JP, Evans AK, Nutt DJ, Lightman SL, Rook GAW, Lowry CA. Tryptophan metabolism in the central nervous system: medical implications. Expert Rev Mol Med. 2006;8(20):1-27.
87. Schwarcz R, Okuno E, White RJ, Bird ED, Whetsell Jr WO. 3-Hydroxyanthranilate oxygenase activity is increased in the brains of Huntington disease victims. Proc Natl Acad Sci. 1988;85(11):4079-81.
88. Tatter SB, Galpern WR, Hoogeveen AT, Isacson O. Effects of striatal excitotoxicity on huntingtin-like immunoreactivity. Neuroreport. 1995;6(8):1125-9.
89. Foster AC, Miller LP, Oldendorf WH, Schwarcz R. Studies on the disposition of quinolinic acid after intracerebral or systemic administration in the rat. Exp Neurol. 1984;84(2):428-40.

90. Bordelon YM, Chesselet M, Nelson D, Welsh F, Erecińska M. Energetic dysfunction in quinolinic acid-lesioned rat striatum. J Neurochem. 1997;69(4):1629-39.
91. Kendall AL, David F, Rayment G, Torres EM, Annett LE, Dunnett SB. The influence of excitotoxic basal ganglia lesions on motor performance in the common marmoset. Brain. 2000;123(7):1442-58.
92. McLin JP, Thompson LM, Steward O. Differential susceptibility to striatal neurodegeneration induced by quinolinic acid and kainate in inbred, outbred and hybrid mouse strains. Eur J Neurosci. 2006;24(11):3134-40.
93. Vazey EM, Chen K, Hughes SM, Connor B. Transplanted adult neural progenitor cells survive, differentiate and reduce motor function impairment in a rodent model of Huntington's disease. Exp Neurol. 2006;199(2):384-96.
94. Borlongan C V, Randall TS, Cahill DW, Sanberg PR. Asymmetrical motor behavior in rats with unilateral striatal excitotoxic lesions as revealed by the elevated body swing test. Brain Res. 1995;676(1):231-4.
95. Borlongan C V, Saporta S, Sanberg PR. Intrastriatal transplantation of rat adrenal chromaffin cells seeded on microcarrier beads promote long-term functional recovery in hemiparkinsonian rats. Exp Neurol. 1998;151(2):203-14.
96. McBride JL, During MJ, Wuu J, Chen EY, Leurgans SE, Kordower JH. Structural and functional neuroprotection in a rat model of Huntington's disease by viral gene transfer of GDNF. Exp Neurol. 2003;181(2):213-23.
97. Furtado JCS, Mazurek MF. Behavioral characterization of quinolinate-induced lesions of the medial striatum: relevance for Huntington's disease. Exp Neurol. 1996;138(1):158-68.
98. Shear DA, Dong J, Haik-Creguer KL, Bazzett TJ, Albin RL, Dunbar GL. Chronic administration of quinolinic acid in the rat striatum causes spatial learning deficits in a radial arm water maze task. Exp Neurol. 1998;150(2):305-11.
99. Isacson O, Brundin P, Kelly PAT, Gage FH, Björklund A. Functional neuronal replacement by grafted striatal neurones in the ibotenic acid-lesioned rat striatum. Nature. 1984;311(5985):458-60.
100. Burns LH, Pakzaban P, Deacon TW, Brownell AL, Tatter SB, Jenkins BG, Isacson O. Selective putaminal excitotoxic lesions in non-human primates model the movement disorder of Huntington disease. Neuroscience. 1995;64(4):1007-17.
101. Camerino I, Ferreira J, Vonk JM, Kessels RP, de Leeuw FE, Roelofs A, Copland D, Piai V. Systematic review and meta-analyses of word production abilities in dysfunction of the basal ganglia: Stroke, small vessel disease, Parkinson's disease, and Huntington's disease. Neuropsychol Rev. 2024;34(1):1-26.
102. Nicholson LFB, Faull RLM, Waldvogel HJ, Dragunow M. GABA and GABAA receptor changes in the substantia nigra of the rat following quinolinic acid lesions in the striatum closely resemble Huntington's disease. Neuroscience. 1995;66(3):507-21.
103. Beal MF, Mazurek MF, Ellison DW, Swartz KJ, McGarvey U, Bird ED, Martin JB. Somatostatin and neuropeptide Y concentrations in pathologically graded cases of Huntington's disease. Ann Neurol Off J Am Neurol Assoc Child Neurol Soc. 1988;23(6):562-9.
104. Roberts RC, Ahn A, Swartz KJ, Beal MF, DiFiglia M. Intrastriatal injections of quinolinic acid or kainic acid: differential patterns of cell survival and the effects of data analysis on outcome. Exp Neurol. 1993;124(2):274-82.
105. Coyle JT, Schwarcz R. Lesion of striatal neurons with kainic acid provides a model for Huntington's chorea. Nature. 1976;263(5574):244-6.
106. Blum D, Gall D, Cuvelier L, Schiffmann SN. Topological analysis of striatal lesions induced by 3-nitropropionic acid in the Lewis rat. Neuroreport. 2001;12(8):1769-72.
107. Naver B, Stub C, Møller M, Fenger K, Hansen AK, Hasholt L, Sørensen SA. Molecular and behavioral analysis of the r6/1 huntington' s disease transgenic mouse. Neuroscience. 2003;122(4):1049-57.
108. Mangiarini L, Sathasivam K, Seller M, Cozens B, Harper A, Hetherington C, Lawton M, Trottier Y, Lehrach H, Davies SW. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. Cell. 1996;87(3):493-506.
109. Sun Z, Del Mar N, Meade C, Goldowitz D, Reiner A. Differential changes in striatal projection neurons in R6/2 transgenic mice for Huntington's disease. Neurobiol Dis. 2002;11(3):369-85.
110. Stack EC, Kubilus JK, Smith K, Cormier K, Del Signore SJ, Guelin E, *et al.* Chronology of behavioral symptoms and neuropathological sequela in R6/2 Huntington's disease transgenic mice. J Comp Neurol. 2005;490(4):354-70.
111. Turmaine M, Raza A, Mahal A, Mangiarini L, Bates GP, Davies SW. Nonapoptotic neurodegeneration in a transgenic mouse model of Huntington's disease. Proc Natl Acad Sci. 2000;97(14):8093-7.
112. Lüesse HG, Schiefer J, Spruenken A, Puls C, Block F, Kosinski CM. Evaluation of R6/2 HD transgenic mice for therapeutic studies in Huntington's disease: behavioral testing and impact of diabetes mellitus. Behav Brain Res. 2001;126(1-2):185-95.
113. Lione LA, Carter RJ, Hunt MJ, Bates GP, Morton AJ, Dunnett SB. Selective discrimination learning impairments in mice expressing the human Huntington's disease mutation. J Neurosci. 1999;19(23):10428-37.
114. Van Raamsdonk JM, Pearson J, Slow EJ, Hossain SM, Leavitt BR, Hayden MR. Cognitive dysfunction precedes neuropathology and motor abnormalities in the YAC128 mouse model of Huntington's disease. J Neurosci. 2005;25(16):4169-80.
115. McBride JL, Ramaswamy S, Gasmi M, Bartus RT, Herzog CD, Brandon EP, *et al.* Viral delivery of glial cell line-derived neurotrophic factor improves behavior and protects striatal neurons in a mouse model of Huntington's disease. Proc Natl Acad Sci. 2006;103(24):9345-50.
116. McBride JL, Ramaswamy S, Kordower JH. GDNF gene therapy in the N171-82Q transgenic mouse model of Huntington's disease. In: experimental neurology. Academic press inc elsevier science 525 B ST, STE 1900, SAN DIEGO, CA 92101; 2004. p. 214.
117. Hodgson JG, Agopyan N, Gutekunst CA, Leavitt BR, LePiane F, Smith DJ, *et al.* A YAC mouse model for Huntington's disease with full-length mutant huntingtin, cytoplasmic toxicity, and selective striatal neurodegeneration. Neuron. 1999;23(1):181-92.
118. Slow EJ, Van Raamsdonk J, Rogers D, Coleman SH, Graham RK, Deng Y, *et al.* Selective striatal neuronal loss in a YAC128 mouse model of Huntington disease. Hum Mol Genet. 2003;12(13):1555-67.
119. Van Dellen A, Welch J, Dixon RM, Cordery P, York D, Styles P, *et al.* N-Acetylaspartate and DARPP-32 levels decrease in the corpus striatum of Huntington's disease mice. Neuroreport. 2000;11(17):3751-7.
120. Menalled LB, Sison JD, Dragatsis I, Zeitlin S, Chesselet M. Time course of early motor and neuropathological anomalies in a knock-in mouse model of Huntington's disease with 140 CAG repeats. J Comp Neurol. 2003;465(1):11-26.
121. Lin CH, Tallaksen-Greene S, Chien WM, Cearley JA, Jackson WS, Crouse AB, *et al.* Neurological abnormalities in a knock-in mouse model of Huntington's disease. Hum Mol Genet. 2001;10(2):137-44.
122. Yu ZX, Li SH, Evans J, Pillarisetti A, Li H, Li XJ. Mutant huntingtin causes context-dependent neurodegeneration in mice with Huntington's disease. J Neurosci. 2003;23(6):2193-202.
123. Wu J, Nan Wu J, Chen T, Cai J, Ren R. Protein Aggregation and its Affecting Mechanisms in Neurodegenerative Diseases. Neurochemistry International. 2024; 11:105880.
124. Casas-Tintó S. Drosophila as a Model for Human Disease: Insights into Rare and Ultra-Rare Diseases. Insects. 2024; 6;15(11):870.
125. Smith KM, Matson S, Matson WR, Cormier K, Del Signore SJ, Hagerty SW, *et al.* Dose ranging and efficacy study of high-dose coenzyme Q10 formulations in Huntington's disease mice. Biochim Biophys Acta (BBA)-Molecular Basis Dis. 2006;1762(6):616-26.
126. Kašparová S, Sumbalová Z, Bystrický P, Kucharská J, Liptaj T, Mlynárik V, Gvozdjáková A. Effect of coenzyme Q10 and vitamin E on brain energy metabolism in the animal model of Huntington's disease. Neurochem Int. 2006;48(2):93-9.
127. Stack EC, Smith KM, Ryu H, Cormier K, Chen M, Hagerty SW, *et al.* Combination therapy using minocycline and coenzyme Q10 in R6/2 transgenic Huntington's disease mice. Biochim Biophys Acta (BBA)-Molecular Basis Dis. 2006;1762(3):373-80.
128. Harper SQ, Staber PD, He X, Eliason SL, Martins IH, Mao Q, *et al.* RNA interference improves motor and neuropathological abnormalities in a Huntington's disease mouse model. Proc Natl Acad Sci. 2005;102(16):5820-5.
129. Machida Y, Okada T, Kurosawa M, Oyama F, Ozawa K, Nukina N. rAAV-mediated shRNA ameliorated neuropathology in Huntington disease model mouse. Biochem Biophys Res Commun. 2006;343(1):1

Cite this article: Diwakar D, Khan S, Iodha S, Pal D, Kumar D, Kumar D, *et al.* Animal Models and Pathogenesis on Neurodegenerative Disorders (Huntington's Disease): An Updated Review. Indian J of Pharmaceutical Education and Research. 2026;60(2):494-510.