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CURRENT APPROACHES TO TREAT HUNTINGTON'S DISEASE- A REVIEW

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ABSTRACT

Huntington's disease (HD) is an autosomal inherited progressive neurodegenerative disease caused by a single mutation in the gene IT15 which codes for the protein huntingtin that result in an expanded polyglutamine stretch in the NH_2 terminus of huntingtin protein (HTT). HD results from destruction of the GABAergic medium-sized spiny neurons (MSNs), which constitute 95% of all striatal neurons. MSNs are projection neurons that primarily innervate the substantia nigra and globus pallidus. Oxidative stress, apoptosis, mitochondrial and metabolic dysfunction, neuroinflammation, excitotoxicity, impaired ubiquitin proteosome activity, defective autophagy-lysosomal function, transcriptional dysregulation are considered to be major contributing factors in mediating pathogenesis of HD. BDNF, Glutamate and Nrf2 plays important role in Huntington's disease. Oxidative stress can be decreased by increasing the concentration of BDNF and Nrf2. The prevalence of HD is much higher in European populations than in East Asia. HD affects approximately 5-10 individuals per 1, 00,000 individuals. There is no cure for Huntington's disease, but various symptomatic treatments are available for it. Different drugs like SSRI, Lithium, and Memantine are available for symptomatic relief in Huntington's disease. Terabenazine is only one FDA approved drug for Huntington's disease. Now a day gene silencing therapies are available for Huntington's disease. Various drugs like Autophagy enhancer, HDAC inhibitor, and Caspase inhibitor are also under the investigation which may become disease slowing treatment for Huntington's disease. Stem cells also used in the treatment of Huntington's disease. Various Animal models and transgenic models are available from which we can evaluate the potential of drugs used in Huntington's disease. We summarize main papers for pathology, genetic basis for the Huntington's disease and new approaches for the treatment of Huntington's disease.

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INTRODUCTION

Neurodegeneration is the progressive loss of the structure or functions of neurons. Neurons are the building blocks of the nervous system which include Brain and spinal cord. Neurons normally do not reproduce or replace themselves, so when they become damaged or die they cannot be replaced by body. Neurodegenerative diseases are caused by genetic mutation, protein misfolding, protein degradation pathway, membrane damage, mitochondrial dysfunction. Many neurodegenerative diseases including amyotrophic lateral sclerosis (ALS), Parkinson's, Alzheimer's, and Huntington's disease (HD) occurs as result of neurodegeneratation. [1, 2]

HD is the autosomal inherited progressive dominant neurodegenerative disorder caused by single mutation in the HTT gene which codes for the protein Huntingtin that result in an expanded polyglutamine cytosine-adenine-guanine (CAG) nucleotide repeat sequence in the NH2 terminus of huntingtin protein (HTT). Physiological HTT is ubiquitously expressed and implicated in several cellular functions including control of transcription, neurogenesis, axonal transport and brain derived neurotrophic factor (BDNF) production. The principal neuropathological hallmarks of disease include loss of striatal and cortical projection neurons. In the neostriatum, the GABAergic medium-sized spiny neurons (MSNs), which constitute 95% of all striatal neurons, are the most affected. HD affects approximately 5-10 individuals per 1, 00,000 individuals and associated with progressive motor and cognitive impairments, loss of self and spatial awareness, depression, dementia, and increased anxiety. Oxidative stress, apoptosis, mitochondrial and metabolic dysfunction, neuro inflammation, excitotoxicity, impaired ubiquitin proteosome activity, defective autophagy-lysosomal function, transcriptional dysregulation are considered to be major contributing factors in mediating pathogenesis of HD. [3-6]

Nrf2 is the redox sensitive transcription factor required for the synthesis of glutathione a natural antioxidant that play important role in HD. Brain Derived Neurotropic Factor also play important role in the survival and activity of the neurons that die in Huntington's disease. Glutamate is also having central role in HD pathogenesis. [7, 8, 9]

There is no cure for Huntington's disease but different symptomatic drugs are available for HD. Hence enormous progress has been made in the laboratories throughout the world. There are different drugs which may become treatment for Huntington's disease. New advancement also takes place like use of genetically altered stem cell. There are different models available for Huntington's disease like excitotoxic models, genetic models and metabolic models. [10, 11]Our Review covers the pathogenesis of Huntington's disease relevant to current and potential future therapeutic targets.

HUNTINGTONS DISEASE:

HD is genetic autosomal progressive neurodegenerative disorder that affects muscle coordination and lead to cognitive decline and dementia. [1, 2,]HD is caused by genetic mutation in the IT 15 gene which encodes for a protein called Huntingtin**.** [3, 4,5]The mutation results in an elongated stretch of Glutamine near the NH_2 terminals. [12] Due to which there is defect in a part of DNA called CAG repeat which is normally repeated 10 to 28 time but in person with HD it is repeated 36 to 120 time. (**Fig.No.1)** It is much common in people of western European decent than in those of Asian or African**.** [5, 6, 12]Huntington's disease has autosomal dominant inheritance, meaning that an affected individual typically inherits one copy of the gene with an expanded trinucleotide repeat (the mutant allele) from an disease affected parent.

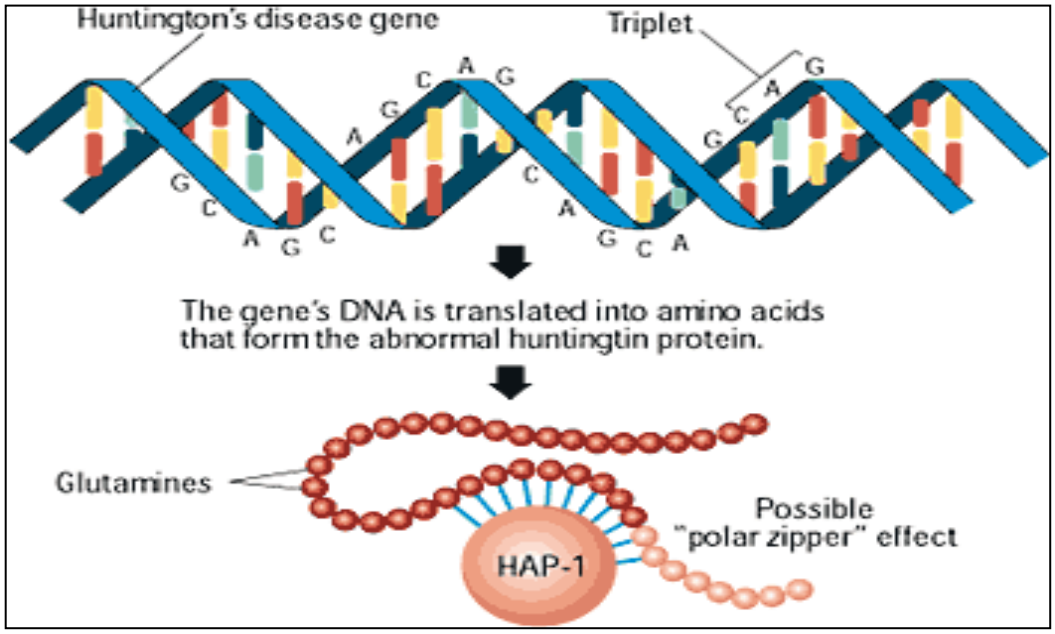

Fig No. 1 Mechanism of Huntington's disease.

HTT is found in all mammalian cells with highest expression in the brain and testes, moderate amounts in the liver, heart, and lungs. The expression of pathological HTT has been reported to be the highest in the striatum nuclei of brain. The regions most affected are the striatum, where there is typically 50-60% loss of cross-sectional area from the caudate nucleus and the putamen. MSNs show dentritic changes including recurving of dentrites and altered density, shape and size of spines.[13] Oxidative stress, apoptosis, mitochondrial and metabolic dysfunction, neuroinflammation, excitotoxicity, impaired ubiquitin proteosome activity, defective autophagy-lysosomal function, transcriptional dysregulation are considered to be major contributing factors in mediating pathogenesis of HD.[5] Symptoms are noticeable between the ages of 35 to 44 year. There is an inverse relationship between CAG repeat number and the age of onset of symptoms. Greater the number of CAG repeats, earlier the age of onset. Most adult onset cases have 40-50 CAG repeats, whereas expansions of >55 repeats frequently cause juvenile-onset disease.[1,4, 13] Physical symptoms are the jerky, random and uncontrollable movements called chorea which precede more signs of motor dysfunction by at least 3 years. Cognitive abilities are progressively impaired especially affected are executive functions which include planning, cognitive flexibility, abstract thinking, rule acquisition, initiation of appropriate actions, and inhibition of inappropriate actions. [1, 3, 12]

PATHOLOGY OF HD

Oxidative Stress

Oxidative stress is caused by the imbalance in the production of reactive oxygen species (ROS) and inability of the biological system to detoxify those species and repair the resulting damage. Oxidative stress includes lipid peroxidation, protein oxidation and DNA mutation which forms oxidative damage products such as malondialdehyde, 8-hydroxydeoxyguanosine, 3-nitrotyrosine and hemeoxygenase that found in areas of degeneration in HD brain. An increase in intracellular Ca^{2+} can activate phospholipase A_2 (PLA_2) and Ca^{2+} dependent proteases. PLA_2 activity results in increased production of arachidonic acid, and the subsequent metabolism of arachidonic acid can induce formation of free radicals. Hydrogen peroxides and superoxides are formed through the activation of Ca^{2+} dependent proteases, and hydrogen peroxide can be converted to hydroxyl radicals, thereby contributing to neurotoxicity. [5, 6, 14]

Excitotoxicity

Excitotoxicity may play a major role in the pathogenesis of HD. Glutamate plays a central role in excitotoxicity. There are different classes of glutamate receptors. The ionotropic receptors are (i) *N*-methyl-D-aspartate (NMDA)-receptor, sensitive to NMDA and quinolinic acid, (ii) α-amino-3- hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor, sensitive to AMPA and kainic acid, and (iii) kainic acid (quisqualate) receptor, sensitive to kainic acid and quisqualic acid. The alteration in Ca^{2+} handling in neurons results in slower recovery rate of cytosolic Ca^{2+} concentration. (Fig.No 2) Upon activation, the NMDA receptor channel becomes permeable to Ca^{2+} and Na^{+}. Metabotropic receptors are thought to enhance NMDA receptor- mediated Ca^{2+} entry through phospholipase coupled protein kinase C activation leads to primarily degeneration of the medium-sized GABAergic spiny efferent neurons projecting from the striatum to the globus pallidus and pars reticulata of the substantia nigra. There is also depletion of NMDA receptor. [5, 6, 13]

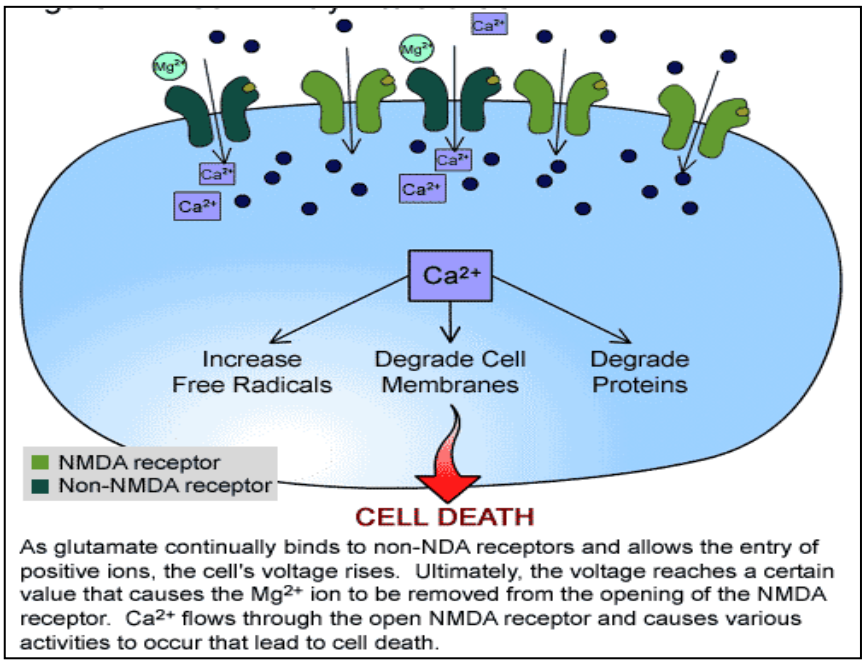

Fig No. 2 Calcium Homeostasis.

Energy impairment

Activation of plasma membrane receptor coupled with G protein leads to IP_3 production which opens calcium channel in IP_3 receptor and releases Ca^{2+} stored in endoplasmic reticulum (ER). Store depletion activate store-operated calcium channel (SOC) and causes Ca^{2+} influx from extracellular space. Passive calcium leak from ER is counterbalanced by Ca^{2+} uptake by sarco-endoplasmic reticulum calcium ATP-ase (SERCA). Similarly to receptor-dependent signal, SERCA inhibition leads to ER depletion which activates store-operated calcium entry (SOCE). [15] Impaired energy metabolism reduces the threshold for glutamate toxicity. Energy depletion can result in partial depolarization of the outer membrane and thereby release the voltage dependent Mg^{2+} ion block of the Ca^{2+} channel in the NMDA receptor complex. When this inhibition has been removed, Ca^{2+} enters the cell more readily after stimulation by glutamate, resulting in the excitotoxic cascade that involves oxidative stress and decreased Ca^{2+} homeostasis.[6] Recent trials in humans have used Remacemide a non competitive NMDA receptor antagonist and lamotrigine which blocks voltage gated sodium channels inhibiting glutamate release.[13]

Transcriptional dysregulation

The expression of mHTT has effects on the transcriptome. mHTT interacts with and disrupts, major components of the general transcriptional machinery, affecting both general promoter accessibility and recruitment of RNA polymerase II. Soluble mHTT oligomers interact with and impede the function of specificity protein 1 (SP1), TATA box binding protein (TBP), the TFIID subunit TAFII130, the RAP30 subunit of the TFIIF complex, and the CAAT box transcription factor NF-Y, all of which are important mediators of general promoter accessibility and transcription initiation. mHTT can bind transcription factors (TFs) and sequesters them into mHTT inclusions. mHTT loses the capacity to bind to transcriptional repressors allowing them to get into the nucleus and represses transcription. Transcription depends on the acetylation status of histones, regulated by activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs). (Fig No.3) The expression of mHTT also disrupts the activity of histone acetyl transferases (HATs). [4]

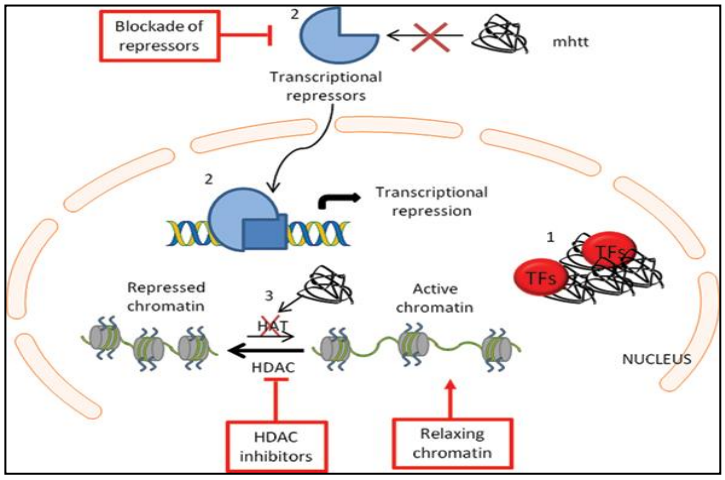

Fig No. 3 Transcriptional Dysregulation.

Apoptosis

Apoptosis is the programmed cell death which is morphologically characterized by membrane blebbing, perinuclear chromatin condensation, swelling of the organelles, and endonuclease mediated internucleosomal DNA fragmentation .overexcitation of NMDA receptor and gradual energy disturbances may lead to release of proapoptic factors from the mitochondria, such as cytochrome C leading to apoptic cell death.[6, 16]

Role of NrF2 Activators in HD

Intracellular redox state is regulated by glutathione (GSH) which is tripeptide consisting of glutamate, cysteine and glycine. It can non-enzymatically detoxify ROS such as superoxide dismutase, hydroxyl radicals and acts as an electron donor for the reduction of peroxides catalyzed by glutathione peroxidase. In neurodegenerative diseases neurons need an optimal GSH supply to defend themselves against free radicals released from activated microglia and astroglia. The rate of GSH synthesis is controlled largely by the activity of γ-glutamyl cysteine ligase. Expression of γ-glutamyl cysteine ligase and of the Xc- system, which facilitates cystine uptake, is regulated by the redox-sensitive transcription factor, nuclear factor erythroid-2-related factor 2 (Nrf2).Extracellular GSH released by astrocytes is metabolized by γ- glutamyltranspeptidase to form the dipeptide, cysteinglycine (cysgly) which is then processed by neuronal electropeptidase, aminopeptidase N, allowing neurons to immediately take up the resultant cysteine and glycine. [7]

Role of Brain Derived Neurotropic Factor (BDNF) in HD

Brain derived neurotropic factor is a small dimeric protein of the NGF family. Particularly abundant in the hippocampus and cerebral cortex where it is transported to its Striatal targets *via* the corticostriatal afferents and also found in the basal forebrain, brainstem, cerebellum. Striatal neurons in the brain required BDNF for their activity and survival. Impaired regulation of BDNF expression has been implicated in mood anxiety disorders, aging, cognitive and neurodegenerative disorders. [17, 18] BDNF having survival promoting activity on the Striatal neurons that dies in HD. It gives idea about that reduced endogenous tropic support may contribute to disease onset and its progression. BDNF controls a variety of brain processes including the growth, development, differentiation and maintenance of neuronal systems, neuronal plasticity, synoptic activity and neurotransmitter mediated activities. Delivery of therapeutically significant amounts of NTFs is challenging. Delivery of many other NTFs, including BDNF, into the HD brain remains a challenge, due to the fact that many NTFs are large, polarized proteins that do not readily cross the blood-brain-barrier, relegating the delivery of NTFs directly into the central nervous system.[8]

Treatment for Huntington's disease [19]

Table No. 1 Treatment for Huntington's disease.

Sr.No.	Class	Examples
01	Antidepressant	Amitriptyline Mirtazapine, duloxetine & venlafaxine
02	Mood stabilizers to treat irritability	Carbamazepine
03	Drugs to suppress involuntary movements	
	Antipsychotic	Risperidone, olanzapine &Quetiapine
	Benzodiazepines Tetrabenazine	Clonazepam Diazepam

Some drugs that increases BDNF level are useful in HD [8]

Serotonin

Serotonin may have protective effect on striatal and cortical neurons by activating cyclic AMP and CREB signals which also leads to BDNF expression. Bcl-2 and NFKB also play important role in neuroprotective effect of SSRIs.

Lithium

Lithium induces the expression of BDNF and TrkB in cortical neurons. The mechanisms underlying this effect include a lithium mediated reduction in excitotoxicity as a result of increased glutamate uptake, and the regulation of a number of signal transduction intermediates such as myo-inositol, protein kinase C, phosphotidylinositol-3 kinase (PI-3K)/protein kinase B(AKT), ras-mitogen-activated protein kinase (MAPK), glycogen Synthase kinase (GSK)-3 alpha and -3beta, and calcium.

Memantine

It markedly increases BDNF and TrkB mRNA levels in rat brain.

FDA approves first drug for Huntington's disease

The US Food and Drug Administration have approved xenazine (Tetrabenazine) for the treatment of chorea associated with Huntington's disease. Xenazine is only one and first FDA approved treatment for any symptoms of HD. The drug is already widely used in Europe, Canada and Australia to treat one of the most disabling symptoms of HD, involuntary writhing movements known as chorea. Chorea is one of the treadmark symptoms of the HD. [20-26]

Hope for disease slowing treatment

Improvement in a model of HD

If the HD gene is switched off in a mouse model of HD even after clinical signs develop, improvement can be seen in brain cells and clinical signs. This gives us reason to believe that, if we can introduce successful treatments in humans, patients may improve clinically, even after they have begun to experience symptoms of HD. [27]

Gene silencing therapy

Gene silencing drugs which tell cells to stop making harmful Huntingtin protein. The Huntingtin gene which is made up from DNA acts as recipe for the Huntingtin protein. When the gene is switched on (transcription), a messenger molecule called mRNA is produced before the protein is built by the cell (translation).But cells make working copy of the gene containing instructions that are read again and again to build the protein many times. Gene silencing drugs are carefully designed to attach to the message molecule of the chosen protein. So that it cannot be read and less of its protein get made. One major problem with gene silencing is getting the molecule where they are needed. RNA and DNA molecule do not enter the brain easily and getting them to spread through the whole brain is difficult. There are several flavors of gene silencing that use slightly different chemical structures and methods of getting the drug into the brain. Antisense oligonucleotides (ASO) are a particular flavor of gene silencing that happens to be able to spread quite well through the nervous system when injected into cerebrospinal fluid and are able to cross BBB.[28, 29, 30]Antisense oligonucleotides are synthetic single stranded strings of nucleic acids, between 8 and 50 nucleotides in length, that bind to RNA.

Depending on sequence and modifications, antisense oligonucleotides can alter RNA function through several distinct mechanisms.[31]Using primary cells from patient with Huntington's disease and the transgenic YAC 18 and BACHD mouse lines antisense oligonucleotide (ASO) were prepared that potently and selectively silence mHTT at both exonic and intronic Single Nucleotide Polymorphism (SNP) site. By using adeno associated viral (AAV) vector a targeted nucleic acid sequence called small interfering RNA was delivered into the cells of affected mice then this siRNA selectively binds to the mutated gene, blocking disease causing Htt production. [32]

Autophagy enhancer

Autophagy is a clearance process and a major degradation pathway for various intracytosolic aggregates prone, disease causing proteins associated with neurodegenerative disorders such as mutant huntingtin.[33] autophagy includes three major types: macroautophagy, microautophagy, and chaperone mediated autophagy (CMA).[34] Some autophagy enhancers are Rapamycin, Glucose, Lithium Carbamazepine, Sodium valproate, Verapamil, Loperamide, Clonidine, Amidarone**.** The mammalian target of rapamycin (mTOR)complex integrates a number of signals that monitor the energy status of cells and negatively regulates autophagosome biogenesis.[30]Rapamycin belongs to a group of drug called mTOR inhibitors which acvtivate autophagy and it has been shown to slow down HD in a mouse model.[33-36]

HDAC inhibitor

Control of which genes are switched on and off is really important for enabling cells to survive. Histones can be opened or locked. Unlocked histones have a chemical tag called acetyl attached to them. Locked histones do not have an acetyl tag, which causes them to wrap up more tightly, keeping the DNA on it hidden from the cell.[37] The acetyl group is the key to keeping the histones unlocked and the DNA around them loose so cells can read it. Histone acetyl-transferase enzymes (HATs) are the machines that tell histones to 'unlock' by adding the acetyl tag. The machines that remove the tags are called histone deacetylases (HDACs).HDAC is an enzyme involved in regulating which genes are switched on and which are switched off. Some HADC inhibitors particularly SAHA have been shown to be effective in slowing down the cellular damage in HD. Two categories of HDACs have been identified- the zinc-dependent ones and the nicotinamide adenine-dinucleotide (NAD) dependent sirtuins.[38, 39]

Caspase Inhibitor

In cells, the abnormal HD protein (huntingtin) is cut into smaller proteins by enzymes called caspases. Some of the smaller fragments that are produced by this are more damaging to cells than the original full-length huntingtin. So, by turning off the caspases, the dangerous huntingtin fragments might be prevented from forming. Minocycline and Doxycycline are the drugs that act as a caspase inhibitor. There are 11 types of caspase, and caspase 6 is thought to be the one that generates the most toxic huntingtin fragment. Work is underway to develop and test inhibitors of caspase 6 that might be more powerful than minocycline, but with fewer side effects.[40]

p53 pathway

p53 is a cell protein with many functions, but it is known to be involved in energy production, the response to stress and controlling when cells divide. Recently, it has been shown that p53 accumulates in the brain cells most affected by HD, and that the huntingtin protein and p53 interact with each other. Some effects of huntingtin might be due to abnormalities of the p53 pathway. This task is under process to target p53 pathway that drugs might be able to alter, so that the negative effects of huntingtin on cells can be minimized. [41]

Apoptosis

Apoptosis is the programmed death of cells in HD patients when brains are malfunctioning, and do undergo apoptosis, but it is also possible that the abnormal huntingtin is making cells undergo apoptosis earlier than necessary, so that relatively healthy cells die prematurely. HD researchers are looking for drugs that influence the apoptosis and help HD cells to live longer. [40-42]

Transplantation of stem cells

Stem cells are cells that can develop into any kind of cell, including brain cells. They could potentially be used to replace dead or damaged cells in the brains of HD patients. Mesenchymal Stem Cells (MSC_S) are multipotent stromal cells, which have main characteristics are plastic adherence, ability to differentiate into a diverse set of tissue within the mesoderm lineage and self-renewal. Later by research it was observed that beneficial effects were the result of a mechanism other than cell replacement. It was later observed that MSCs transplanted into a 3-nitropropionic acid (3-NP) rat model of HD improved latency to fall on the Rota rod as well as reduced the size of the lesion to the striatum, which was hypothesized to be a result of NTF release from the cells. With the knowledge that BDNF is neuroprotective, researchers have attempted to increase BDNF production from endogenous cells within the striatum via adenoviral injections or through an adeno-associated virus (AAV) vector injections into the striatum and it was observed that increases in the numbers of cells expressing dopamine- and cAMP-regulated phosphoprotein of 32 kDa which are specific for MSNs. MSCs possess beneficial properties when transplanted in the HD brain, providing a micro-environment suitable for supporting the degenerating brain, as well as long-term survival post-transplantation. It has been established that MSCs can rescue cellular dysfunction caused by mitochondrial depletion by the transfer of mitochondria through cytoplasmic extensions and that RNA and other nucleic acids can be transferred by various cell-to-cell mechanisms. Induced pluripotent stem cells (IPSC) also be a good alternative for the treatment of HD.[43-51]

Memantine

In some neurodegenerative illnesses, some of the damage is thought to be caused by too much stimulation of brain cells by incoming transmitter chemicals. This is called excitotoxicity. It is not clear whether excitotoxicity is to blame for any of the cell damage in HD, but it is a possibility. Memantine has been suggested as a possible therapy for Huntington's disease, to help with the symptoms and possibly to slow down the disease process. Memantine might also improve memory and thinking ability in patients with HD. [43, 44] Chemical miscommunication is happening in HD brains and that if we could correct it, we might have an impact on the disease. Memantine prevents excessive stimulation by a transmitter chemical called NMDA by blocking NMDA receptors. [52-55]

Cystamine and cysteamine

These drugs decrease the activity of a group of enzymes called transglutaminases. These enzymes are thought to be involved in the formation of huntingtin aggregates, the lumps of protein that are seen in unhealthy brain cells in HD. [56-59]

There are different models available for Huntington's disease. But there are important anatomic differences between the brains of humans and rodents that became especially relevant when studying HD, including the lack of a gyrencephalic (convoluted) cortex, the structure of the basal ganglia, and lack of neuromelanin in the substantia nigra. A rodent's small brain often produces the use of advances neuroimaging techniques and it is not clear how intracellular application of tropic factor, transplant therapies, and gene therapies in small animals might translate to the larger human brain. As far non-human primates, there are HD transgenic monkeys but this model faces hurdles such as limited availability, high cost (for purchase and maintenance), and a low rate of infant viability. In addition, there could be practical and ethical challenges arising from keeping a monkey with motor, cognitive and psychiatric issues for long term.

Animal models for Huntington's disease [10, 11]

There are different models available for Huntington's disease like excitotoxic models and genetic models. (Table No. 2.1 & 2.2) Yeast models of Huntington's disease have been created primarily by transgene approaches using glutamine encoding trinucleotide expansions. The sheep, Ovisaries L., is an ideal alternate mammalian model for studying Huntington's disease. Sheep are relatively easy to care. They live for more than a decade, allowing for the study of chronic effects of full length Huntington's expressing transgene. [60] The fly is also an excellent choice for modeling neurodegenerative disease because it contains a fully functional nervous system with architecture that separates specialized functions such as vision, olfaction, learning and memory [61]

Table 2.1 Excitotoxic models.

Animal model	Species	Route of administration	Mechanism of cell death	Motor symptoms	Cognitive symptoms
Quinolinic acid	Rat (Sprague-Dawley and Fischer)	Intrastriatal injections, Intraputamenal injections	Excitotoxicity	Hyperkinesia, Apomorphine induced dystonia and dyskinesia	Visuospatial deficits, procedural memory deficits, poor memory recall
3 Nitropropionic Acid (3-NP)	Rat (All except Fischer), mouse.	Systemic injections, Intrastriatal injections, intraputamenal injections	Mitochondrial impairment by irreversibly inhibiting succinate dehydrogenase	Hyperkinesia (low dose) , hypokinesia (high dose), Apomorphine induced Dystonia and dyskinesia, spontaneous dyskinesia with long-term administration	Deficits in ORDT in non humanpriaes

Table No. 2.2 Genetic models.

Animal model	Species	CAG repeat size	Motor symptoms	Cognitive symptoms
R6/2	Transgenic mouse	144	Decline on the rotarod test. Resting tremor, chorea-like movements, clasping behavior, epileptic seizures, narcolepsy, weight loss, and spontaneous shuddering movements	Increased exploratory behavior in open-field test. Deficits on Morris water maze and T maze
R6/1	Transgenic mouse	116	Body weights plateau after which they begin to decline. Gait abnormalities as measured by footprint analysis and hind limb clasping behavior	Decreased anxiety on open-field test
N171-82Q	Transgenic mouse	82	Rotarod deficits, clasping behavior, weight loss.	Deficits on radial arm water maze text of reference and working memory
N171-82Q	Transgenic mouse	82	Rotarod deficits, clasping behavior, weight loss	Deficits on radial arm water maze text of reference and working memory
YAC	Transgenic mouse	72, 128	Hyperkinesia on an open-field test. Hypokinesia on open-field test. 50% decrease in body weight compared to the Wild-type littermates. Gait abnormalities, ataxia, and hind limb clasping. Progressive decline on the rotarod test.	Deficits on T-maze
Transgenic rat	Rat	51 human derived repeats	Transgenic rats perform better on the Rotarod test compared to wild-type littermates but progressively decline thereafter. Gait abnormalities and dyskinesias of the head. Slower in traversing an elevated beam.	Deficits on radial arm maze and elevated plus maze

CONCLUSION

HD is the autosomal inherited progressive neurodegenerative disease caused by single mutation in the gene those codes for the protein Huntingtin. HD is primarily characterized by cognitive abnormality, pschychiatric deterioration loss of medium spiny neurons. BDNF and Nrf2 plays important role in Huntington's disease. There is no cure for Huntington's disease but various symptomatic drugs are available for it. Several drugs like Memantine, Autophagy enhancer, HDAC inhibitor, Caspase Inhibitor are under investigation which may become disease slowing treatment for Huntington's disease. There are different models available for HD. By using these models we can assess the activity of drugs which may have potential to treat Huntington's disease.

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