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A Review on Structure Based Therapeutic Approach for Huntington Disease

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ABSTRACT

Huntington disease (HD) is a fatal and progressive neurodegenerative disease that has affected the social and personal life of patients. The disease causes the most disturbing symptoms of chorea, which is characterized by uncontrolled body movements. HD patients are being treated by providing drugs that maintain neurotransmission balance and relieve chorea symptoms. HD has been associated with mutant Huntingtin protein (mHtt) with more than thirty-six polyQ stretches at N terminal of 34 kDaHtt protein. mHtt protein undergoes misfolding, which leads to accumulation of toxic mHtt aggregates in the brain. The phenomenon of protein aggregation initiates a cascade of events, eventually leading to endoplasmic reticulum (ER) stress and misregulated unfolding protein response (UPR). Different molecular targets have been identified from ER stress and UPR pathways for finding potential molecules that can treat HD. Overall, the mechanism causes structural transitions in mHtt, which can be controlled at the subatomic and molecular level by molecular dynamic simulations (MDS). The MDS strategies help to observe structural changes in the mHtt protein and association pattern between the protein and novel drug compounds. Hence, this study explains the journey of HD research to computational strategies and the scope of structural drug designing in psychologically disturbing Huntington's disease.

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INTRODUCTION

Huntington's disease (HD) is a deadly genetic disorder responsible for the degeneration of nerve cells progressively. The incurable disease leads to deterioration of physical and mental abilities of the patient during their working age (30 to 40 years). The disease follows genetic inheritance with 50% probability of receiving disease-causing genes from parents (Chen *et al.*, 2012). HD is a disabling disorder with a characteristic triad of dementia, behavioural and body movement disorders. The disease prevalence of 4 to 8 patients per 100,000 population has no gender predominance (Bhidayasiri, 2004). HD patients are expected to survive for 10 to 25 years after disease onset and have a mortality rate of 5 to 10%. The disease onset has been characterized by a mutation in the huntingtin gene (IT15) leading to cytosine-adenine-guanine (CAG) triplet repetitions (Aronin *et al.*, 1995). These repetitions are then translated to poly-glutamine (poly-Q) stretches in the huntingtin protein. Normally, poly-Q stretch repetitions vary from 9 to 34; however, repeats occurring beyond a threshold of 36 results in disease onset (Bonfanti *et al.*, 2019). These unregu-

lated repeats cause abnormal protein folding leading to aggregation of protein fibers. Abnormally folded protein aggregates accumulated as inclusion bodies are the characteristic pathological hallmark of HD (Arrasate and Finkbeiner, 2012). The molecular mechanisms of protein aggregates are common targets for drugs against Huntington's disease.

The common symptoms associated with HD include dysfunction in thinking ability, behavioural problems and uncontrolled body movements (Table 1). The most dangerous symptoms are related to involuntary body movements such as fidgeting, which can cause severe damage (Bates *et al.*, 2015). Currently, HD is incurable and scientists are looking for treatments that can prevent disease onset at a molecular level. There are different drug treatments available for symptomatic relief in order to make patients' life comfortable. However, HD symptoms greatly vary among different patients and change with disease progression. Due to which there has been a problem of severe drug side effects in case of prolonged HD treatments (Liou, 2010). This review elaborately discusses HD treatments from the perspective of symptom relief as well as molecular mechanisms. This study explains the importance of structural based studies on protein aggregation to expand research horizons in structure-based drug designing for HD.

Huntington Disease and Chorea

A chorea is an uncontrollable form of movement disorder characterized by involuntary movements beginning from one body part and flowing to another. The disorder has been hypothesized to be generated by neurotransmission imbalance in pathways related to ganglia (Bhidayasiri, 2004). The neurotransmitter, dopamine is responsible for excitation of thalamus through direct and indirect pathways, resulting in cortical signalling. Dopamine causes stimulation of excitatory receptors on GABA-ergic neurons. Alternatively, dopamine inhibits body movement by stimulation of inhibitory receptors on GABA-ergic neurons of the striatum (Feinstein and Walker, 2018). It has been hypothesized that decreased indirect pathway activity and increased direct pathway activity is responsible for uncontrollable body movements in chorea, which are the most common symptoms of HD.

An anti-choric drug known as Tetrabenazine (TBZ) has been commonly advised for treating chorea as it helps in reducing dopamine amounts in the brain to regulate neuronal excitation. According to Mehvar et al., TBZ binds with vesicular monoamine transporters (VMATs), preventing them from storing dopamine (Mehvar and Jamali, 1987). Due to this, VMATs fail to store and release dopamine at a synapse, reducing dopamine amount in the brain. In-vitro studies have shown that TBZ also binds with dopamine receptors on nerve cells and decreases chorea. However, some dystonic side effects have been reported for TBZ (Burke *et al.*, 1985). Commonly, TBZ helps in relieving body movement dysfunction in HD patients.

Common Treatments for Chorea in Huntington Disease

The physiological hallmark of HD includes involuntary muscle movements associated with chorea. Clinicians have been using drugs against chorea to provide symptomatic relief to HD patients (Table 2). Several drugs that have been studied for chorea can be divided into different groups based on their targets. One such group is for 'dopamine targeting drugs' which includes tetrabenazine (TBZ), which is the only drug approved by the FDA for HD treatment. Narcoleptics such as Clozapine, Olanzapine, Quetiapine and Risperidone have been used by HD specialists as they cure behavioural and body movement problems (Videnovic, 2013). However, there is less clinical proof on the role of these drugs in chorea. Some practitioners do not recommend these drugs because of their severe behavioural symptoms.

Another group of drugs is 'Glutamatergic modifying drugs' which change glutamate levels in the brain. Drugs such as amantadine and riluzole help in treating body movement dysfunction by anti-glutamergic and anti-excitotoxic properties (Armstrong and Miyasaki, 2012). Both the drugs have shown severe side effects in terms of blood problems, hypersensitivity, liver problems and suicidal behaviour. Other drugs reported for HD chorea include Donepezil which treats memory-related problems. According to Fernandez et al., Donepezil improved memory loss in two out of eight patients; however, a study was not statistically completed (Fernandez *et al.*, 2000). Later, Donepezil's effect on restoring cognitive functions was proved by Cubo et al. (Cubo *et al.*, 2006). The drugs that have shown a considerable effect on chorea regulation have been used in HD patients. However, severe side effects persist in long term treatments which should be considered while prescribing HD treatments.

Protein Aggregation in Huntington's Disease

Normally, huntingtin protein (Htt) is expressed everywhere in the human body, but Htt expression levels are high in the brain. Htt protein is soluble and usually found in nucleus and membrane vesicles (Cattaneo *et al.*, 2005). It is a 348 kDa protein

having poly Q and proline-rich stretches at N terminal. It acts as a scaffold in different cellular mechanisms due to various protein interaction motifs such as HEAT domain. As per in vitro molecular studies, the interaction between normal Htt and HAP1 (Huntingtin-associated-protein-1) is important for trafficking of vesicles in neuronal cells. Another function of Htt includes binding with transcription factors for repression of transcription (Zuccato *et al.*, 2003). Hence proper folding of Htt is required for normal metabolic functions in the brain.

In contrast to normal Htt, mutant Htt (mHtt) consists of more than thirty-six polyQ stretches at N-terminal. These unregulated increase in polyQ stretches affect protein flexibility required for interaction with N17 (first 17 amino acids in Htt) and proline domain. The reduction in flexibility promotes Htt protein aggregation into insoluble amyloid deposits rich in beta-sheet structures (McClellan *et al.*, 2005). According to a study by Sanchez et al., intra-peritoneal injection of azo-dye congo-red promoted in-vivo clearance of Htt protein aggregates and showed a positive effect on motor functions (Sánchez *et al.*, 2003). In another study involving trehalose, it was found that the prevention of protein aggregation in HD had an effect on motor functions and striatal atrophy in a transgenic HD mouse model (Tanaka *et al.*, 2004). However, later it was reported that both congo red and trehalose couldn't pass through the blood-brain barrier (BBB) and hence their effect on HD was questioned. In solution, guanine residues peptide known for cell penetration were introduced to trehalose and this led to an improvement in BBB penetration by new trehalose derivative (Im *et al.*, 2013). Similar effects on relieving disease symptoms were observed.

The other form of therapeutic strategies against HD includes inhibition of aggregating protein at the monomer stage. Small molecules such as poly Q binding peptide (QBP-1) have been reported to suppress polyQ aggregation and improve neurodegeneration symptoms in HD model of drosophila (Nagai, 2003). C2-8 small inhibitor capable of penetrating blood-brain barrier has also been known to reduce motor dysfunction and atrophy in HD mouse model (Chopra *et al.*, 2007). Hence according to these reports, targeting Htt aggregation and subsequently removing downstream effects should be the rational approach to drug target discovery in HD.

ER stress and unfolded protein response in Huntington's disease

Endoplasmic reticulum (ER) stress is one of the common characteristic features of neurodegenerative disorders such as HD (Ogen-Shtern *et al.*, 2016). HD has been associated with misfolding and aggregation of mutated Htt protein which cause accumulation of toxic species, thus generating ER stress and deregulation in cell functions. ER stress happens when mHtt aggregates interfere with ER-associated degradation (ERAD) components, thus triggering unfolded protein response (UPR). UPR has the aim of unfolded protein clearance which occurs by regulation of different transcription factors, ultimately inhibiting protein translation (Hetz and Papa, 2018) ER is known to balance protein misfolding by inhibiting protein translation, elevating chaperones production and enhancing degradation leading to apoptosis (Sano and Reed, 2013). The combined effect of ERAD inhibition and unregulated UPR increases toxic aggregates accumulation and causes ER stress. Thus, a mitochondrial function has been found majorly affected in HD, causing severe cytotoxicity.

According to Nyugen et al., sigma-1 receptor (S1R) activated during ER stress can be a prospective target for treating HD symptoms. S1R agonist PRE-084 has been used in mHtt neuronal cell lines, and neuroprotective behaviour was observed, including S1R restoration along with regulation of antioxidant activity (Nguyen *et al.*, 2015). Pridopidine, another S1R agonist, also showed a similar effect in HD mouse models (Garcia-Miralles *et al.*, 2017). Alternatively, the UPR sensor called PERK is another target for HD drugs. Two activities of PERK have been found to be associated with UPR. Low activity of PERK mediated phosphorylation of eIF2 in the mouse brain has been observed to be linked with elevated mHtt toxicity (Leitman *et al.*, 2013). Additionally, ER stress accounts for upregulated CHOP through the PERK pathway, which cascades into cell death. PERK inhibitor such as GSK2606414 has been found to be protective in dementia mouse models (Moreno *et al.*, 2013). Also, compounds inhibiting downstream pathway of eIF2 have been successful in treating neurodegeneration in prion related diseases (Sidrauski *et al.*, 2013). Therefore PERK inhibition can be beneficial by reducing cell death, but other positive roles of PERK have to be accounted.

Structural study of Huntington's disease targets

Structural characterization of Huntingtin protein (mHtt)

The large size of huntingtin protein (348 kDa, 3144 residues) has made it difficult to study aggregation conditions and its effects on mutant protein. Most research studies are focused on poly Q fragment and part of the protein responsible for amyloidosis. It has been already reported that mHtt has direct

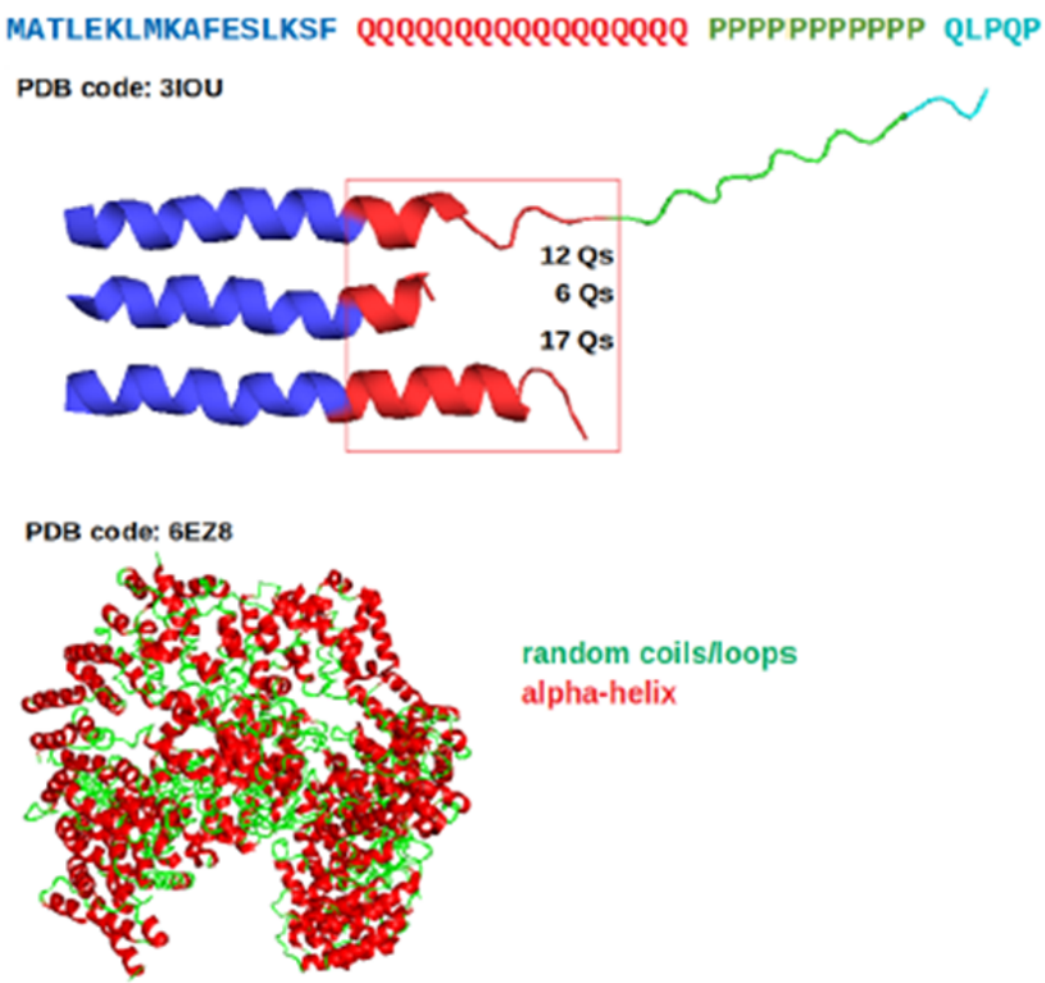

Figure 1: Secondary structure of exon 1 of Htt protein (top) and full sequence secondary structure representation of Htt protein (bottom).

involvement in the aggregation process. However, clarity lacks information on amyloids. In order to study aggregation behaviour, it is important to study conformational changes in different structures. All-atom molecular dynamics simulations of full-length Htt protein have shown that the structure remains the overall conserved, the however secondary structure of poly Q regions show variations. The secondary structure of N terminal of Htt has been determined through X-ray crystallography and structures are available as PDB files for computational studies (Kim *et al.*, 2009). The full-length sequence structure of Htt and N17 domain of Htt are also available under PDB. Different PDB codes exist for modifications done in the structure of the protein such as insertion of three Histidine residues in N terminal of Htt. Figure 1

Several theoretical models of aggregation in Huntingtin disease exist and correlate with experimental data as well. According to Perutz et al., Q side chains can form hydrogen bonds with the main-chain atoms. These interactions were later on proved to be essential in providing structural stability to poly Q aggregates (Perutz, 1994). It has also been shown that stability of aggregates is dependent on the antiparallel orientation of beta-sheets, where amine group from one side chain can bind to the carboxyl group of side chain following the subsequent turn. Apart from full length mutated protein, conformational variations in the starting point of the protein exon-1 Of Htt has been found to be linearly correlated with disease threshold. In order to study these possibilities, classical molecular dynamics simulations have been performed to study mutant protein's stability. Although, these studies propose poly-Q aggregation models contradictions among the studies exist, and the structural transitions among the mHtt remain unclear.

Structural dynamics study of Huntingtin protein confirmations

The structural properties of poly Q have been studied by experimenting with different number of Qs

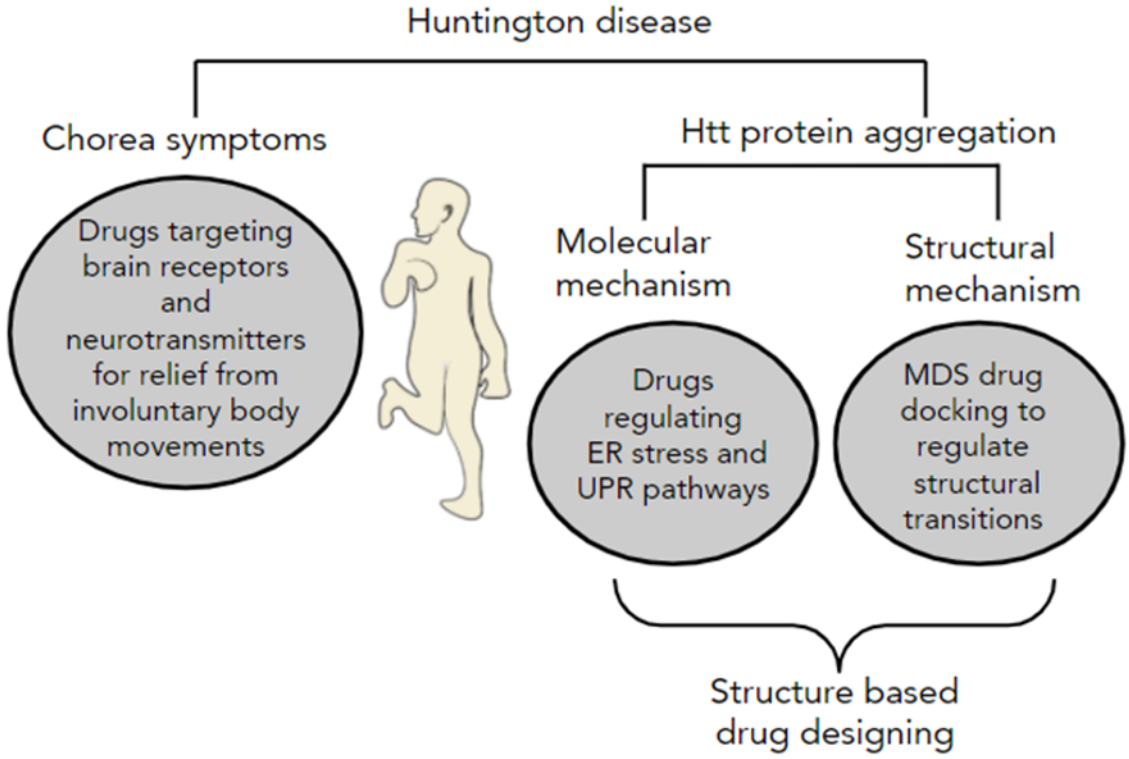

Figure 2: Research concepts focused on molecular and structural mechanisms providing a prospective strategy of structure-based drug designing.

Table 1: Different symptoms of Huntington disease (HD) and associated pathological characteristics.

HD symptoms	Pathological characteristics
Behavioural changes	Hallucinations, Irritability, Impulsiveness, Paranoia, Psychosis
Thinking problems	Confusion, Loss of memory, loss of judgment, Personality changes
Body movements	Restlessness, fidgeting, Facial movements, Head turning to shift eye position, Slow, uncontrolled movements, Speech problems, Swallowing problems, Unsteady gait (walking pattern)

Table 2: Chorea related drugs used for Huntington disease (HD) and their side effects

Chorea related HD drugs	Type of drug	Side effects
Tetrabenazine	Dopamine regulating drug	Parkinsonism, Falls, Depression, Narcoleptic malignancy, Restlessness
Clozapine	Serotonin antagonist	Tremors, weight gain, blurred vision
Olanzapine	Dopamine receptor antagonist	Restlessness, Depression, body imbalance, unusual behaviour
Risperidone	High-affinity binding with dopaminergic and serotonergic receptors	Anxiety, Agitation, Abnormal vision, Sleep disturbance, tremor.
Riluzole	Glutamatergic modifying drug	Liver problems, High WBC count, Suicidal thoughts Heart problems
Amantadine	High-affinity binding with glutamate receptors	Dizziness, Blurred vision, Sleeping problems
Donepezil	Acetylcholinesterase enzyme inhibition	Muscle cramps, uncontrolled urination, Appetite loss, Nausea

and oligomeric states that are achieved by computational analysis. The stability of monomers and oligomers structures have been done by atomistic MD simulations on designed models of poly Q length more or less than the disease threshold. It has been devised that β helices having 3 turns are unstable as circular confirmations but stable at triangular β-helices confirmation. During dimerization, the stability of triangular confirmation helps in structural formations, whereas individual triangular confirmations are relatively unstable (Zhou *et al.*, 2011). These studies helped in an understanding number of Qs responsible for disease threshold at the aggregation point of mHtt.

Inter-atomic interactions in Huntingtin protein aggregation

Molecular dynamics (MD) simulations with force fields are classical methods for studying atomic behaviour according to Newton's law under predefined potential energy environment. The technique offers imitations in terms of time scale, which is generally of nanoseconds, and biological concepts study require extended time scales. Thus more relevant results can be attained by a combination of MD simulations with enhanced computational techniques. Hybrid techniques such as quantum-classical (QM/MM) MD simulations have been used to understand factors contributing to β-sheet conformational stability (Rossetti *et al.*, 2010). Such techniques have been used to study the correlation of poly Q in initial aggregation seed formation. Another approach that has gain importance in studying atomic interactions are coarse-grain models (CG), where reactive groups are considered as single beads. The strategy has been devised to study cooperative effects of aggregation process where CG model helps in evaluation of H-bond interactions (Ma and Nussinov, 2006). Discrete molecular dynamics (DMD) represent another molecular dynamics strategy based on inter-particle potentials. DMD has been used in studying the structural folding behaviour of chimeric monomer with poly Q repeats. The advance computational tools like these have helped in understanding nucleation mechanisms in protein aggregation. Kelley et al. showed that structural transition occurs between two-helix and singe helix confirmation of N17 of Htt. Further, it was demonstrated that direct interactions exist between N17 and poly Q chains (Angeli *et al.*, 2010). Thus the computational methods and MD can help in devising essential structural transitions, interactions involved in Huntingtin protein aggregation.

Scope of finding HD treatments

A clear understanding of protein misfolding and its conformational changes are theories of great interest for computational scientists. Understanding the landscape of structural transitions in response to aggregation mechanisms can be an elevated step towards the discovery of drug targets for HD. In 2018, Caterino et al. devised interesting findings regarding post-translational modifications in mHtt. The important conclusion drawn through MD was regarding aptamer binding with Htt gene (Caterino *et al.*, 2018), which can be a prospective treatment strategy in future. Moreover, oligonucleotides have been studied for inhibiting pathological cascades in HD (Zaghloul *et al.*, 2017).

DNA aptamers have the ability to bind with a wide range of proteins, viruses, ions for molecular interventions. Using aptamers can be an interesting therapeutic strategy for HD, but the research needs more intricate mechanistic details and clinical data assessment. Similarly, other drug chemicals are usually formulated to modify structural and behavioural patterns of proteins associated with diseases.

This involves the identification of target proteins which play a key role in signalling pathways responsible for disease severity (Zaghloul *et al.*, 2017). Structure-based drug designing can be one of the strongest approach towards protein misfolding related diseases like HD (Figure 2). In this regard, molecular dynamics simulation (MDS) has been discovered as a powerful tool for understanding structural transition at the atomic stage.

The tool has been famous for its recent applications in Alzheimer disease's Aβ protein. Klimov and Thirumalai have provided useful information about Aβ, suggesting the significance of antiparallel β-sheets and α helical intermediates (Zhao *et al.*, 2007). Thus, MDS is a potential tool that can be implemented in other misfolded protein-related diseases such as HD.

In an extensive study performed by Vopel et al., a molecular tweezer was discovered to inhibit aggregation of Htt exon-1. The authors identified N-17 as a target for therapeutic interruption using molecular tweezer CLR01 (Klimov and Thirumalai, 2003; Vöpel *et al.*, 2017). Different molecular simulations were employed to understand the structural transition during aggregation. They proved that the binding of CLR01 is capable of inducing structural rearrangements that can prevent Htt exon-1 aggregation. At this stage, MD simulations should be performed with different protein targets and promote structural drug designing algorithms in the upcoming future of drug discovery.

CONCLUSION

In this review, Huntington's disease has been elaborately discussed in terms of drug targets. The most usual way of treating HD patients has been found as symptomatic relief. The occurrence of involuntary movements associated with chorea is the most disturbing symptoms of HD. Hence drugs targeting regulation of neuronal transmission have been mostly employed for HD patients. Alternatively, scientists have been trying to understand structural and molecular targets for drug discovery in HD. The disease has been associated with incorrect protein folding, which leads to a cascade of molecular deregulation related to control the accumulation of misfolded protein aggregates. This creates regulatory stress on endoplasmic reticulum leading to cytotoxicity. Several molecular agonists and inhibitors have been studied to understand molecular regulation in HD in-vivo models. In parallel terms, molecular dynamics simulations have provided a useful understanding of aggregation mechanisms from a structural point of view. MDS has been successful in the discovery of novel therapeutic interventions to control Htt aggregation, which can be important as a drug docking mechanism for further studies. Overall, at this stage, it is required that a biological experimental approach should be employed in coordination with computational strategies to elaborate on the scope of structural drug designing in psychologically disturbing Huntington disease.

Conflict of interest

The authors declare that they have no conflict of interest for this study.

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