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REVIEW ARTICLE

A Review on Pathophysiology and Treatmnent Approaches of Huntington's Disease

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ABSTRACT

Huntington's disease is a complex degenerative disorder that affects the central nervous system. Huntington's disease is an autosomal-dominant, progressive neurodegenerative disorder typically presents during mid-life with a distinct phenotype, including chorea and dystonia, incoordination, cognitive decline, and behavioural difficulties. Attempts to study early disease are not unique in neurology (e.g., mild cognitive impairment and vascular cognitive impairment), but studying otherwise healthy-appearing individuals who have nearly 99% certainty of manifesting the symptoms of brain disease does provide distinct but valuable information about the true natural history of the disease. The review aims majorly on four areas namely: mehanisms, features, treatment and other aspects of Huntington's disease.

INTRODUCTION

Huntington's disease (HD) is an inherited, progressive and always fatal, neurodegenerative disorder characterized by degeneration of neurons in the striatum and cerebral cortex, which results in involuntary motor movements. It is an autosomal dominant neurodegenerative disorder characterized by involuntary movements, psychiatric disturbance, and cognitive decline. [1] [2] [3] In 1872, George Huntington (1850-1916), a medical practitioner of Pomeroy, Ohio, USA made the first complete description of this disorder among the population of Long Island in New York State. The disorder was then named after him as **Huntington's disease**. [4] Huntington's disease can begin at any age from infancy to old age, but usually begin between 35 and 44 years of age. On rare occasions, when symptoms begin before about 20 years of age, they progress faster and vary slightly, and the disease is classified as **juvenile**, **akinetic-rigid** or **Westphal variant HD**. [5] [6]

NEUROBIOLOGY OF HUNTINGTON DISEASE

The Gama-amino butyric acid (GABA-ergic) medium spiny projection neurons in the striatum are the main casualties, in contrast to the interneuron in this region which appear to be relatively spared. As the basal ganglia play a central role in the control of psychomotor behavior, disturbances in the anatomical and or biochemical integrity of these neural circuits are thought to explain the motor, cognitive and psychiatric components of the disease profile. [7]

NEUROPATHOLOGY OF HUNTINGTON DISEASE

Adult-onset HD is characterized by loss of neostriatal projection (medium spiny) neurons accompanied by reactive astrocytosis and a less severe, but prominent degeneration of the globus pallidus. Variable degrees of neurodegeneration can occur in the claustrum, subthalamic nucleus, amygdala, neocortex, Pons, olivary complex, and cerebellar cortex (i.e., Purkinje cells); Pathologic changes in nonstriatal areas consist of astrocytosis with or without mild neuronal loss. Pediatric-onset (juvenile) HD, a relatively rare entity representing less than 1% of all HD cases, presents with rigidity and seizures rather than chorea, and is associated with more widespread brain pathology than adult-onset HD. In addition to caudate, putamen, and globus pallidus, most pediatric HD cases show cerebellar atrophy with loss of Purkinje and granule cells. [8][9]

GENETIC ASPECTS OF HUNTINGTON DISEASE

The genetic defect in HD is an expansion of an unstable CAG (cytosine-adenine-guanine)

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repeat encoding polyglutamines at the 5' end of a gene on chromosome 4, termed "interesting transcript15 (IT15)". cDNA analysis reveals a predicted 348kD gene product containing 3144 amino acid termed "**huntingtin**" protein. In unaffected individuals the IT15 trinucleotide repeat typically contains 11-34 CAGs. Expansion to 35-39 CAG repeats in one or both alleles confers the likelihood of developing HD, whilst individuals with greater than 39 CAG repeats in either allele will develop the disease. [10] The trinucleotide repeat is polymorphic and undergoes alterations during meiosis generally fluctuating by 1-5 repeats per transmission, although larger increases can occur following paternal transmission. At present the physiological functions of both normal and mutant huntingtin are unknown. However it is known that several features of the HD phenotype are influenced by CAG repeat length in the mutant gene. Most individuals develop the first symptoms of HD in adulthood, although age of onset of the disease is inversely correlated with size of the CAG repeat expansion, and a small proportion of cases have a juvenile onset associated with large CAG repeat lengths. CAG repeat length has also been correlated with neuropathological severity, although this observation is controversial since grade of disease at time of death is dependent on a number of factors also influenced by repeat length, including age of onset and disease duration. [11] [12]

Table 1-Classification of the trinucleotide repeat and resulting disease status, depends on the number of CAG repeat. [13]

Repeat count	Classification	Disease status
<28	Normal	Unaffected
28–35	Intermediate	Unaffected
36–40	Reduced Penetrance	+/- Affected
>40	Full Penetrance	Affected

PATHOLOGICAL MECHANISMS OF HUNTINGTON DISEASE

The huntingtin mutations cause degeneration of neurons in the striatum resulting in uncontrolled body movements. Studies of HD patients, and of rodents given the mitochondrial toxin 3-nitropropionic acid (3NP), suggest that impaired mitochondrial function and excitotoxic death are central to the disease. 3NP induces selective damage to striatal neurons that is associated with Par-4 production, mitochondrial dysfunction, and caspase activation; blockade of Par-4 expression or caspase activation protects striatal neurons against 3NP-induced death. The ability of activation of the anti-apoptotic transcription factor NF-B to protect striatal neurons against 3NP-induced death provides further support for apoptosis as a major death pathway in HD. Caspase-8 is redistributed to an insoluble fraction in striatal tissue from HD patients, and expression of mutant huntingtin in cultured cells induces caspase-8-dependent apoptosis. Expression of mutant huntingtin in the brains of adult rats using viral vectors results in the formation of intraneuronal inclusions and cell death. However, the formation of nuclear inclusions containing huntingtin may not be required for apoptosis; in fact, such inclusions may be part of a cytoprotective response. Moreover, wild-type but not mutant huntingtin can protect cells by suppressing cell death before mitochondrial dysfunction. Lymphoblasts from HD patients exhibit increased sensitivity to stress-induced apoptosis associated with mitochondrial dysfunction and increased caspase-3 activation suggesting an adverse effect of mutant huntingtin that is not limited to neurons. [14]

The selective neuronal dysfunction and subsequent loss of neurons in the striatum, cerebral cortex, and other parts of the brain can explain the clinical picture seen in cases of Huntington disease. There are various selective mechanisms of neuronal cell death have been proposed for Huntington Disease, including excitotoxicity, oxidative stress, impaired energy metabolism and apoptosis. There is some other phenomenon like myelin breakage and iron changes which plays an important role in etiology of Huntington disease. [15]

MUTANT HUNTINGTIN PROTEIN AND HD BRAIN-

The late onset and progressive development of the behavioral abnormalities, cognitive impairment and involuntary choreiform movements which characterize Huntington's disease (HD) are the physical manifestations of a mutation in a gene on chromosome 4 encoding so-called "huntingtin" protein. In neurons, huntingtin protein has a cytoplasmic distribution in perikarya, axons, dendrites and some nerve terminals. Potential roles in intracellular trafficking and synaptic function have been proposed on the basis of sub cellular fractionation studies which indicated an association of huntingtin with synaptic vesicles and microtubules. Huntingtin protein has also recently been identified in neuronal nuclei. N-terminal fragments of huntingtin have been found in ubiquinated protein aggregates deposited in

neuronal nuclei (neuronal intranuclear inclusions, NII) and in dystrophic neurites (cytoplasmic inclusions, CI). [16, 17]These protein aggregates have been identified in both HD brain, and in the brains of transgenic mice expressing a fragment of human mutant huntingtin. The CAG repeat length appears to be critical for aggregate formation and earlier researches demonstrated for formation of insoluble high molecular weight protein aggregates following proteolytic cleavage of a GST huntingtin fusion protein containing 51 glutamine residues. However no protein aggregation occurred when polyglutamine repeat stretches were reduced to 20 or 30. It is yet to be determined whether these huntingtin protein aggregates are directly involved in processes of cellular dysfunction, or whether deposition is secondary to another pathogenetic process. [18] [19]

NEURONAL APOPTOSIS-

Apoptosis has been classically defined by morphological characteristics which have been detected during the course of developmentally regulated cell death and more recently as a consequence of tissue injury and disease. Thus apoptosis is a form of cell death that is mediated by specific biochemical cascades involving mitochondrial changes and activation of proteases called caspases. Apoptosis provides a mechanism for cells to die without adversely affecting their neighbors. This contrasts with a nonregulated form of cell death called necrosis, in which cellular organelles swell and the plasma membrane becomes permeable, resulting in release of cellular contents and massive death of groups of cells throughout a tissue. [3][20]

MECHANISMS-

The events that occur upstream of the mitochondrial changes are complex and involve interactions of several types of proteins. The Bcl-2 family of proteins was originally discovered in the nematode *Caenorhabditis elegans and* includes both pro- and anti-apoptotic members Anti-apoptotic members in neurons include Bcl-2 and Bcl-xL, while pro-apoptotic members include Bax and Bad.Bcl-2 increases resistance of neurons to death induced by excitotoxic, metabolic, and oxidative insults relevant to AD, stroke, and other disorders On the other hand, neurons lacking Bax are protected against apoptosis Bcl-2 proteins may control the cell process by interacting with mitochondrial membranes in a manner that either promotes or prevents ion movements across mitochondrial membranes.

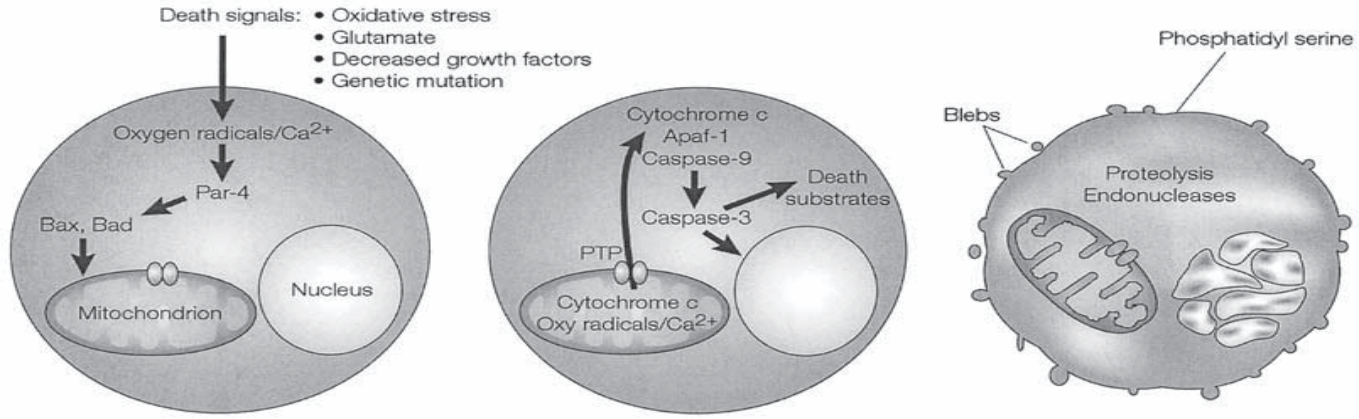

Fig.1- Examples of morphological and biochemical features of apoptosis. During the initiation phase of apoptosis (left), the death signal activates an intracellular cascade of events that may involve increases in levels of oxyradicals and calcium, production of Par-4, and translocation of pro-apoptotic Bcl-2 family members to the mitochondrial membrane. The effector phase of apoptosis (middle) involves increased mitochondrial calcium and oxyradical levels, the formation of permeability transition pores (PTP) in the mitochondrial membrane, and release of cytochrome c into the cytosol. Cytochrome c forms a complex with Apaf-1 and caspase-9.

Activated caspase-9, in turn, activates caspase-3, beginning the degradation phase of apoptosis in which various caspase and other enzyme substrates are cleaved, resulting in characteristic changes in the plasma membrane (blebbing and exposure of phosphatidyl serine on the cell surface, which is a signal that stimulates cell phagocytosis by macrophages/microglia). The nuclear chromatin becomes condensed and fragmented during the degradation phase of Apoptosis (right), and the cell is then at the point-of-no-return. [21]

The premitochondrial phase of apoptosis can also be regulated by other proteins including prostate apoptosis response-4 (Par-4), caspases, and telomerase. Par-4 was discovered because its expression is markedly increased in prostate tumor cells undergoing apoptosis. A series of studies subsequently showed that Par-4 has an essential role in developmental and pathological neuronal death. [22]

In neurons, Par-4 levels increase rapidly in response to various apoptotic stimuli through enhanced translation of Par-4 mRNA. A leucine zipper domain in the C-terminus oPar-4 mediates its pro-apoptotic function; Par-4 interactions with protein kinase C (PKC) and Bcl-2 may be central to the mechanism whereby Par-4 induces mitochondrial dysfunction. Cysteine proteases of the caspase family are evolutionarily conserved effectors of apoptosis. Caspases can act during the premitochondrial phase (e.g., caspases 2 and 8) or post mitochondrial phase (e.g., caspases 3 and 9) of apoptosis. A variety of substrate proteins are cleaved by caspases and may regulate the cell-death process. Caspase substrates include: enzymes such as poly-ADP-ribose polymerase and ataxia-telangiectasia mutated (ATM) kinase; ion channels including subunits of the AMPA subtype of neuronal glutamate receptor; and cytoskeleton proteins such as actin and spectrin. The progression of the disease could be reduced by using caspase inhibitors, which protect against the formation of truncated huntingtin. [23]

Table 2. Examples of Proteins That Can Either Promote or Suppress Neuronal Apoptosis-

Proapoptotic	
Glutamate receptor proteins	Calcium influx Initiate death cascade Pore formation in mitochondrial
Fas Bax,Bad	Membrane, Cytochrome c release
Par-4	Mitochondrial dysfunction; Suppression of survival signals (NF-B)
P53	Transcription of death gene; Enhancement of Bax action
Capsases	Cleavage of various enzyme, cytoskeleton and ion channel substrates
Antiapoptotic	
Bcl-2, Bcl-XL	Stabilize mitochondrial function; suppress oxidative stress
IAPs	Caspase inhibition
PKCz	Stimulate survival gene expression
Neurotrophic factors and cytokines	Induce expression of survival genes (antioxidant enzymes, calcium-regulating proteins, IAPs, Bcl-2)
Antioxidant enzymes	Suppress oxidative stress
Calcium-binding proteins	Stabilize calcium homeostasis

The tetracyclines are broad-spectrum antibiotics, inhibitors of caspase-1 and -3 and matrix metalloproteases, and of the aggregation of amyloids. Although tetracycline itself does not cross the blood-brain barrier, the related compounds minocycline and doxycycline do, and their levels in the CSF have been estimated to be 14–30% of the blood levels. Tetracycline, doxycycline and minocycline reduce the aggregation of huntingtin in the organotypic slice culture assay and inhibit caspase-1 and -3. Treatment with minocycline, like that with creatine, can delay the disease progression in animals, but not cure HD. The results of in vivo trials by different groups are controversial. [24]

MITOCHONDRIAL DYSFUNCTION AND EXCITOTOXICITY-

The definitive answer of the question what are the common pathways linking the huntingtin mutation with bioenergetic defects, oxidative damage and cell loss in HD is currently unknown, but one hypothesis is that bioenergetic defects could lead to neuronal death via so-called secondary excitotoxicity Energetic defects might occur as a primary event in HD, or as a consequence of oxidative damage to cellular elements. Reduced ATP production due to impaired mitochondrial energy metabolism can result in partial cell depolarization, by making neurons more vulnerable to endogenous levels of glutamate. The concomitant increase in Ca-influx into neurons may trigger further free radical production, exacerbating damage to cellular elements. Further, excitatory amino acid antagonists such as MK-801 can ameliorate cerebral lesions induced by mitochondrial toxins including AOAA, malonate, 3-NP and 3-acetylpyridine, 3-AP. Excitotoxic mechanisms have been implicated in the mechanism of cell death in HD largely on the basis of observations of NMDA glutamate receptor distribution within striatal cell populations, and findings that excitotoxic striatal lesions in animal models closely resemble those seen in HD brain.[25]

Impaired activity of components of the energy metabolism pathways including pyruvate dehydrogenase and succinate dehydrogenase have been reported in HD. Direct impairment of the mitochondrial oxidative phosphorylation pathway, or reduced substrate trafficking into this pathway as a result of disruption of glycolysis or the Krebs cycle, will result in reduced ATP production by mitochondria. The bulk of ATP production within cells takes place within the mitochondrial electron transport chain. It is comprised of five protein complexes: NADH ubiquinone oxidoreductase (complex I), succinate ubiquinol oxidoreductase (II), ubiquinol cytochrome c oxidoreductase (III),

and cytochrome c oxidase (IV) which act in series to oxidize NADH and $FADH_2$, generated in the mitochondrial matrix by the Krebs cycle, via electron transfer, ultimately to oxygen. [26]

Reduced ATP production can result in cell death via disruption of energy-dependent processes. ATP is essential to fuel ionic pumps which generate and maintain ionic and voltage gradients across neuronal membranes, including Na^+/K^+-ATPase pumps which control the restoration of the resting membrane potential after depolarization, and ATPases which regulate intracellular levels of Ca^{2+}. Impaired Na^+/K^+-ATPase pump activity will inhibit membrane repolarization, resulting in prolonged or inappropriate opening of voltage-dependent ion channels. If severe enough, this partial membrane depolarization may facilitate activation of NMDA receptors by endogenous levels of glutamate, by alleviating the voltage-dependent Mg^{2+} blockade of NMDA receptor channels. [24] The resultant excessive inward flux of Na^+ and Ca^{2+} ions can set in motion neurotoxic cascades. Increased intracellular Na^+ levels will decrease the activity of the Na^+/Ca^{2+} antiport system, which would normally extrude Ca^{2+} from the cell. In addition, reduced ATP levels will impair ATP-dependent extrusion and storage of Ca^{2+}, further increasing intracellular concentrations of free Ca^{2+}. [27] [28]

POLYGLUTAMINE EXPANSIONS AS A CAUSE OF NEURODEGENERATION-

There have been a number of suggestions as to how expanding CAG repeats in widely expressed genes may lead to delayed onset neurodegeneration of specific neurons. The dominant mode of inheritance observed suggests that the expansion in the disease gene constitutes a gain-of-function mutation. One hypothesis is that the association of some protein that binds to the normal sized polyglutamine tract is adversely affected by the polyglutamine expansion and, thus, mediates neurodegeneration. A protein that associates with the huntingtin protein has recently been identified, although the biological significance of this association is unknown. Alternatively, the length of the polyglutamine tract could affect the proposed action of the proteins as transcription factors, thus changing the expression of other genes that may induce neurodegeneration. Another suggestion is that the expanded polyglutamine tract may provide a better substrate for transglutaminase, an enzyme which catalyses the cross-linking of glutamine residues. The isodipeptide linkages produced by transglutaminase are not easily degraded and their accumulation is proposed to affect cell function. Alternatively, the inversely proportional relationship between the size of the CAG repeat and the age of disease onset may be best explained by a concentration dependence, related to polyglutamine tract size, which is independent of any normal function of the polyglutamine. [29]

Changes in intracellular glutamate concentrations may affect extracellular glutamate levels through glutamate transporters. Consequently, alterations in glutamine levels in cells expressing the expanded gene could have an impact on cellular and vascular concentrations of glutamate to an extent proportional to the length of the polyglutamine tract. The subtle changes in glutamate levels that result may chronically affect neurons specifically sensitive to the concentration of glutamate via glutamate receptors. The relationship between polyglutamine expansion and onset of neurodegeneration could, therefore, be mediated by a concentration effect of glutamate, leading to chronic excitotoxic neuronal death in this subset of affected neurons.

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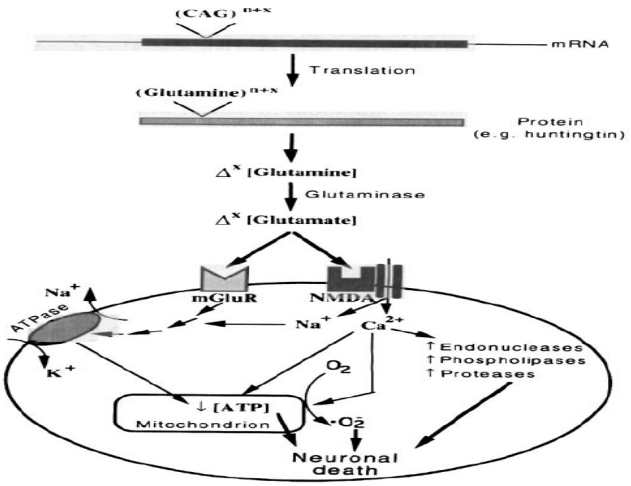

Fig.4- A model for the induction of slow excitotoxic neuronal death by CAG repeats expansions in neurodegenerative disease genes. The expansion of a CAG repeat from a normal size (n) to a disease size (n + x) is transcribed into mRNA and then translated into an expanded polyglutamine tract in the disease protein. This change may act through metabotropic glutamate receptors (mGluR) and/or the ionotropic NMDA receptor, present on specific neuronal populations, to affect energy metabolism and induce slow neuronal death via one or more of the illustrated pathways. [30] [31]

GLUTAMATE EXCITOTOXICITY, OXIDATIVE STRESS AND NEURONAL DEATH-

The proposed mechanism for glutamate-induced slow excitotoxic neuronal death in neurodegenerative diseases requires further explanation of the intermediate molecular events involved in neurodegeneration. It has been suggested that such neurodegeneration may occur via chronic oxidative stress. Oxidative stress is

defined **as** the cytotoxic result of oxygen radicals, such as the superoxide anion 0^{2-} and hydrogen peroxide (H_2O_2), which are produced during normal and aberrant metabolic processes involving oxygen. The cumulative, damaging nature of this process is consistent with the delayed onset and slow progression observed in neurodegenerative diseases. There is some evidence to suggest that glutamate, acting through ionotropic glutamate receptors, may be a cause of oxidative stress leading to neurodegeneration. [17]

The proposed mechanism that links polyglutamine expansion, glutamate excitotoxicity and oxidative stress in a slow neurodegenerative pathway is shown schematically in Fig. 1. This mechanism may be shared by the neurodegenerative diseases DRPLA, HD, MJD, SBMA and SCA1. Transcription of the gene containing a CAG-repeat expansion, from a normal repeat size (n) to a disease repeat size (n + x) produces mRNA. This mRNA is translated into a protein, with an expanded polyglutamine tract size (n + x), which will later be degraded. Subtle changes in glutamine concentration proportional to **x** would result from synthesis and degradation of the mutant protein. Through the catalysis of glutaminase, glutamine is converted to glutamate, leading to chronic changes in glutamate levels. It is known that neurons can be exquisitely sensitive to glutamate Alterations in extracellular glutamate concentrations in the neuronal environament could impact on glutamate receptors. [32]

Glutamate receptors are known to exist in two ‘flavours’, ionotropic and metabotropic. The ionotropic receptors, which have been studied most extensively, consist of cation-specific ion channels: alpha-amino-3-hydroxy-5-methyl4-isoxazole propionate (AMPA) kainate receptors and N-methyl-D-aspartate (NMDA) receptors. These receptors mediate the rapid neuronal excitation typical of glutamate neurotransmission. In contrast, the metabotropic glutamate receptors (mGluR) are coupled to intracellular signal transduction via G-proteins and thus mediate slow glutamate neurotransmission. A recent study that linked mGluR activation with Na^+/K^+-ATPase suggested a role for these receptors in glutamate excitotoxicity. Studies of HD patients, however, strongly implicate the NMDA receptor in the pathogenesis of this neurodegenerative disease. [33]

The NMDA receptor consists of a glutamate-regulated Na^+/ Ca^{2+} channel. There is evidence that glutamate excitotoxicity of cultured neurons may be mediated by transmembrane influx of Ca^{2+}. Multiple pathways are illustrated whereby increased levels of intracellular Ca^{2+} may contribute to gradual neuronal death. Intracellular Ca^{2+} is a critical regulator of many neuronal activities.3T~h e influx of Ca^{2+} and Na^+ via the NMDA receptor would increase demand for ATP by the ion pumps (such as Na^+/ K^+-ATPases) and consequently deplete ATP levels. At high intracellular Ca^{2+} concentrations mitochondria absorb Ca^{2+} from the cytosol and decrease synthesis of ATP. This may contribute to mitochondrial damage, energy failure and gradual neuronal death.

The differences in neuronal populations that degenerate in DRPLA, HD, MJD, SBMA and SCAl require an explanation. This variability is most likely to arise from the differences in the spatial (both neuronal and non-neuronal) and temporal expressions of the disease genes, which harbour the CAG repeat expansions. The proposed spatiotemporal gradients in neural glutamate concentration may cause neurodegeneration through local sources. For example, the ITI5 gene is expressed, as is the huntingtin product, in the brain regions affected in HD as well as other regions. Detailed quantitative analysis of the spatiotemporal expression patterns of the neurodegenerative disease genes, in parallel with spatiotemporal regulation of glutamate levels, is required to test this hypothesis. The complement of glutamate receptors that different neurons possess during development and at maturity could subsequently mediate their vulnerability to alterations in glutamate concentrations. This may control the regional selectivity of neuronal death characteristic of the neurodegenerative diseases. [34]

MYELIN BREAKEDOWN AND IRON CHANGES IN HD AFFECTED BRAIN-

In many degenerative brain diseases myelin breakdown and iron accumulation begin before the first appearance of pathological changes. There is therefore a decades-long period in which therapeutic interventions could modify the course of these diseases, before clinical evidence such as behavioral, cognitive, and motor decrements appear. Thus, it may be possible that medication development could be carried out in very early disease stages using non-invasive in vivo combined neuroimaging markers of both myelin breakdown and iron levels.

The molecular mechanisms through which mutant huntingtin could precipitate premature myelin breakdown that preferentially affects early

and heavily myelinated axons and regions are worth considering. The thick myelin sheaths of these axons depend on myelin basic protein for their integrity to a greater extent than smaller axons with thinner myelin sheaths. Expression of myelin basic protein is normally supported by brain derived neurotrophic factor (BDNF) that is distributed by vesicular axonal transport.

Alternative explanations for the increase in ferritin iron involving neurons, astrocytes, or microglia and oxidative stress are possible especially for the later disease stages. Oligodendrocytes are enriched in iron and have the highest ferritin content of all brain cell types. By comparison neurons and astrocytes have relatively low ferritin level. The severity and progression of HD pathology is associated with increased microglia numbers and their activation however, although these cells can achieve high ferritin levels, their activation may decrease these levels Our observation that increased ferritin iron is present very early in the HD disease process is consistent with the doubling of oligodendrocytes in presymptomatic HD Together with the higher numbers of oligodendrocytes in healthy adult brain these factors make it likely that oligodendrocytes underlie the ferritin iron increases especially early in the disease process. [35]

GROSS NEUROPATHOLOGICAL FEATURES OF HD

Motor dysfunction in HD results from the disruption of basal ganglia-thalamocortical pathways regulating movement control. The primary site of neuronal loss and atrophy in HD brain is in the caudate-putamen, although in many cases atrophy also occurs in a number of non-striatal regions, including cerebral cortex, thalamus, globus pallidus (GP), cerebellum and white matter tracts. The typical pattern of striatal cell loss in HD occurs gradually along a topographically well defined pathway. Neurodegeneration in both the caudate and putamen follows a caudo-rostral progression, with a preferential dorsal to ventral gradient.[36, 37] Thus, at end stage cell loss is maximal in the tail of the caudate nucleus, less severe in the body, and least in the head of the caudate, although in severe cases neuronal populations is devastated throughout the neostriatum. Fibrillary astrogliosis follows the path of cell loss in striatum, however reactive gliosis does not accompany the chronic cell loss seen elsewhere in the brain, and no inflammatory response is involved. [38][39]

On the basis of the progressive involvement of striatal regions, for grading HD patients based on gross and microscopic measures of neuropathological severity, determined in three standardized coronal brain sections including the striatum Grades range from 0 to 4 with increasing severity and extent of striatal involvement. Briefly, Grade 0 cases are generally indistinguishable from normal brains on gross examination, but exhibit 30-40% neuronal loss in the head of the caudate, with no visible signs of reactive gliosis. In contrast, in Grade 4 the striatum is severely atrophic with loss of more than 95% of neurons and markedly increased oligodendrocytic density. Cell loss in the nucleus accumbens is evident in approximately 50% of Grade 4 cases. The majority of HD cases (approximately 80%) are Grades 3 or 4 at time of death. The grade of striatal pathology appears to correlate closely with the involvement of other cerebral regions. Non-striatal regions are largely unaffected in grades 1 and 2, whilst atrophy and neuronal loss are evident in the GP, cortex, and to a lesser extent thalamus, subthalamic nucleus, substantia nigra, white matter and cerebellum in Grade 3 and 4 cases. Cerebellar atrophy is particularly prevalent in cases of juvenile onset HD. [40]

Surviving neostriatal neurons generally appear morphologically normal, but may be reduced in size and contain elevated levels of the oxidative damage marker lipofuscin. However there is a sub-population of neurons scattered largely between the zones of atrophic and healthy cells, referred to as “neostriatal dark neurons (NDN)” because of their relatively intense staining with Luxol-fast-blue and haematoxylin and eosin. These cells have characteristically scalloped membranes, granulation of the cytoplasm and condensation of nuclear chromatin, and some can be labeled by(TdT)-mediated (dUTP)-biotin nick end-labeling (TUNEL), suggesting that they may be undergoing apoptosis. [41] [42]

TREATMENT

At present treatment of Huntington disease at present is only symptomatic. Appropriate drugs for depression agitation, irritability, anxiety, or frank psychosis may manage the psychiatric and psychological problems. The motor difficulties may be more complicated and harder to control. Muscle relaxants of central origin and GABAergic medications have not proven to be overly helpful. [43-48] Neuroleptic agents may partially control the

chorea but may cause tardive dyskinesia or enhance cognitive dysfunction in sedated patients. [49]

Treatments under investigation target relevant pathophysiologic mechanisms, including transcriptional dysregulation, free radical stress, metabotoxicity, and excitotoxicity. Although preliminary investigation suggests slowed progression with ubiquinone treatment further study is needed. Recently, 2-year benefit after transplantation of human striatal primordia has been reported. Alternate sources of graft tissue are under investigation as is delivery of trophic factors and grafting of trophic factor–producing cell lines.

Diet And Lifestyle Of Hd Patients-

- There is no specific dietary composition that has been demonstrated to impact the course of HD.
- Increase in dietary calorie content is needed because the characteristic hyperkinetic involuntary movements consume large quantities of calories, resulting in notable weight loss.
- In advanced disease, increasing troubles with swallowing can be dealt with by provision of multiple daily small meals that will help ensure adequate caloric intake.

PHARMACOLOGIC TREATMENT

Symptomatic therapies target specific manifestations of the disorder and are presented in this order. When there are multiple medications within a given category, a prototypical compound is discussed. Because symptoms typically develop during the peak wage-earning years, cost often plays a major role in medication selection. [50]

- **Nutritional Supplements-**

o Energy metabolism is known to be impaired in Huntington's disease. Both ***Creatine*** and ***CoQ10*** boost energy in the cell. In addition both act as antioxidants. Phase III clinical trials have been funded for both. The creatine trial will begin recruiting later in 2008; the CoQ10 trial has already started.

o ***Ethyl EPA*** is a purified version of eicosapentaenoic acid, an Omega 3 fatty acid found in fish oil. A Phase III clinical trial managed by the Huntington Study Group and sponsored by Amarin Pharmaceuticals was suggestive of benefit after six months of use but not conclusive. There may be an additional trial to resolve the issue.

- **Dopamine Blokers Or Stabilizers-**

o Blocking or stabilizing the neurotransmitter dopamine has been shown to reduce chorea. In addition, there is evidence to suggest that normal amounts of dopamine may be toxic in the brain in Huntington's disease.

o ***Tetrabenazine*** is a dopamine depleter available in Europe and Canada; In August 2008 the U.S. Food and Drug Administration approved tetrabenazine to treat Huntington's chorea, making it the first drug approved for use in the United States to treat the disease.

o ***ACR-16*** is a dopamine stabilizer in Phase III clinical trials in Europe; a Phase IIb trial is now recruiting in the U.S. and Canada.

- **Anti-Apoptosis-**

o ***Minocycline*** is an antibiotic which has been used for decades; it inhibits apoptosis, programmed cell death.

o ***Tauroursodeoxycholic acid*** or TUDCA is an endogenous bile acid which inhibits mitochondrial apoptosis. It is currently in Phase I trials sponsored by the HSG; results are expected soon.

o ***Methazolamide*** is an inhibitor of cytochrome c, an enzyme involved in apoptosis.

o ***Neurologix*** is investigating the potential of gene therapy using a mutated form of the XIAP gene. XIAP stands for x-linked inhibitor of apoptosis protein.

- **Glutamate Blockers Or Stabilizers-**

o The excitotoxicity theory holds that neurons are abnormally sensitive to glutamate; overstimulation by this important neurotransmitter can lead to cell death.

o ***Memantine*** is a glutamate stabilizer that is FDA approved to treat Alzheimer's dementia. Because memantine might also address excitoxicity in HD and because clinical reports from physicians try memantine for HD patients have suggested that it may improve cognitive symptoms, memantine is now in Phase II clinical trials.

o ***Dimebon*** has several promising mechanisms. In addition to regulating glutamate, it also inhibits acetylcholinesterase and is thought to regulate calcium homeostasis, preventing the

pathological opening of the mitochondrial permeability transition pores. Calcium handling is impaired in Huntington's disease. Following promising results in a phase II trial, Medivation is planning a Phase III trial to be managed by the HSG.

- **BDNF Inducers-**

o Brain derived neurotrophic factor (BDNF) protects brain cells and promotes neurogenesis, the growth of new ones. Levels of BDNF are known to be reduced in the brains of HD patients. SSRI (selective serotonin reuptake inhibitor) antidepressants are known to elevate BDNF and one such antidepressant, ***Celexa***, is in Phase II clinical trials. In addition, Cortex pharmaceutical has an ***Ampakine*** in preclinical testing and Raptor pharmaceutical is planning Phase II trials of ***cysteamine***; both induce BDNF.

o ***CEP-1347***, an anti-apoptosis drug was found to improve the R6/2 mice by increasing BDNF levels.

- **Other Neurotrophic Factors And Mimetics-**

o In addition to BDNF, researchers are also looking at other neurotrophic factors and synthetic compounds that mimic their effects with the hope that they will be neuroprotective in HD patients. One candidate is fibroblast growth factor 2 which promoted neurogenesis and extended survival time in the R6/2 mice. It is still in preclinical testing.

o ***Ceregene*** has developed a viral vector for delivering a gene for the neurotrophic factor neurturin into the brain. This potential treatment is in Phase II clinical trials for Parkinson's disease and preclinical testing for Huntington's disease. Trophos has a lead candidate which is neuroprotective in a striatal cell model of HD.

- **HDAC INHIBITORS-**

o The dysregulation of gene transcription has been shown to be a significant problem in Huntington's disease. The HD protein interferes with the normal expression of genes. Histone deacetylase inhibitors may be able to reverse or partially reverse this dysfunction. Envivo has a candidate drug which performed well in performed well in preclinical testing and a Phase I clinical trial is planned for later in 2008. Repligen has licensed an HDAC inhibitor from Scripps Research Institute which reduced pathology and at least partially restored gene transcription.

- **Antioxident/Antiaging-**

o Huntington's disease is a disease of aging in that cells in the areas of the brain that are affected by HD are for some time able to cope with the challenges presented by the mutant protein. As we age, our cellular defense mechanisms become less efficient. There is a group of genes called sirtuins which appear to regulate aging. In the spring of 2008 Sirtris Pharmaceuticals announced that there is new data showing that in a preclinical model of Huntington's disease, mice live longer and have less disease pathology in the brain with increased SIRT1 expression. Sirtris has several compounds with induce SIRT1 expression.

o One problem that increases with aging which is thought to be particularly damaging in HD is oxidative stress. During energy metabolism, free radicals of oxygen are produced which can damage proteins, lipids, and DNA if there aren't enough antioxidants available with which to bond. As mentioned above, creatine and CoQ10 are antioxidants. Intellect Neurosciences is doing preclinical studies with their synthetic version of Indole-3-propionic acid.

- **AUTOPHAGY-**

o The normal huntingtin's protein is cleared away from the cell through the ubuiqitin proteosome system. This housekeeping process is not effective with the HD version of the protein. There is an alternate way to clear away the HD protein called autophagy. Two drugs which are already approved were found to be inducing autophagy in cell and drosophila models. The next step is to test these drugs in the HD mice.

- **METAL CHELATORS-**

o Both excess copper and excess iron have been shown to contribute to HD pathology. Pipex Pharmaceuticals, in collaboration with researchers at the VA Medical Center at Ann Arbor, is doing preclinical testing of their copper chelator. Varinel, an Israel Pharmaceutical company is testing their copper chelator in HD mouse models with funding from CHDI.

- **A2A RECEPTOR ANTAGONISTS-**

o Research shows that there is an aberrant amplification of the adenosine 2A receptor

signaling in striatal cells in people with Huntington's disease. Kyowa Pharmaceuticals has an A2A receptor antagonist called ***KW-6002*** (istradefyllin) that is in clinical testing for Parkinson's disease.

- **CASPASE 6 INHIBITOR-**

o When an HD mouse model was engineered to be resistant to caspase 6, the HD protein was not cleaved, the protein did not accumulate in the nucleus of the cell, and the mice did not develop Huntington's disease. CHDI is funding the development of a safe and effective caspase 6 inhibitor.

- **GENETIC APPROCHES-**

o If the HD gene could be stopped from expressing itself, the result could be a virtual cure. Two pharmaceutical companies, Sirna and Anylam are working on ways to interference with messenger RNA so that instructions to make the HD protein are not sent out. An issue is that it may be necessary to develop allele specific ways to do this so that only the HD protein is shut down and the normal huntingtin's protein continues to be expressed.

o The antisense approach being taken by Isis is somewhat different in that it is possible for a drug to do this on a periodic basis; the goal is to find an optimal time in which the cell can recover from the HD protein without being harmed by the absence of the normal protein.

- **RESTORATIVE TECHNOLOGIES-**

o Research with the HD mice suggests that stopping the HD gene from expressing itself would result in improvement even well into the progression of the disease. However, restorative treatments will likely be necessary for full recovery of later stage patients. ReNeuron has a line of stem cells which has shown efficacy in a cell model of HD. Preclinical work is being done. [51] [52] [53]

In the next page, there is a chart of different phases of clinical trials of various drugs which are under research process and hopefully will be use for treatment of Huntington disease in future.

CONCLUSION

The present era is one of tremendous excitement and rapid innovation in Huntington's disease (HD) research. The pace of research seems to be rapidly quickening. The discovery of the gene and the subsequent development of transgenic mouse models of HD have been major breakthroughs. Now, after a large number of experimental studies in animals, a few pilot clinical trials have been initiated. As the root cause of neuronal degeneration in HD disease is yet unknown thus Over the coming years, the key steps in the field of Huntington disease will lie in using disease relevant animal models to identify the precise sequence of events leading to neurodegeneration and the subsequent verification in human samples.

The therapeutic benefits of current symptomatic treatments remain to be determined. Extensive studies have greatly advanced our understanding of the molecular mechanisms of HD pathogenesis. The main challenge in finding a cure for HD is the selection of molecular targets. Multiple parallel and sequential signaling pathways are involved in cultivating ultimate neuronal dysfunction and death induced by mutant huntingtin. Identifying upstream and core molecular events could be crucial for therapeutic development. Many novel therapies targeting molecular pathogenesis are awaiting safe and clinical studies. With regards to fetal tissue transplantation, the resources are limited and there is still debate on the ethical issues of using this technology. The safety and rationale of tissue transplantation have also now been questioned. Compounds improving energy production are safe but their effectiveness needs to be further evaluated. The use of Chinese medicine for HD treatment also needs further investigation. We have made great progress, but we still have long way to go in developing a cure for HD.

Although much remains to be done, this project report provides us with an update on the most salient advances made in the past decade in the field of HD, suggests pathological scenarios as to how mutant huntingtin may lead to HD, and most importantly, discusses the many steps in the process of functional decline and cell death that might be targeted by new neuroprotective therapies.

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