Possible Treatments of Huntington's Disease: A Comprehensive Review

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
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Approval

The thesis titled "Possible Treatments of Huntington's Disease: A Comprehensive Review" submitted by Sadia Zaman Lopa (18346034) of Spring, 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons) on.

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Ethics Statement

This study did not involve any human participants, human specimens or tissue, vertebrate animals or cephalopods, vertebrate embryos or tissues and field research.

Abstract

Huntington's disease (HD) is characterized by chorea, cognitive impairment, and behavioral problems; it is a hereditary, progressive neurological condition. HD is becoming easier to diagnose and learn about, but it is still tricky to treat due to severe symptoms and a lack of authorized therapeutic approaches. Both non pharmacologic and pharmacologic approaches have been studied, with more than 80 medicines from different classes having been the subject of clinical trials or case reports. However, antidopaminergic drugs are typically only used to treat motor dysfunction while antidepressants are used to treat mood problems, leaving cognitive impairment untreated. Clinical trials have focused on multiple potential mechanisms for altering symptoms and disease progression.

Keywords: Huntington; Pharmacologic; Cognitive Impairment; Treatment; Therapeutics.

Dedication

I'd like to dedicate this artwork to my wonderful family.

Acknowledgment

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Table of Contents

List of Acronyms

- HD- Huntington's disease
- HTT- Huntingtin gene
- CAG-Cytosine-adenine-guanine
- mHTT- Mutant huntingtin protein
- cAMP-Cyclic adenosine monophosphate
- PGC-1a-Peroxisome proliferator-activating receptor-g coactivator-1 a
- TAFII130-Human transcription factor
- BDNF-Brain-derived neurotrophic factor
- TrkB-Tropomyosin receptor kinase B
- UPS-Ubiquitin-proteasome system
- TIM23-Integral protein of the inner membrane
- ROS-Reactive oxygen species
- NMDA-N-methyl-D-aspartate
- AMPA- α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)
- GLAST-Glutamate aspartate transporter
- HIP1-Huntingtin-interacting protein 1
- HAP1-Huntingtin associated protein 1
- EGF-Epidermal growth factor
- (AP-2)-Alpha-adaptin component
- PolyQ- Polyglutamine
- Akr1p-Ankyrin repeat protein
- PSD-95-Postsynaptic density protein 95
- VMAT-2-Vesicular monoamine transporter 2

- CBP- Creb-binding protein
- OCD- Obsessive-compulsive disorder
- NeuroD1- Neurogenic differentiation 1

Chapter 1

Introduction

1.1 Background

Hereditary chorea, or Huntington's disease, was first described in 1872 by George Huntington. He explained that it runs in families and typically presents itself in adults between 30 and 40, alongside several psychological and mental health issues. There have been cases of HD diagnosed in patients as young as two years old and as old as 87 years old. The typical age at which symptoms first appear is forty years old. The term "Juvenile HD" refers to the kind of disease that first manifests in people younger than 20 (Finkbeiner, 2015). Huntington's disease (HD) is a terrible brain ailment without a cure. This condition has hallmarks of involuntary movement, impaired cognition, and psychological distress. Depression, psychosis, and obsessive-compulsive disorder are just a few psychiatric symptoms frequently seen in HD patients. They are highly upsetting to them (Rosenblatt, 2007). Five hundred to ten thousand out of every ten thousand persons in the West will contract the disease. HD is a neurodegenerative disease with a median survival of about 20 years from the onset of symptoms (Pan & Feigin, 2021).

The condition is caused by an accumulation of trinucleotide repeats in the huntingtin gene (HTT), which is located on chromosome 4. The huntingtin protein, which is produced by this gene, is highly expressed in human neurons and has a variety of roles in the cell. A general population survey found that the average number of CAG repeats in the HTT gene was between 17 and 20. HD develops with complete penetrance in cases with 40 or more CAG repeats. Symptoms often appear between the ages of 20 and 65, and the average lifespan of a person

with the disease is 20 years. Despite the lack of effective treatments, neurodegeneration and general function loss can still be slowed with therapy.

More clinical trials of therapies that alleviate symptoms and protect neurons have been conducted in the last decade. In addition, preliminary tests of human gene-silencing approaches are now being undertaken (Wyant et al., 2017).

Previously discovered aberrant proteinaceous clumps of mutant huntingtin protein (mHTT) in the brains of Huntington's disease patients. Following that, studies of neurotransmitter receptor levels in transgenic mice expressing mHTT suggested that transcriptional dysregulation may have an early role in developing HD. Since then, numerous studies have blamed mHTT for various events contributing to HD pathogenesis. Today, the primary focus of HD treatment is on symptomatic control of chorea and mental and cognitive impairments (Anderson, 2011)(Pla et al., 2014).

The FDA has approved only two drugs for the treatment of HD: tetrabenazine and deutetrabenazine. It's been demonstrated that they can successfully minimize chorea in HD. Furthermore, neuroleptics are widely utilized off-label to treat chorea and psychosis, both of which are associated with HD. Sadness, stress, and restlessness are some of the other psychological symptoms of HD that can be addressed with SSRIs/SNRIs and benzodiazepines. Acetylcholinesterase inhibitors can be used to treat dementia caused by HD. However, the treatment is ineffective (Pan & Feigin, 2021).

1.2 Clinical Characteristics

1.2.1 Cognitive Disorder

HD is characterized by severe cognitive deficits. Memory, mental quickness, and spatial awareness all decline early. Even in the earliest stages of HD, patients can plan for exams, test executive function, think creatively, and solve problems. Multiple studies have shown that the severity of motor symptoms, the degree of difficulty in voluntary movement, and the duration of HD are all connected to the deterioration of cognitive function. Dementia affects 90% of HD patients at some point during the illness. There is no doubt that there is great variety due to the several demographics and cognitive tests. Dementia, as defined by the American Psychiatric Association in 1994, is a syndrome of acquired intellectual impairment characterized by memory impairment and another cognitive impairment (aphasia, apraxia, agnosia, or deficits in executive functioning). However, HD dementia does not fit this definition, at least in its earliest stages (Puigdellívol et al., 2016).

The most noticeable abnormalities are impairments in executive functioning, which is a sort of sophisticated cognitive functioning that manages various domains of cognition. As a result, issues with action planning and initiation, as well as organizational dysfunction, emerge, as does a failure to adapt to societal upheavals caused by the emergence of logical thought. Task management issues are a common early symptom of HD and may have significant ramifications for one's job. Another indicator of cognitive impairment is a general slowdown of mental processes. Short-term memory loss can make learning new skills difficult and, in certain cases, cause a general decline in patients' abilities. Patients' sense of their bodies about

their environment may be altered. When a patient's cognitive impairment progresses to a severe level, they may develop frontotemporal and subcortical dementia (Anderson, 2011).

1.2.2 Discomfort in the Nervous System

Patients with multiple sclerosis often have trouble expressing, eating, and sleeping, particularly addition to the more common physical, intellectual, and mental deficits. Dysarthria is just one of several potential causes of speech impairment (caused by an inability to coordinate the muscles of the mouth and tongue), mental issues such as having trouble choosing the correct terms, and difficulty efficiently ordering speech.

Patients who have developed to the point where extreme stiffness and akinesia, as noticed in advance, are present have a chance of becoming entirely anarthrous (mute) in a manner comparable to how a motor disability (characterized by incoordination of the oral and pharyngeal muscles) and intellectual disabilities lead to issues with swallowing. HD patients typically report having trouble sleeping, which can result in significant emotional agony and distress. Insomnia can have a variety of causes, including secondary factors such as a negative mood, feelings of anxiety, or nighttime chores; nevertheless, it is generally accepted that the major cause of insomnia is an issue with the circadian rhythms that regulate sleep. Treatment for insomnia that is geared toward the underlying cause of the condition is more likely to be successful (Pla et al., 2014).

1.2.3 Deficits in Executive Memory

One of the most frequently observed cognitive abnormalities induced by HD is the inability to work appropriately in executive memory. This umbrella phrase encompasses essential cognitive abilities such as reasoning, planning, judgment, decision-making, concentration,

learning, memory, adaptability, and timing. Executive dysfunction has far-reaching consequences that can be shown in IQ testing and everyday life.

The executive function tests Tower of London, Wisconsin Card Sorting Test, and Stroop Color Word Test all showed poorer results in HD patients. Diagnostic tools can be derived from brief evaluations of organizational functions. Some cognitive tests have shown sensitivity to HD cognitive abnormalities; these include the Serial Sevensitem from the Mini-Mental Status Exam and a condensed battery of frontal brain tests (Phillips et al., 2008).

Similarly, the Montreal Cognitive Assessment, a brief evaluation focusing on executive function, is sensitive to (Anderson, 2011)cognitive change associated with HD. Even though patients with HD, healthy controls, and those with Parkinson's disease all had similar levels of cognitive impairment, the researchers discovered that when placed in simulated gambling environments, the HD patients continuously made less effective choices. Several HD patients indicated that even though they were aware of one or more "poor" card decks, they preferred picking their cards from them despite knowing they had inferior cards.

The inability to learn, pay attention, inhibit oneself, or have an impaired understanding of the consequences of one's actions are just a few examples of cognitive deficits that can lead to poor decision-making. People with HD may have a more difficult time accepting criticism positively and may also have a more difficult time changing their behavior in response to new information. These limits have a profound impact on a person's day-to-day existence (Anderson, 2011).

1.2.4 Memory and Learning Deficiencies

Learning Even patients with HD diagnosed at an early stage demonstrate verbal learning impairments on sensitive tests. The problem is in the process of encoding and retrieval rather than recognition memory, which is frequently unaffected. Patients with HD have performance very close to normal when a less taxing memory test, such as identifying things or giving a choice, is employed.

Memory for recognizing faces may be lost in patients with intermediate to severe illness, according to research by Kramer et al. (1988) and Lang et al. (2000). In HD, memory loss is not nearly as severe as it is in "cortical dementias" such as Alzheimer's disease. Retention is largely average in HD. Memory performance is minimally affected throughout all phases of HD patients' life. HD patients do not show any temporal gradient in memory performance or problems with memory (Anderson, 2011).

1.2.5 Psychotic Symptoms

When it comes to Huntington's disease, psychiatric symptoms might show up at any time, even before motor symptoms do. This behavior often accompanies the onset of depression. Subtle personality shifts have also been observed before a neurological diagnosis, albeit many of these studies are constrained by the retrospective nature of their data. It has been noted that there is a lack of empathy, impulsivity, and emotional instability. Research has found that 30% to over 70% of people with HD also experience mental health issues. Patients with HD frequently report emotional blunting, poor self-care, poor judgment, poor motivation and drive, and low levels of determination and output, as stated by Craufurd and colleagues (2001).

A comprehensive assessment, standard measurements, and data from caregivers found that 98% of HD patients in an outpatient study experienced at least one psychiatric symptom. Based on the findings of this study, it appears that most patients will have behavioral difficulties when access to more information and examinations increases. Patients with HD display an extremely wide range of mental health issues. Nonetheless, it seems that a number of them are condition-dependent. Individuals who have not yet displayed the condition but are just beginning to show symptoms, as well as those who have advanced in the disease and are losing their independence and capacity to operate, have the highest rates of suicide ideation. Since this is the case, asking about suicidal thoughts during the assessment is crucial. Individuals with HD who are depressed or impulsive are at a higher risk of taking their own lives.

Many patients also exhibit obsessive and compulsive thought patterns and actions. Body-focused preoccupations (such as obsessive worry about urination or defecation), interpersonal preoccupations (like adultery fantasies), and ritualistic behaviors all fit into this group. A lack of motivation and an inactive attitude are the hallmarks of the apathetic state. Distinguishing it from depression can be challenging, but the distinction depends on the advancedment of the disease. The hardest aspect of most activities is usually just getting started, but once patients get going, they can participate fully. On rare occasions, patients may acquire feelings of hatred and annoyance. It is highly unusual for these signs to lead to actual physical violence. Psychosis, which involves both paranoid beliefs and acoustic hallucinations, is a symptom that occurs less frequently and is seen in the later stages of the disease (Anderson, 2011).

1.2.6 Easily Irritated and Hostile

It has been suggested that irritability results from faulty inhibitory function and impaired ability to filter incoming stimuli. Anxiety, sadness, and eating disorders are just some mental health problems for which irritability is a risk factor. Having to go into a nursing home increases dramatically when irritation is left untreated for an extended period. A wide range of violent conduct is associated with HD, from making threats to wrecking devastation on property. Minor or no provocation can quickly cause a person's irritability to explode into aggressive physical behavior. Rapid occurrences are possible.

Caregivers must learn to recognize situations that can exacerbate their patients and take steps to prevent them. Advice for caregivers on how to keep patients from getting frustrated. Both aggressive and irritable behavior often respond positively to medication, typically administered in conjunction with behavioral therapy. Medication has been demonstrated to successfully treat these disorders in most cases (Anderson, 2011).

1.2.7 Apathy

A lack of motivation is one definition of apathy, one of the symptoms associated with HD. Patients with moderate apathy might not initiate novel activities but might participate in novel activities already in progress. On the other hand, patients suffering from excessive apathy need to be coaxed into engaging in even the most routine of tasks. According to the findings of several different studies, up to fifty percent of all patients were afflicted by indifference. It has been proven that an elevated risk is associated with the illness's progression (Butters, 1984).

Depression and apathy are often hard to tell apart, especially as the illness worsens and communication becomes harder because of poor thinking or dysarthria. For apathy,

pharmacological therapies are not particularly effective. As with anger and violence, organizing everyday activities may be effective. Educating family members about the distinctions between apathy and depression and how to interact with apathetic individuals may be the most effective intervention (Pla et al., 2014).

1.2.8 Mood Swings

Mood swings are more common than not. The percentage of patients who report depression ranges between 30 and 70%. It is no longer considered that reactive mood swings are the only cause of sadness; depression can occur before or after motor abnormalities develop. Suicide is four times more common in HD patients than in general. Annual suicide rates are estimated to be between 3-7%. Suicide attempts occur in about 25% of people, increasing in the fifth and sixth decades of the disease (Schoenfeld et al 1984; Farrer, 1986). According to Paulsen et al. (2005a), 10% of HD patients attempted suicide at some stage.

According to statistics, persons with HD had double the rate of depression as the national average. Depression, the availability of weapons, singleness, living alone, a lack of children, a recent loss (such as a divorce or job loss), and childlessness all contribute to a larger proportion of HD patients committing suicide than the overall population. Patients with HD who report suicidal thoughts should have their condition evaluated as soon as possible due to the high risk of both suicide attempts and completion. According to Paulsen, a colleague search the risk of suicide is substantially higher at two key phases in HD. The first is the period immediately preceding receiving an HD diagnosis, and the second is the period immediately preceding the commencement of severe loss of independent functioning. According to preliminary research, approximately 5% of people have manic symptoms. 10% of patients had hypomanic symptoms as well (Pla et al., 2014).

1.2.9 Anxiety Problems

Very little research has been done on anxiety disorders. Anxiety is often cited as a precursory symptom in ancient medical writings. Recent research suggests that anxiety may contribute to the onset of overt illness. OCD is more common in people with HD. Obsessive and compulsive symptoms are roughly three times more likely in patients with obviously evident disease than in at-risk individuals who do not exhibit any obvious motor symptoms, as reported by Beglinger & colleagues (2007). Compulsive worrying and checking were also present before diagnosis in the at-risk group, which was confirmed when comparing them to a healthy control group. Patients with depression are typically given a selective serotonin reuptake inhibitor (SSRI). Clomipramine is an effective treatment for OCD. However, it is often poorly tolerated due to its side effects.For the same degree of symptom control seen in the general population, it may be necessary to utilize greater dosages of medication when antidepressants, especially SSRIs, are used. Extremely rarely, supplementing with an atypical neuroleptic may prove beneficial. There is a lack of evidence supporting the use of behavior therapy for managing anxiety in HD. These strategies have broad applicability in treating anxiety disorders and can definitely produce excellent results for the general population (Anderson,2011).

1.3 Mechanism of Pathogenesis

Even though it is widely accepted that the expression of an expanded polyglutamine is toxic and thus contributes to the toxicity seen in HD, It is not possible to conclude with certainty that the absence of wild-type huntingtin or its inactivation do not also play a role in the onset of neurodegenerative symptoms (Ramaswamy et al., 2007).

1.3.1 Aggregation of Mutant Huntingtin

HD is diagnosed by brain aggregates, like other polyglutamine diseases. These were first considered crucial to HD etiology. Mutant huntingtin's polyglutamine strands form a hydrogen-bonded b-sheet, forming an amyloid structure like other polyglutamine-containing proteins. HD aggregates were first discovered in the nucleus of HD patients' brains, but were later discovered in the cytoplasm and neuronal processes of these same brains., contain ubiquitin, proteasome subunits and chaperones, transcription factors, and even wild-type huntingtin. Thus, the idea of a negative consequence from removing functioning proteins from these aggregates appeared appealing.

The association between polyglutamines, aggregation rate, and disease onset supports their pathogenicity. However, aggregation may be incidental or protective in HD and other polyglutamine diseases. These inclusions trap toxic soluble chemicals, protecting healthy neurons from cell death. Mutant huntingtin species are feared to be poisonous. Many studies show that monomeric huntingtin's soluble oligomers before fibrils and inclusions are toxic. Identifying hazardous species helps devel op effective therapy methods. The aggregates are more common in the nucleus in juvenile-onset HD than in adult-onset HD (MacDonald et al., 1993).

Recent research reveals that perinuclear aggregates may have a nuclear appearance (i.e., cytoplasmic). The aberrant activation of the cell cycle that might result from the presence of hazardous substances known as perinuclear aggregates can induce cell death. Since diffuse mutant huntingtin did not influence cell mortality and genuinely nuclear aggregates were less detrimental than perinuclear aggregates, this discovery may help settle the HD aggregation controversy (Jimenez-Sanchez et al., 2017).

1.3.2 Fragments of Huntingtin are Highly Toxic

HD is characterized by an accumulation of huntingtin N-terminal fragments, which are toxic. Various proteases, including caspases and calpains, are responsible for producing these pieces. The abnormal splicing of the huntingtin protein's first exon is another potential cause. Mutant fragments correlate with enhanced toxicity compared to wild-type or enlarged huntingtin because they are more likely to form nuclear rather than cytoplasmic, less toxic aggregates. Different tissues may have different cell susceptibilities due to variances in the composition of these fragments (Jimenez-Sanchez et al., 2017).

1.3.3 Transcriptional Dysregulation

HD DNA microarray research has found considerable gene expression alterations. Polyglutamine expansion is incompatible with glutamic acid-rich transcription factor activation domains. Indeed, mutant huntingtin interacts with transcription regulators like p53, cAMP response element-binding (CREB) protein, and CBP involved in cell proliferation and survival PGC-1a (peroxisome proliferator-activating receptor-g coactivator-1 a), which is essential for energy metabolism Sp1 and its coactivator TAFII130, which affects transcription of genes like D2 dopamine receptor; and cystathion. In HD, the striatum is more vulnerable due to lower amounts of brain-derived neurotrophic factor (BDNF), which optically promotes

striatal neuron survival. BDNF or TrkB receptor malfunction in transcription or axonal transport may induce this deficit. Due to an influence on the postsynaptic p75 neurotrophin receptor, which binds to BDNF and TrkB (Jimenez-Sanchez et al., 2017).

1.3.4 Protein Degradation Systems Impairment

At least two intracellular protein degradation pathways exist: the ubiquitin-proteasome system (UPS), which destroys wild-type huntingtin, and the autophagy-lysosome system, which reduces mutant versions. Furthermore addition, the effect of mutant huntingtin on UPS and autophagy has been investigated. However, research has mostly focused on improving methods of upregulating certain mechanisms to lower mutant protein levels. Mice were used to show that UPS dysfunction resolves shortly after the appearance of inclusions, suggesting an adaptive mechanism.

Recent studies have shown that proteasomes can degrade enlarged polyglutamine, and the finding that proteasomes may be recruited to inclusions in a dynamic fashion without altering their activity is consistent with an improvement in HD competence.. Even though HD models have an increased number of autophagosomes, neither mutant nor wild-type huntingtin affects autophagosome formation. After researching the autophagic apparatus, researchers discovered that HD autophagosomes, once created, could not optimally sequester substrates.

Recent hypotheses imply that wild-type huntingtin has a role in recruiting autophagy machinery during selective autophagy, which may explain this discovery but has not been examined due to the lack of information on the impact of triplet expansion on this scaffold function. It has also been postulated that autophagosomes in HD have impaired axonal transport, which prevents autophagosome-lysosome fusion and reduces the quantity of autophagosome material that is destroyed (Jimenez-Sanchez et al., 2017).

1.3.5 HD Mitochondrial Disorder

Alterations in mitochondrial function, such as decreased ATP synthesis, impaired Ca2+ buffering capacities, and apoptosis, have been associated with Huntington's disease neurodegeneration (HD). There is a link between mitochondrial calcium anomalies and mutant huntingtin interactions with the outer mitochondrial membrane. Furthermore, mutant huntingtin can impair mitochondrial transport to synapses and ATP production by interfering with normal organelle axonal transport. This is because mutant huntingtin is a kind of huntingtin. Reduced transcription of mitochondrial genes can also result in mitochondrial dysfunction. This can be caused by factors such as the inhibition of PGC-1a, a nuclear coactivator that regulates the expression of genes involved in mitochondrial biogenesis and respiration, or the depletion of the enzyme required for cysteine synthesis, which is responsible for maintaining mitochondrial homeostasis. These two causes contribute to mitochondrial dysfunction (Paul et al. 2014). Mitochondrial dysfunction can also be caused by a decrease in the transcription of mitochondrial genes. Depletion of the enzyme necessary for cysteine synthesis, which is important for maintaining mitochondrial homeostasis, and the suppression of PGC-1a, a nuclear coactivator that regulates the expression of genes involved in mitochondrial biogenesis and respiration, are two potential causes. Mitochondrial dysfunction is caused in part by these two factors. Defects in protein transport into mitochondria can cause respiratory failure and neuronal cell death when they interact with TIM23 and then inhibit it. Huntingtin is the root cause of both of these side effects. In response to external signals and metabolic demands, mitochondria go through fusion and fission cycles. As a result, mitochondria become active organelles.

Fragmentation causes mitochondrial disintegration, which delays cell death by inhibiting mitochondrial fission and eventually leads to caspase activation and apoptosis.

Reduced mutant hunting, on the other hand, can be accomplished by either upregulating enzymes that favor fusion or generating an inhibitory version of Drop-1. Multiple HD models have shown that specific Drop-1 inhibitors can decrease disease progression by blocking tin from generating mitochondrial damage and toxicity (Guo et al. 2013). The generation of uncontrolled reactive oxygen species (ROS) results from mitochondrial failure, contributing to further mitochondrial damage. Oxidative damage has been detected in HD animal models and in postmortem examinations. As a result, antioxidant research is being conducted to examine their ability to lower ROS levels and aid mitochondrial dysfunction (Jimenez-Sanchez et al., 2017).

1.3.6 Huntington's and Cellular Mechanism

A complex circuitry of cell connections regulates the regular operation of neurons in different brain sections. While the autonomic effect of mutant htt on neuronal function has garnered much attention, the significance of cell-cell interactions in HD pathogenesis has received a lot less. Created conditional HD mice with exon1 mutant htt expressed in specific neuronal populations. It was observed that mutant htt aggregates in a cell-independent manner.

Motor deficits and cortical neuropathology progress over time only when mutant htt is expressed in multiple cell types, not simply cortical pyramidal neurons. Because the transgenic is defined under a neural promoter in their study, the researchers found strong evidence for the role of neuronal cell interactions in HD pathogenesis. Glial cells make up 90% of the brain's cells and play critical roles in neuron survival and function by delivering nutrients, growth stimulants, and structural support. They protect against excitotoxicity by removing excess excitatory neurotransmitters from the extracellular area. Because excitotoxicity has been proposed as the cause of HD, this protective role may be especially relevant to the

neuropathology of HD. As previously stated, glutamatergic axons are principally important for innervating MSNs in the striatum, and degeneration of these axons is preferred in HD. Glutamate stimulates ionotropic glutamate receptors such as N-methyl-D-aspartate (NMDA) and AMPA/kainate receptors. Excitotoxicity is caused by excessive extracellular glutamate through the overstimulation of glutamate receptors. Animals given NMDA receptor agonists in their striatums undergo selective loss of MSNs and neurological symptoms similar to those seen in HD patients, whereas animals given NMDA receptor antagonists benefit in HD animal models by lowering excitotoxicity. More particular, NMDA receptor activation in neurons of HD transgenic mouse models has increased. Because of the high levels of glutamatergic innervation that MSNs receive, cell-cell interactions may play a critical role in their susceptibility to extracellular glutamate. The glial cell type astrocyte is essential in the clearance of extracellular excitatory neurotransmitters. After entering the cytoplasm via membrane receptors (GLT-1 and GLAST) on these cells, glutamate is metabolized by glutamine synthase. According to certain studies, HD may be linked to decreased GLT-1 function. GLT-1 expression is reduced in the brains of HD mice, increasing extracellular glutamate. It has been demonstrated that the presentation of the glutamate transporter is inhibited in transgenic mutant htt in Drosophila glia, which reduces the fly's lifetime. According to Shin et al., glial cells express mutant htt in the brains of HD mice and HD patients. They also discovered that glial glutamate uptake provides less protection against htt-mediated neurotoxicity in mutant htt. These data suggest that glia-neuron interactions are essential in the genesis of HD (S. Li & Li, 2006).

1.3.7 Effect of Mutant Huntingtin on the Cytoplasm

Caspase activity increases, and signaling pathways are altered when mutant htt is present. Based on these findings, it appears that mutant htt affects the processes in the cytoplasm of

cells. Interactions between htt and cytoplasmic proteins were hence the subject of extensive research. In yeast two-hybrid screens and in vitro binding investigations, htt was found to interact with several different cytoplasmic proteins. Both HAP1 and HIP1 have received much research. Both proteins can move into cells. The HAP1 receptor is bound more tightly by the mutant htt. The microtubule-dependent retrograde transporter dynactin p150 and the anterograde transporter kinesin light chain two are both connected to HAP1. HAP1 plays a role in the trafficking or endocytosis of membrane receptors, including those for epidermal growth factor (EGF), type 1 inositol (1,4,5)-triphosphate receptor (InsP3R1), GABA, and nerve growth factor (NGF). Microtubules and axonal terminal synaptic vesicles both contain HAP1, similar to the way that htt does.The neuronal degeneration in the hypothalamus of HAP1-deficient mice causes death on postnatal day 3. The function of the hypothalamus that is carried out by HAP1 is essential to both the behavior of eating and the metabolism. Any dysfunction in this function may result in HD hypothalamic illness or degeneration. It is required for both the cytoskeleton's development and endocytosis's process that HIP1 binds the clathrin and alpha-adaptin component AP-2. HIP1 may combine with these proteins to form a clathrin-mediated endocytosis protein complex. HIP1 weakly binds mutant htt, unlike HAP1. This demonstrates that HIP1 requires htt to function normally and that mutant htt may prevent it from doing so. Although investigations with mutant htt cells provide more persuasive evidence, the interactions of htt with HAP1, HIP1, and other cytoplasmic proteins imply that it is involved in intracellular trafficking. Recent research has shown that normal Drosophila htt functions in the axonal transport route and that PolyQ expansion causes soluble htt to bind more microtubule transporter proteins, resulting in a reduced concentration of soluble htt in axons. In cultured neurons, the presence of the mutant htt gene disrupts the HAP1-associated anterograde and retrograde BDNF axonal transport. It was discovered by Trushina and colleagues (2004) that full-length mutant htt impeded the transport of vesicles and

mitochondria in mouse neurons. Caenorhabditis elegans can develop axonal abnormalities before cell body degeneration if there is an increase in polyQ in the first exon of the htt gene. This can occur even in the absence of cell body aggregation. Through the expression of polyQ proteins, mutated htt can cause disruptions in the axonal transport of cultured neurons (S. Li & Li, 2006)

1.3.8 Huntingtin and Intracellular Trafficking

Htt interacts with several cytoplasmic proteins, which raises the possibility that it participates in endocytosis and other forms of intracellular trafficking. HIP14 is a brain-enriched protein that interacts with other proteins and is essential for endocytosis in S. cerevisiae. It shares sequence similarity with the ankyrin repeat protein Akr1p. The neuron-specific phosphoprotein PACSIN 1 interacts with other proteins and has been linked to synaptic vesicle recycling. Synaptic vesicle recycling protein dynamin I have a binding partner in SH3GL3, and we found that mutant htt binds to this protein. In addition, normal htt binds to PSD-95, a scaffold protein that gathers receptors together and turns them on in the postsynaptic membrane. In HD, more PSD-95 is produced to activate N-methyl-D-aspartate (NMDA) receptors compared with unaffected persons, which raises an intriguing idea. According to electrophysiological research, elevated NMDA receptor activity and aberrant synaptic transmission have been observed in mouse models of this condition. The presence of htt aggregates in neuronal processes and axonal terminals is a notable feature of neuropathology in HD, alongside nuclear inclusions. Proteins involved in microtubule-dependent transport, recycling of synaptic vesicles, and receptor endocytosis are all found in neuronal processes, lending credence to the pathogenic significance of htt's interactions with these proteins. Suppose large htt aggregates are unable to fit into the confined area of neuronal processes and axonal terminals. In that case, this could directly impact endocytosis and trafficking, as well as neurotransmitter release. Neuropil

aggregates are connected to the development of the illness in mice and axonal degradation in the first stages of HD. To sum up, neuropil aggregates and dystrophic neurites, which may develop from neuropil aggregates, are more prominent than intranuclear aggregates in the brains of presymptomatic and early-onset HD patients. Neurons in HD brains do not show htt aggregates in their perikarya (cytoplasm in cell body), which may be because misfolded or aggregated htt fragments are removed more quickly due to comparatively higher activity of chaperones and proteasomes in perikarya than in the nucleus and processes. The dysfunction in prokaryotes may, therefore, be due mostly to soluble mutant htt, the most toxic form of htt. Interactions with other proteins show htt may participate in, or at least affect, signaling networks critical to cellular function. As one example, htt can interact with proteins involved in growth factor-mediated signaling cascades. These signaling molecules may be negatively affected by the mutant htt's abnormal interactions with them, which in turn may have an effect on cell survival and caspase activity. In vitro tests show that mutant htt binds to and sequesters wild-type htt . It has to be shown whether or whether this interaction contributes to the cytotoxicity of transfected cells or the lower expression of wild-type htt in the late stage of the disease in HD animals (S. H. Li & Li, 2004).

1.4 Aim of the Study

This is the review paper where clinical characteristics, pathogenesis and possible treatments of Hungtington’s disease has been discussed. We know Hungtington’s disease is a neurodegenerative disease usually affecting patients of age 30-40 years. The disease may also affect adolescence patients but they have a very low chance of being affected. In this paper all types of symptoms of HD’s disease has been discussed briefly. Also, it was discussed how pathogenic organisms attack the human host to cause this particular type. Lastly, the conventional therapy, drugs and emergence of therapy have been discussed. Different papers

have covered different topics of HD's disease. In this paper, all the knowledge have been summarized to get a comprehensive idea about the disease.

Chapter 2

Methodology

After conducting extensive study, I began by gathering seventy papers that were relevant to my research topic from a variety of online sites, including PubMed, Research Gate, Elsevier, and Science direct, among others. Out of all of those papers, 50 were picked based on their relevance, and then 20 papers that had been published in the most recent years were chosen in order to obtain the most up-to-date information. After that, all of the information was combined, rearranged, and rethought, and then an outline was developed by using secondary research method which was then followed by an in-depth analysis of all of these articles. In the end, all of the selected information was rewritten, and references were inserted with the assistance of the Mendeley library in order to specify the origins of that particular pieces of information. As a result, I decided to conduct this research on the topic of "Possible Treatments of Huntington's Disease: A Comprehensive Review"

Chapter 3

Result and Discussion

3.1 Possible Treatment Strategies for HD

3.1.1 Pharmacological Approach

HD is often linked with reduced motor function; nevertheless, significant behavioral changes can occur years before motor disruptions. Despite the fact that most people experience depression's early phases, the disease's mental indication spectrum can expand. Examples of abnormal behavior include abnormalities in a person's sexuality, impatience, aggressiveness, broad paranoia, hallucinations, stress, forgetfulness, obsessive-compulsive disorder (OCD), indifference, and a lack of motivation in anything. Clinicians do not have access to enough randomized controlled studies that would assist them in making therapy decisions for specific elements of HD dysfunction. In most cases, it is determined by the response history of the patient as well as their side effect profile.

There is a chance that benzodiazepine anxiolytics, SSRIs, SNRIs, conventional and atypical antipsychotics, and tranquilizers could all be worthwhile. In the context of clinical studies for HD, the medications flibanserin, atomoxetine, citalopram, and venlafaxine have all been evaluated. An investigation including Seventeen HD patients who did not feel depressed and a randomly selected, double-blind, placebo-controlled trial that after four months of therapy with fluoxetine (20 mg/day), there were no significant clinical benefits in motor or cognitive performance. The trial was carried out after fluoxetine was administered (Phillips et al., 2008).

Patients with moderate HD participated in double-blind crossover research that lasted for ten weeks. Like fluoxetine, atomoxetine (80 mg daily) did not show any meaningful benefit in cognitive, mental, or motor skills compared to the placebo. The mental, motor, and executive functions of HD patients are being investigated with citalopram at 20 milligrams per day. Recent research conducted with 26 HD patients who suffered from severe depression found that venlafaxine XR (75 mg daily) was beneficial despite commonly causing side effects such as nausea and restlessness (Venuto et al., 2012).

3.1.2 Tetrabenazine

The FDA has only approved tetrabenazine (TBZ) to treat chorea in HD patients. TBZ briefly inhibits the brain's vesicular monoamine transporter 2 (VMAT-2). However, this action is reversible. Because VMAT-2 transports monoamines such as serotonin, dopamine, and norepinephrine from the cytoplasm into presynaptic vesicles, inhibiting it promotes neurotransmitter breakdown at an early stage. Chorea is relieved by dopamine deficiency, although melancholy and anxiety may be exacerbated by serotonin and norepinephrine deficiency. Some people respond well to low doses of TBZ, while others require much larger levels, making dosing tricky. Typically, the recommended dosage is 12.5mg once daily, up to 3x daily for a total of 100mg.It is highly individual and may necessitate modifications throughout treatment to determine the best dose. A long-term safety review, for example, discovered a link between age and an increased risk of parkinsonism. The hepatic isoenzyme CYP2D6 is in charge of TBZ metabolism, however, its activity varies widely between individuals. In addition to clinical monitoring, patients who require daily doses of 50 mg or above should be genotyped for CYP2D6 activity. If it is determined that you are a poor CYP2D6 metabolizer, your daily dose should be at most 50 mg. (Kenney et al., 2007)It is critical to remember that if access and reimbursement for these diagnostic tests are unavailable,

a patient's clinical response may continue to act as the primary dosage signal. Because CYP2D6 is involved in the metabolism and activation of several drugs, drug interactions may raise TBZ concentrations to dangerous levels (Wyant et al., 2017).

Sleepiness, sluggishness, sadness, restlessness, akathisia, and hyperkinesis were all more common in the TBZ group. No significant differences between and placebo persisted by the end of the maintenance period, when patients were probably at their maximum dosage . Restlessness (akathisia), sorrow, drowsiness, tiredness, and even parkinsonism are all possible side effects. During titration, individuals may experience tiredness, drowsiness, or stomach difficulties. During the double-blind study, one TBZ-treated patient committed suicide. TBZ can exacerbate sadness that already exists in HD patients. However, impulsiveness, OCD-like behavior, and socioeconomic position should be assessed in relation to suicide attempts and completions (Frank, 2014).

3.1.3 Deutetrabenazine

For over fifty years, deuterium, a benign form of hydrogen, has been used in medicinal medications to reduce liver metabolism. 8 Drug half-life is increased without changing the drug's protein-binding interactions due to the replacement of deuterium, this results in a carbon bond that is both stronger and more resistant to being broken.

A longer half-life for medicine has the potential clinical benefit of reducing dose frequency, which could boost patient adherence to therapy**.** No direct comparison between deutetrabenazine and tetrabenazine for the treatment of chorea in HD has been conducted. Since tetrabenazine (TETRA-HD) and deutetrabenazine (First-HD) were both examined in Phase III clinical trials versus placebo for the treatment of HD-associated chorea, it may be acceptable to compare their respective findings. The Huntington Study Group, which oversaw

both the TETRA-HD4 and First-HD6 investigations, used essentially the same methodology in both (Dean & Sung, 2018).

3.1.4 Others

The goal of treatment is to reduce or eliminate symptoms. Given that at least some degree of dopaminergic hyperfunction would contribute to the chorea-like movements seen in HD, dopaminergic antagonists are utilized to treat the condition. Phenothiazines, butyrophenones, benzoquinones, and rauwolfia alkaloids are all examples of such compounds. Carbamazepine is more effective than lithium for treating mania in HD. Alternatives to this include clonazepam and valproic acid. Neuroleptic drugs are another option for treating psychotic symptoms. (Levin et al., 2006) However, there is strong evidence suggesting that the response to these traditional antipsychotic treatments is less than ideal. Dosages are typically higher than those employed for motor symptoms. Benzodiazepines effectively treat anxiety and other disorders where anxiety or agitation is present. Neuroleptics, antidepressants, and beta-blockers may all help people who are too aggressive. The HD patient population is not a good candidate for surgical intervention. As part of a holistic strategy, a patient with HD may also benefit from supportive treatments such as psychotherapy, occupational therapy, dietary guidance, and family counseling (Orth, 2017)

Clozapine, fluphenazine, risperidone, and olanzapine are also viable choices for people with chorea. An emerging category of "dopamine stabilizers," dopiness is now in research and development. Their effects on dopamine transmission vary depending on the individual's current state, as a result of their intricate pharmacodynamics. Although the antichorea impact is mild, patients have reported significant improvements in gait, balance, and dystonia. In order

to establish this medication as a breakthrough in symptomatic therapy, larger and more rigorous trials are required (Wyant et al., 2017).

3.2 Emerging Treatments for Huntington's Disease

Many attempts at disease modification have been made in the twenty-plus years following the identification of Huntington's disease gene based on hypotheses of neuronal injury and the likely activities of huntingtin. A wide variety of approaches, from metabolic interventions to shield neurons to gene-silencing therapies, have been proposed. The search for genetic moderators of symptom onset is also continuing. However, progress has been slow because scientists still don't understand things like htt's primary role in the body or how mhtt causes disease.

Htt plays a critical role in embryonic development and survival, although its function later in life is less well understood. Supportive data suggests a function in intracellular signaling, apoptosis prevention, BDNF synthesis, and intra- and intercellular transport. Huntington's disease (HD) is believed to be caused by mhtt through toxic gain-of-function mechanisms. These include transcriptional interference, cytoskeletal disruption, synaptic dysfunction, mitochondrial damage, excitotoxicity, accumulation of toxic aggregates, loss of derived neurotrophic factor (DNF), and changes in axonal transport (Venuto et al., 2012).

3.2.1 Conversion of Gene Therapy

The innovative approach of converting gene therapy is now being studied in preclinical phases for the treatment of HD. By reprogramming adult endogenous glial cells into neurons using in vivo cell conversion technology, the requirement for an external transplant and the risk of immune rejection can be avoided. Astrocytes, NG2 cells, and the adult brains of mice and monkeys have all been shown to be responsive to reprogramming into neuronal cells. It is feasible to transform fibroblast cells into medium spiny neurons by reprogramming them in vitro. Co-administration of NeuroD1 and Dlx2 led to the effective transformation of adult striatal astrocytes into GABAergic striatal neurons in two HD transgenic mouse models, R6/2 and YAC128. The reprogrammed neurons have the same electrical properties as the original neurons, and the reprogrammed mice models result in a partial recovery of motor functional impairments and enhanced longevity.

Another cutting-edge method is active and passive vaccination against the mutant HTT protein. As shown by active immunization-based preclinical investigations in HD animal models, exon1 of the mutant HTT protein can be targeted by host B cell-mediated antigen-specific antibodies. This further downregulates aberrant neuro inflammation and cell death pathways. Researchers have developed antibody fragments that target a specific area in the N-terminus of the mutant HTT protein in order to prevent protein misfolding. These antibody fragments are currently being tested in additional preclinical trials. It has been demonstrated that this therapeutic antibody fragment can lower the amount of mutant HTT aggregates in HD mouse models when it is injected into the striatum using an AAV vector. Many of the treatments that are being discussed here require invasive administration through intraparenchymal or intrathecal delivery; therefore, research is currently being carried out to determine the efficacy of orally bioavailable small-molecule therapies for alternative splicing in RNA (STAR)

technology in the treatment of Huntington's disease. This is because many of the therapies that are being discussed here are not curative. This innovative technique intends to generate tiny compounds that are capable of repairing faulty and damaged RNA by utilizing splicing modifiers that are present in RNA structures (Pan & Feigin, 2021).

3.3 Therapy for Protecting and Replacing Damaged Neurons

3.3.1 Neuroprotective Therapy

Preserves restore, or replaces neurons. These treatments don't require HD molecular knowledge. Thus, they may aid HD treatment. Neurotrophins interact with TrKA, TrKB, and TrKC membrane receptors. These receptors tyrosine kinase. NGF, BDNF, and NT-4/5 bind to TrkB, while NT-3 preferentially binds TrkC. Neurotrophic factors protect neurons and improve functional recovery in several neuronal damage paradigms. Excitotoxins and mitochondrial toxins cause striatal neuron loss in animal models of HD. Neurotrophic factors reduced neuronal degeneration and behavior in HD animal models. Direct injection, engineered cell implantation, or viral expression vectors transfer neurotrophins into brains. Neurotrophins cannot be injected into brains clinically. Neurotrophin delivery can be sustained by transplanting neurotrophin-producing cells into brains [54]. Cell encapsulation strategies reduce immunological response to implanted cells. Polymer-encapsulated cells secreting human NGF survived one year in rat ventricles (Hospital & Unit, 2005).

3.3.2 Neurotransplantation

Researchers have proposed grafting new cells into brain regions to replace damaged neurons and restore functions for years. Early HD disease affects the striatum most. Many animals and human research have given HD patients hope for a new treatment. In early rodent HD investigations, intrastriatal injection of striatal neurons from 14- to 15-day-old rat fetuses reestablished a new striatum-like structure at the site of ibotenic acid-induced lesions. This reduced striatal atrophy by 50%–70% in rats with lesions and 30%–40% in rats receiving grafts. The striatum accepts cell suspensions and tissue pieces.

But grafts from cell suspensions triturated with trypsin had more striatal tissue and DARPP-32-positive medium spiny neurons than tissue fragments. Functional recovery after cell transplantation in a monkey HD model supports neuronal replacement as an HD treatment. A frontal-type cognitive task recovered completely and persistently 2–5 months after intrastriatal allografting. Striatal allografts reduced HD-related dystonia.Grafted cells cannot operate without target neurons. Neural precursor cells transplanted into a rat model of HD established a neuronal network. After transplantation, many neural precursors developed to produce neuronal markers, such as DARPP-32, indicating a mature striatal phenotype.

Neuronal fibers from the grafts spread throughout the host brain without target-directed outgrowth. Phaseolus vulgaris-leucoagglutinin (PHA-L) axonal tracing examined thalamo-striatal projections to rat neostriatal grafts. . Labeled graft fibers generated intense focal arborizations. Grafted striatums had altered synaptic connections. Grafts lose route specificity in dendritic spine development on neostriata neurons due to the relocation of postsynaptic elements. QA lesioning lowered striatal DA responses. Lesioned rats needed a much higher dose to block striatal neuron activity. Fetal striatal tissue transplantation restored DA-sensitive electrophysiology in the lesioned striatum. Graft survival and its impact on neurological

abnormalities in HD transgenic mice have been investigated. Hemizygote transgenic and wild-type littermate female mice received striatal grafts at ten weeks and survived for six weeks. Standard healthy grafts survived and differentiated in the striatum of transgenic mice like control mice. Transgenic mice lost weight and were hypoactive in an open-field test of general locomotor behavior from 9 weeks of age. Although striatal grafts had a statistically significant effect on various indicators of this impairment, all behavioral effects were minor and did not affect the substantial neurological insufficiency of transgenic mice. HD patients have evaluated neural transplantation safety and efficacy. Two HD patients received homotopic fetal striatal homotransplantations in their experiment. Each patient received stratum from a 13-week-old and 12-week-old human fetus in the right caudate nucleus ventricular wall (Pan & Feigin, 2021).

Chapter 4

Conclusion

Huntington's disease (HD) is a degenerative neurological condition that causes a person's motor, behavioral, and cognitive abilities to deteriorate over time. It is a deadly condition. Despite the fact that the underlying genetic abnormality was identified more than 20 years ago, the treatment has concentrated on relieving symptoms. Chorea, the most obvious sign of Parkinson's disease, can be treated using medications that block the transmission of dopamine in the brain. It's possible that treating mental health issues like anxiety and depression with symptomatic therapy will be effective.

So far molecular models have had minimal success in identifying disease-modifying medications. The genetic mutation that causes all HD cases extends the HTT protein's polyQ tract abnormally. PolyQ increase grants HTT one or more detrimental activities and

intracellular accumulation. Thanks to extensive molecular networks in every cell, protein misfolding can be prevented and corrected or destroyed. These networks may perceive mutant HTT as a threat and engage preventive coping mechanisms, but they will only delay HD. Insufficient native folds intracellularly could overwhelm the molecular chaperone system, causing the cellular proteostasis system to collapse or stimulating too much of HTT's normal duties, although the specific method by which a polyQ expansion in mutant HTT causes neurodegeneration is unknown. Pharmacologically enhancing proteasome action or autophagy to diminish HTT misfolding or mutant HTT levels is unknown. However, a breakthrough in treating this lethal ailment may be on the horizon, thanks to one of the latest gene silencing techniques.

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