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REVIEW

Surface-Engineered Precision Nano-Systems for Targeted Treatment of Huntington's Disease: A Review of Recent Advancements

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Abstract: Huntington's disease is a progressive neurological disorder marked by motor, cognitive, and psychiatric symptoms. Currently, there are no definitive diagnostic tools or effective treatments to halt or reverse the disease. In recent years, surface-engineered nanosystems have emerged as innovative therapeutic platforms, offering significant promise in overcoming the limitations of traditional approaches. These nano systems, including liposomes, dendrimers, polymeric nanoparticles, and solid lipid nanoparticles, offer significant potential by targeting and modulating intricate biochemical pathways involved in the progression of Huntington's disease. Their defining advantage lies in the ability to selectively deliver therapeutic agents to specific regions of the brain with high precision. Through the use of various nanoscale carriers, these particles can successfully traverse the protective barrier between the blood and brain tissue, enabling the direct delivery of treatment agents to the regions affected by Huntington's disease. This targeted approach not only enhances the therapeutic efficacy but also minimizes unwanted systemic side effects. This review highlights recent advancements in nanosystem development, addressing previous challenges and setbacks in the field, particularly in overcoming the blood-brain barrier and improving treatment delivery. The review further explores the evolving mechanisms of nanosystem delivery and their functional impact in experimental models of Huntington's disease. While the primary focus remains on therapeutic applications, we also briefly discuss recent developments in nanoparticle-based diagnostics. Although several challenges, particularly regarding comprehensive safety assessments and the current absence of nanoparticles approved by the United States Food and Drug Administration for Huntington's disease, this review underscores the transformative potential of nanosystems for future therapeutic applications.

Keywords: Huntington's disease, precision nano systems, targeted drug delivery, blood-brain barrier, nanomedicine, neurodegenerative disorders

Introduction

Neurodegenerative diseases represent a broad group of chronic disorders characterized by progressive structural and functional deterioration of the central and peripheral nervous systems. Since neurons are terminally differentiated and have limited capacity for regeneration, they are particularly vulnerable to irreversible damage. The key pathological features common to these diseases are summarized in Figure 1. As neural circuits degrade, essential functions such as cognition, memory, motor coordination, behavior, and sensory processing progressively decline.[1,2] HD was first clinically described by Waters in 1842, but it was formally recognized and named after George Huntington's detailed account in 1872. The prevalence of HD varies significantly across different populations. In European communities, it affects approximately 10 to 13 individuals per 100,000 people, whereas in East Asian countries, the prevalence is considerably lower, ranging from 1 to 7 cases per million. In South Africa, the condition is more frequently observed among white and mixed-ancestry populations compared to Black populations.[3–5]

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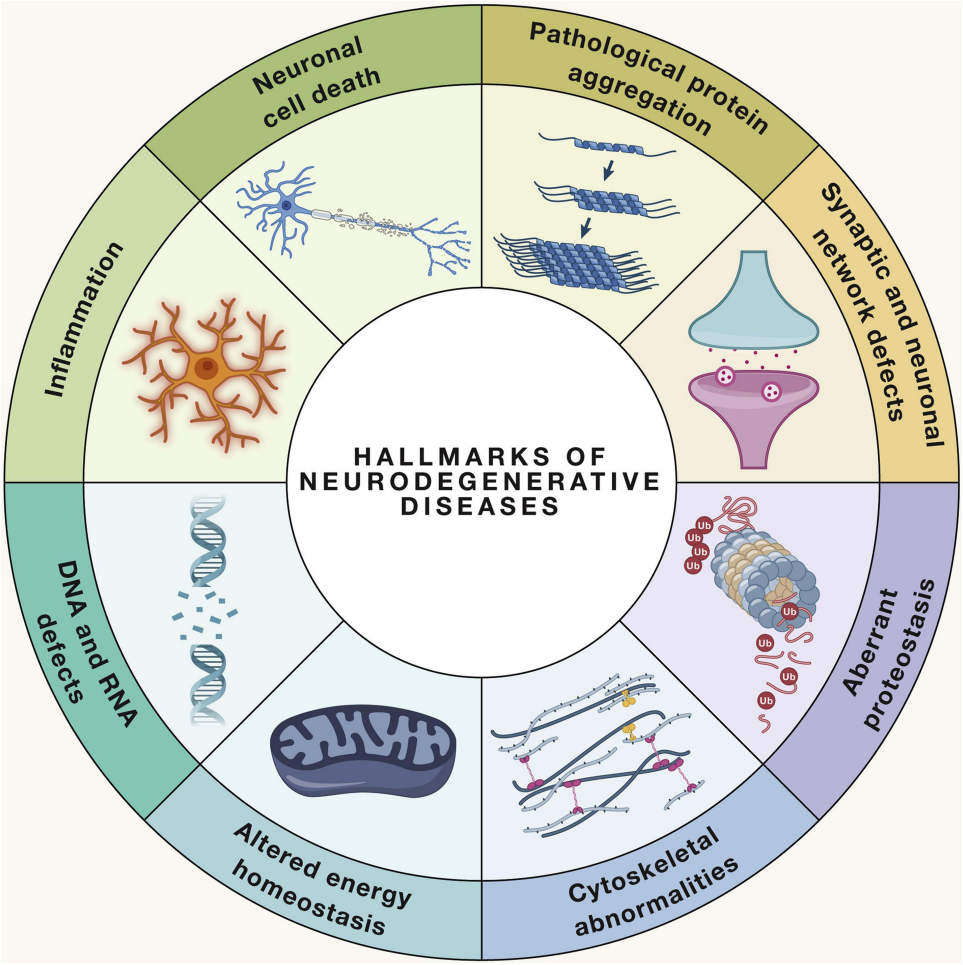

Figure 1 The scheme identifies and illustrates the hallmarks of basic, translational, and clinical research, genetic factors, and biochemical pathways underlying many like pathological protein aggregation, synaptic and neuronal network dysfunction, aberrant proteostasis, cytoskeletal abnormalities, altered energy homeostasis, DNA and RNA defects, inflammation, and neuronal cell death. Adapted with permission from reference.[2]

Huntington's disease (HD) is a hereditary neurodegenerative disorder typically manifesting in mid-adulthood, characterized by progressive motor dysfunction (notably involuntary choreatic movements), cognitive decline, and psychiatric disturbances,[6] an autosomal dominant disorder caused by the abnormal expansion of CAG trinucleotide repeats in the huntingtin gene located on chromosome 4. This expansion results in the production of a mutant huntingtin protein containing an elongated polyglutamine tract. The misfolded protein disrupts cellular homeostasis, leading to neurotoxicity and apoptosis, particularly affecting the medium spiny neurons of the striatum, which are highly susceptible. These neurons rely a lot on the dopamine signaling to perform their tasks, and the depletion of dopamine observed in HD in particularly in D2 receptor-expressing MSNs, worsens their degeneration.[7] MSNs are also prone to excitotoxicity because they also demonstrate glutamate receptors. The build-up of mutant huntingtin (mHTT) protein disrupts the activity of glutamate receptors, causing calcium influx and death of neurons.[8] Recent studies show that MSNs in the striatum show early transcriptional dysregulation and excitotoxic signatures before neuronal death,[9,10] with MSNs showing a higher vulnerability to glutamate toxicity and polyglutamine aggregation than other neuronal subtypes.[11] Furthermore, MSNs also develop mitochondrial dysfunction and deficiency in axonal transportation that are aggravated by mHTT, leading to their further degeneration.[12] Individuals carrying more than 39 CAG repeats exhibit full penetrance and invariably develop the disease, whereas those with 36 to 39 repeats show reduced penetrance and variable age of onset. Paternal transmission frequently results in further expansion of the CAG repeats, owing to higher instability in sperm cells compared to other tissues. While environmental factors such as pesticide and heavy metal exposure may

modulate disease progression, genetic testing remains the definitive tool for diagnosis.[13–15] The huntingtin gene is present in all individuals in two allelic forms, and while the disorder follows an autosomal dominant inheritance pattern, the parental origin of the expanded allele can influence disease severity. Specifically, expansions inherited from the father tend to show greater instability, often resulting in longer repeat lengths and earlier onset in successive generations.[16]

Current treatment strategies for HD are primarily symptomatic and fail to effectively slow or reverse disease progression. The development of successful therapies is significantly challenged by the intricate barriers of central nervous system (CNS) drug delivery, most notably the blood-brain barrier (BBB), which limits the penetration of therapeutic compounds into the brain. Furthermore, issues such as poor drug bioavailability and rapid metabolic degradation critically reduce treatment efficacy.[17] Recent therapeutic strategies for neurodegeneration focus on targeting underlying molecular and cellular mechanisms. Emerging approaches for HD treatment include direct intracerebral interventions, transient disruption of the blood-brain barrier via osmotic opening of tight junctions, prodrug utilization, and carrier-mediated drug delivery systems.[18] Nanotechnology offers promising solutions to these challenges by enabling targeted delivery, controlled release, and enhanced brain uptake of therapeutic agents. Functionalized nanoparticles, decorated with surface ligands such as apolipoproteins, facilitate crossing of the BBB, protecting the active compounds from degradation and reducing systemic side effects.[19] HD is a potentially fatal disorder requiring prompt diagnosis and intervention.

Recent breakthroughs in nanotechnology present a good plan to surmount significant challenges in the treatment of HD, such as low bioavailability and the limited BBB. Various therapeutics may be carried by engineered nanoparticles to deliver therapy in a targeted and more efficient manner. As an example, nanoparticles can be tagged with small interfering RNAs (siRNAs) or antisense oligonucleotides to target the mutant huntingtin gene, thus silencing the aggregates of the toxic protein.[20] Neuronal support (eg, neurotrophic factors, ie, BDNF) may also be encapsulated,[21] oxidative stress (eg, curcumin or epigallocatechin-3-gallate) can be delivered using nanocarriers,[22] and even stem-cell or gene-therapy payloads can be transported with the help of nanocarriers.[23] When functionalized on nanoparticles with targeting ligands (eg, apolipoproteins or antibodies), these therapeutic cargos facilitate the receptor-mediated transcytosis across the BBB, selective uptake to different brain parts, and reduce systemic side effects - providing a groundbreaking path to HD therapy.[24]

Symptoms of Huntington's Disease

Chorea, a hallmark symptom of HD, manifests as involuntary, irregular jerking or twisting movements, initially affecting the lower limbs. Severe chorea contributes to fatigue, bradykinesia, dystonia, rigidity, and postural instability, resulting in progressive motor impairment and increased risk of falls.[25] Neuroimaging studies have demonstrated that brain abnormalities can be detected in presymptomatic HD individuals before the onset of motor symptoms.[26] The cortical dementia characteristic of Alzheimer's disease, marked by prominent memory loss, communication deficits, and learning impairments, differs from the cognitive profile observed in HD. Currently, there are no effective therapies for HD cognitive symptoms, partly due to limitations of standard screening tools like the Folstein Mini-Mental State Examination, which are more effective in diagnosing dementia than HD.[27] Psychiatric symptoms constitute a major component of HD and have a profound impact on both patients and their families. These manifestations can range from depression and anxiety to irritability, apathy, and, in some cases, psychosis. They are frequently linked to dysfunction in the frontal cortex and thalamic nuclei, particularly the ventral anterior and mediodorsal regions. Behavioural disturbances often emerge alongside cognitive decline as the disease progresses, although they are generally more manageable than cognitive impairments in terms of treatment and care strategies.[28]

A rare but severe form of HD, known as Juvenile HD, typically presents before the age of 20 and is commonly associated with more than 60 CAG repeats in the huntingtin gene. This early-onset form, often referred to as the Westphal variant, is characterized by pronounced motor rigidity, seizures, and progressive cognitive decline. Juvenile cases account for approximately 7% of all HD diagnoses and generally exhibit a more rapid and aggressive clinical course compared to adult-onset forms.[29] Affected parents have a 50% chance of passing the mutant HTT gene to their children. CAG repeats in the 28–40 range are unstable and may expand during transmission, potentially leading to

disease in future generations. This instability contributes to genetic anticipation, where symptoms appear earlier or more severely in successive generations.[30]

Pathogenesis of Huntington's Disease

mHTT causes neuronal dysfunction and death through multiple pathways, including abnormal aggregation of its exon 1 fragment, disrupted axonal transport, transcription, translation, proteostasis, mitochondrial, and synaptic functions. Figure 2 depicts the Key pathological mechanisms of HD. The striatum, especially medium-sized spiny neurons (MSNs), is highly vulnerable. Early MSN loss leads to a hypokinetic phenotype. Dopamine D2 receptors influence MSN circuit sensitivity and are involved in HD pathology. Other proposed mechanisms include toxic effects of RAN translation proteins, glutamate excitotoxicity from corticostriatal inputs, and impaired neurotrophic support.[7] Post-mortem analyses of individuals with HD consistently reveal progressive atrophy of the caudate nucleus and putamen,

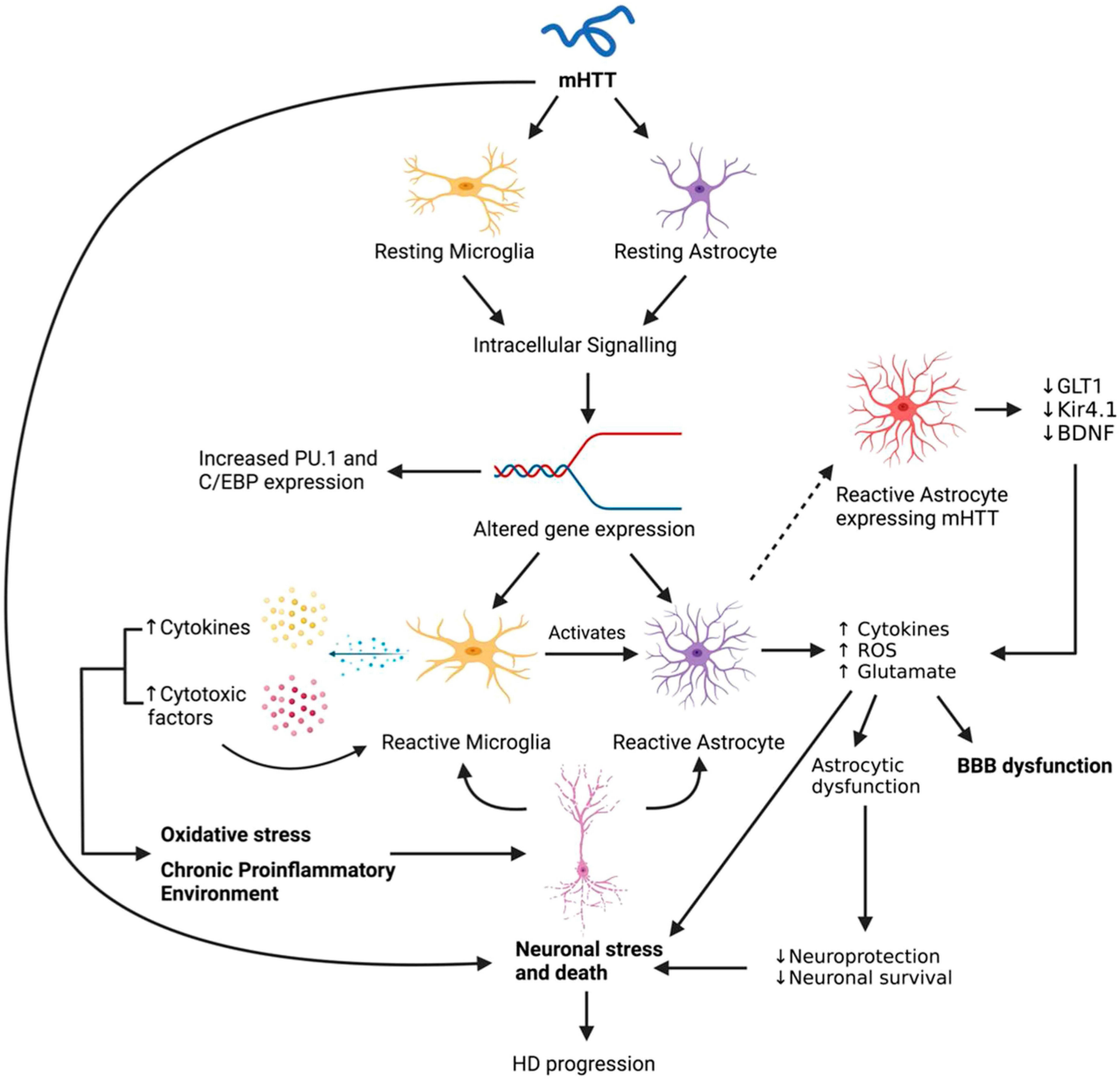

Figure 2 Mechanisms involved in the Pathology of Huntington's disease. Reproduced with permission from reference.[33]

typically following dorsoventral, caudo-rostral, and mediolateral gradients. Neuropathological staging divides the disease into five grades: initial stages show subtle astrocytic changes without visible structural alterations, while advanced stages involve macroscopic degeneration of the striatum, globus pallidus, nucleus accumbens, cortical regions, and ventricular enlargement. In later phases, additional degeneration is observed in the thalamus, subthalamic nucleus, and cerebral white matter. Magnetic resonance imaging supports these findings by demonstrating progressive grey matter loss in both the striatum and cerebral cortex as the disease advances.[31,32]

Treatment of Huntington's Disease

General therapeutic strategies for HD are illustrated in Figure 3. They primarily target chorea, the most recognizable motor symptom, which arises from early degeneration within the basal ganglia, particularly the striatum. The basal ganglia modulate movement through coordinated activity of the direct and indirect pathways. In HD, early loss of enkephalin-expressing medium spiny neurons in the indirect pathway disrupts inhibitory control over the globus pallidus externus, resulting in excessive inhibition of the subthalamic nucleus. This cascade reduces excitatory output to motor-inhibitory regions such as the substantia nigra pars reticulata and globus pallidus internus, ultimately decreasing thalamic inhibition and causing excessive cortical excitation. This dysregulation underlies the involuntary, hyperkinetic

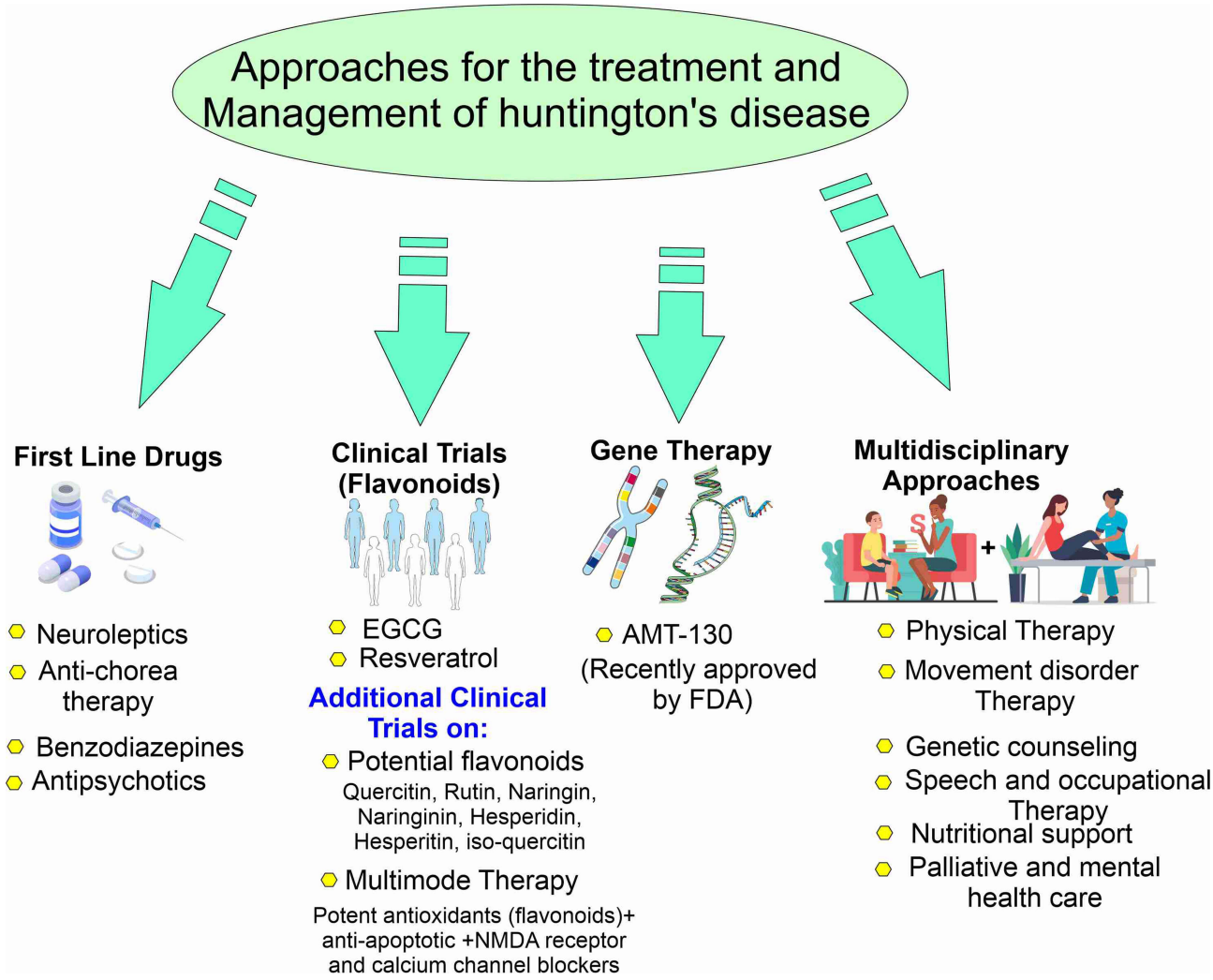

Figure 3 Overview of current therapeutic approaches for the management of HD. The illustration summarizes symptomatic treatments, including neuroleptics, antidepressants, and multipurpose medications, as well as emerging strategies like gene therapy (AMT-130). It also highlights the role of natural antioxidants, particularly flavonoids (EGCG, resveratrol, quercetin), which have shown promise in preclinical and limited clinical studies for mitigating oxidative stress and improving neurological outcomes. The figure is drawn by the authors themselves.

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movements characteristic of chorea. Notably, cognitive and affective disturbances often precede the onset of motor symptoms by several years, underscoring the multifaceted nature of the disease.[8]

Pharmacological Treatments

Tetrabenazine was the first pharmacological agent approved for the treatment of chorea in HD. It functions by reversibly inhibiting vesicular monoamine transporter 2, depleting central monoamines; however, the precise mechanism by which it alleviates chorea remains incompletely understood. In a randomized controlled trial involving 84 patients, tetrabenazine significantly reduced chorea severity, with a mean decrease of 5.0 units on the Unified HD Rating Scale, compared to a 1.5-unit reduction with placebo over 12 weeks. Common adverse effects included somnolence, Parkinsonism, depression, insomnia, anxiety, and akathisia. While side effects led to treatment discontinuation in four participants, most were manageable through dose adjustment.[34]

Deutetrabenazine, a deuterated derivative of tetrabenazine, offers improved pharmacokinetics and requires less frequent dosing due to its extended half-life. In a 12-week randomized trial with 90 patients, it significantly reduced chorea severity compared to placebo. While both agents carry warnings for depression and suicidality, deutetrabenazine is associated with fewer neuropsychiatric side effects, such as agitation and Parkinsonism. The elevated suicide risk in HD reported in 10–25% of patients is likely disease-related rather than drug-induced.[35] Dopamine D_2 receptor antagonists, primarily used for managing psychosis, are considered second-line agents for Huntington's disease-related chorea. Given the role of glutamate excitotoxicity in disease pathology, anti-glutamatergic agents such as amantadine and riluzole have also been investigated for symptomatic relief.[36] Amantadine, a non-competitive antagonist of N-methyl-D-aspartate receptors, also modulates dopaminergic pathways and is approved for levodopa-induced dyskinesia in Parkinson's disease. In a double-blind study involving 24 HD patients, a daily dose of 400 mg amantadine led to a median 36% reduction in chorea scores within two weeks.[37] Riluzole, an anti-glutamatergic drug, improved chorea by 35% in six weeks, but symptoms returned after stopping. A 12-month study showed sustained benefit at three and twelve months with 50 mg twice daily.[38] The long-term efficacy of riluzole for HD chorea remains uncertain. Olanzapine, an antipsychotic commonly used for schizophrenia, is frequently prescribed for behavioral symptoms in Huntington's disease. In a study of 11 patients, olanzapine significantly improved behavioral scores over six months but had minimal impact on chorea. These findings suggest that tetrabenazine and deutetrabenazine may be more effective for chorea, whereas olanzapine better addresses behavioral symptoms. Due to potential drug interactions, combination therapy is often necessary in patients with multiple manifestations. Olanzapine acts by antagonizing α1-adrenergic, muscarinic, histamine (H1), serotonin (5-HT2A, 5-HT2C), and dopamine (D1, D2, D4) receptors. Olanzapine is categorized as an atypical antipsychotic because, in contrast to most other antipsychotic drugs, it has a greater affinity for 5-HT receptors than D2 receptors. Olanzapine can cause dyslipidemia and excessive weight gain, observed in both clinical trials and animal studies. Therefore, patients' metabolic status should be considered before prescribing.[39,40]

Risperidone, an atypical antipsychotic, antagonizes dopamine D2 and serotonin 5-HT2 receptors. In a 14-month study of 17 HD patients, risperidone improved behavioral and psychiatric symptoms and stabilized motor function. Although results are promising, larger trials are necessary to confirm efficacy. In schizophrenia, olanzapine and risperidone show comparable benefits, with olanzapine causing greater weight gain (27% vs 12%).[41] Approximately 10% of HD patients attempt suicide post-diagnosis, with 40% experiencing partial or persistent depression. Antidepressants, primarily selective serotonin reuptake inhibitors, are commonly prescribed for depression but do not alleviate chorea or psychosis. SSRIs increase extracellular serotonin by inhibiting its reuptake, leading to postsynaptic receptor desensitization, which may underlie both side effect tolerance and therapeutic efficacy. They also downregulate serotonin 5-HT2 receptors, sustaining neurotransmission modulation.[42,43] Further research is required to determine which SRRIs are most effective for HD patients and if they are appropriate medications to address the high incidence of suicidality. Citalopram was tested in a 20-week trial with 33 HD patients. It improved depression scores but did not affect executive function.[44] Fluoxetine, another commonly prescribed SSRI for Huntington's disease, showed mood improvement and reduced obsessive-compulsive symptoms in a small case study. Though clinical trials are limited, they offer short-term depression relief. Sertraline is also used, effectively reducing depression and controlling aggression and OCD symptoms in HD.[45] HD patients often face bipolar disorder, obsessive-compulsive disorder, aggression, and other behavioral issues.

Anticonvulsants such as carbamazepine, lamotrigine, and sodium valproate are commonly prescribed and have shown efficacy in alleviating these symptoms.[46]

Anticonvulsants reduce neuronal overactivity by modulating ion channels and neurotransmitters. Sodium valproate and carbamazepine also enhance cellular resilience through key signaling pathways and epigenetic effects. These actions help stabilize mood symptoms in HD.[47,48] Lamotrigine inhibits the excitatory neurotransmitters glutamate and aspartate and blocks voltage-gated sodium channels. Used as a mood stabilizer in Huntington's disease, it may reduce excitotoxicity, but its neuroprotective effects are limited. A 30-month placebo-controlled trial in early-stage patients showed no significant slowing of disease progression, indicating symptomatic benefit without disease modification.[49] Carbamazepine primarily works by blocking voltage-gated sodium channels, though its exact pharmacodynamics remain unclear. Although it is prescribed as a mood stabilizer in HD, no clinical studies have specifically evaluated its benefits for HD patients.[50] Anticonvulsants can cause side effects like hypersensitivity, blood disorders, dizziness, gastrointestinal issues, depression, and hyponatremia. Carbamazepine, in particular, may lead to serious skin conditions such as Stevens-Johnson syndrome and toxic epidermal necrolysis, which is why alternatives are often preferred.[50] HD treatment must be personalized, with medications tailored to symptoms and closely monitored for benefits and side effects.

Non-Invasive Strategies and Lifestyle Adaptations

Comprehensive HD management requires a multidisciplinary healthcare approach. Lifestyle changes and non-invasive therapies also play key roles. Physiotherapists help improve balance and gait affected by chorea, advising when mobility aids are needed. Occupational therapists support patients by conducting home assessments and recommending adaptations like handrails to enhance safety and independence.[51] Hyperkinetic dysarthria, caused by involuntary movements of the mouth, throat, and respiratory muscles, often affects speech in HD patients, leading to abnormal prosody and hoarseness. Speech and language therapy can help improve communication, and therapists may provide electronic devices or communication charts for those who lose speech ability. Malnutrition is common due to weight loss, so dietitians develop meal plans and suggest strategies like blended or liquid foods to manage feeding difficulties. In severe cases, patients may require a Percutaneous Endoscopic Gastrostomy (PEG) for nutrition.[52,53] Psychologist sessions, combined with medication, can help manage the psychosocial and cognitive symptoms of HD. They also monitor the patient's response to treatment and support overall mental well-being.[50]

Surgical Treatments

Deep brain stimulation (DBS) can reduce chorea in pharmacologically resistant HD patients but does not improve bradykinesia or dystonia. Due to its invasiveness and the rarity of resistant cases, DBS is rarely used. Effective HD care requires a multidisciplinary medical team beyond just medication.[50]

Emerging Treatments

Nanotechnology-Based Treatments

Nanocarriers composed of polymers, metals, proteins, or lipids enable targeted delivery of treatments like siRNAs, stem cells, antioxidants, and neurotrophic factors, improving efficacy while minimizing side effects due to their small size and modifiable surfaces.[54] Figure 4 depicts an overview of the key types of nanoparticles employed in neuronal disease treatment strategies. Nanoparticles are used clinically for diagnosis and treatment, including Huntington's disease. They improve drug efficacy by prolonging half-life, reducing resistance, and protecting drugs from degradation. Their small size enables better cellular uptake and targeted release. Particles between 20 and 100 nanometers effectively cross the blood-brain barrier and avoid renal clearance, making them ideal for neurodegenerative therapies. Notably, siRNA-based therapies can selectively silence the mutant huntingtin gene, offering promising treatment potential.[55,56] By offering necessary protection during the delivery process, NPs safeguard cargos, including siRNA, which is protected against enzyme degradation in the circulation, premature removal, and controlled release after getting to the brain. Indicatively, compared to free cargos, functionalized polymeric or lipid NPs exhibit longer half-life of circulation and greater

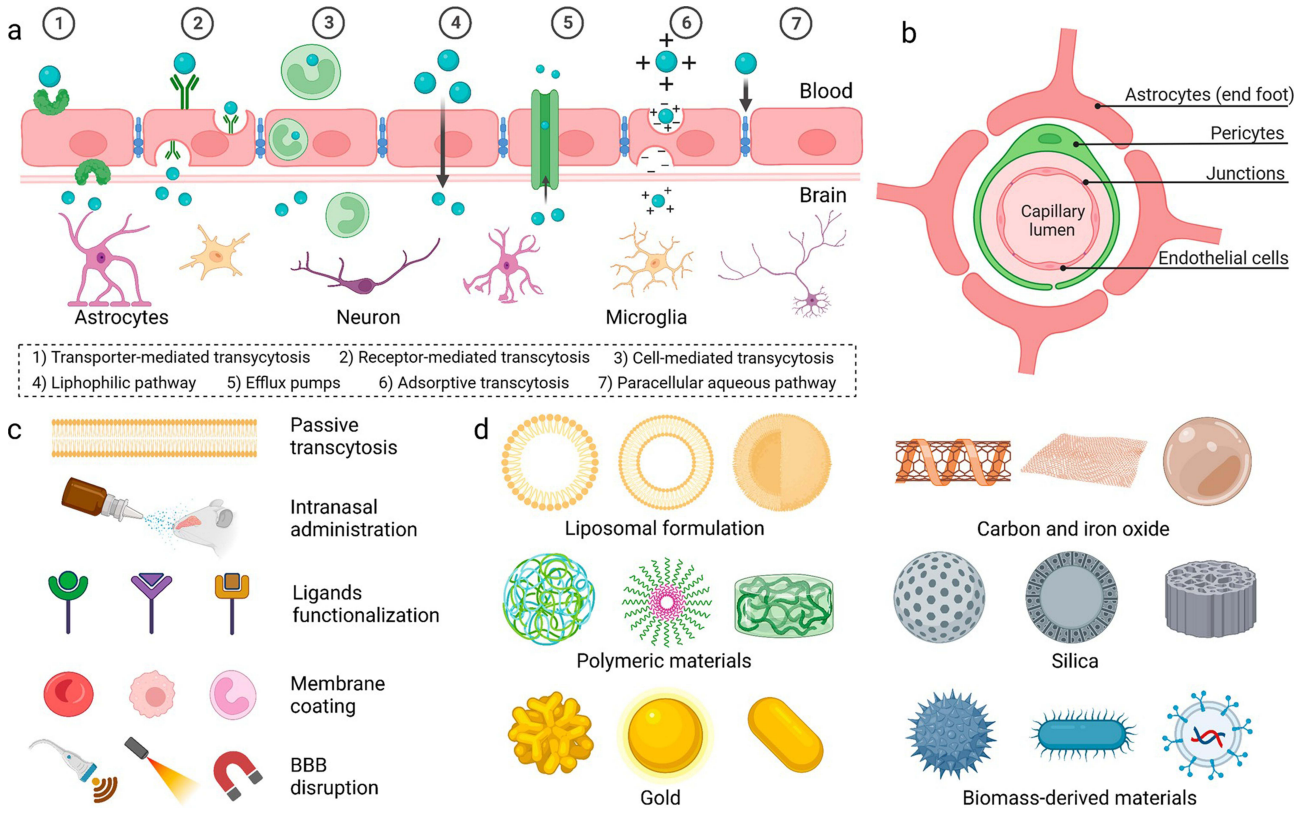

Figure 4 Schematic representation of key strategies and engineered materials used for blood–brain barrier (BBB) regulation and brain-targeted drug delivery. (**a**) The illustration includes various mechanisms by which nanoparticles and therapeutic agents traverse the BBB, such as passive diffusion, carrier-mediated transport, receptor-mediated transcytosis, and adsorptive-mediated transcytosis. (**b**) The structural components of the BBB are depicted, including endothelial cells connected by tight junctions, pericytes, astrocytic end-feet, and the basement membrane, all of which contribute to the restrictive nature of the barrier. (**c**) Further, the figure highlights a range of engineered nanocarriers such as polymeric nanoparticles, dendrimers, liposomes, and solid lipid nanoparticles functionalized with specific ligands to enhance targeting efficiency and penetration into diseased brain regions such as the striatum and cortex. (**d**) Finally, several non-invasive approaches to facilitate BBB crossing are shown, including focused ultrasound, magnetic targeting, nasal delivery, and chemical modulation, which aim to enhance central nervous system drug bioavailability while preserving BBB integrity. Adapted from the reference[60] under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

accumulation of nucleic acids in the brain.[57–59] They are also able to achieve specific delivery (through BBB-crossing ligands or intranasal routes) and decreased off-target exposure, and hence systemic side-effects are reduced.[59]

Moreover, NPs prolong the half-life of siRNA and facilitate its cellular uptake and accumulation, enhancing the effectiveness of gene-silencing therapies (Figure 5).[61,62] To target cells or organelles specifically, NPs can be easily functionalized with certain ligands.[63–65] For example, nanoparticles may be functionalised with transferrin or TfR-binding peptides to exploit receptor-mediated transcytosis across the BBB, or with glucose-derivatives to target GLUT1 transporters at the brain endothelium.[66–68] In case of HD, brain-targeting ligands such as transferrin, lactoferrin, or GLUT1-targeting moieties have been incorporated on nanoparticle surfaces to exploit receptor-mediated transport across the BBB in neurodegenerative disease models.[69]

Surface functionalization enables targeted delivery to eradicate amyloidogenic proteins involved in aggregation and fibril formation in HD.[70] Nanoparticles (NPs) functionalization on surfaces allows two complementary strategies of HD: (i) BBB transcytosis with ligands, including Angiopep-2 (LRP1 shuttle), RVG29 (nicotinic AChR), transferrin/insulin, aptamers, or PEGsurfactant surfaces; and (ii) direct interaction with amyloidogenic/polyQ species with anti-aggregation cargos or surfaces. Poly(trehalose) NPs in HD models inhibited the aggregation and toxicity associated with polyglutamine in the mouse brain, and PLGA NPs containing polyQ-binding peptides (eg, PGQ9/QBP1/NT17) inhibited aggregation in Neuro-2A/PC12 cells and enhanced the Drosophila motor phenotypes. Ligand-targeted BBB delivery and anti-aggregase activity demonstrate the capabilities of size/charge/PEG optimization and surface ligands to reduce off-target accessibility and enhance delivery to target neurons.[65,71–73] Delivering therapeutic agents across the BBB to the

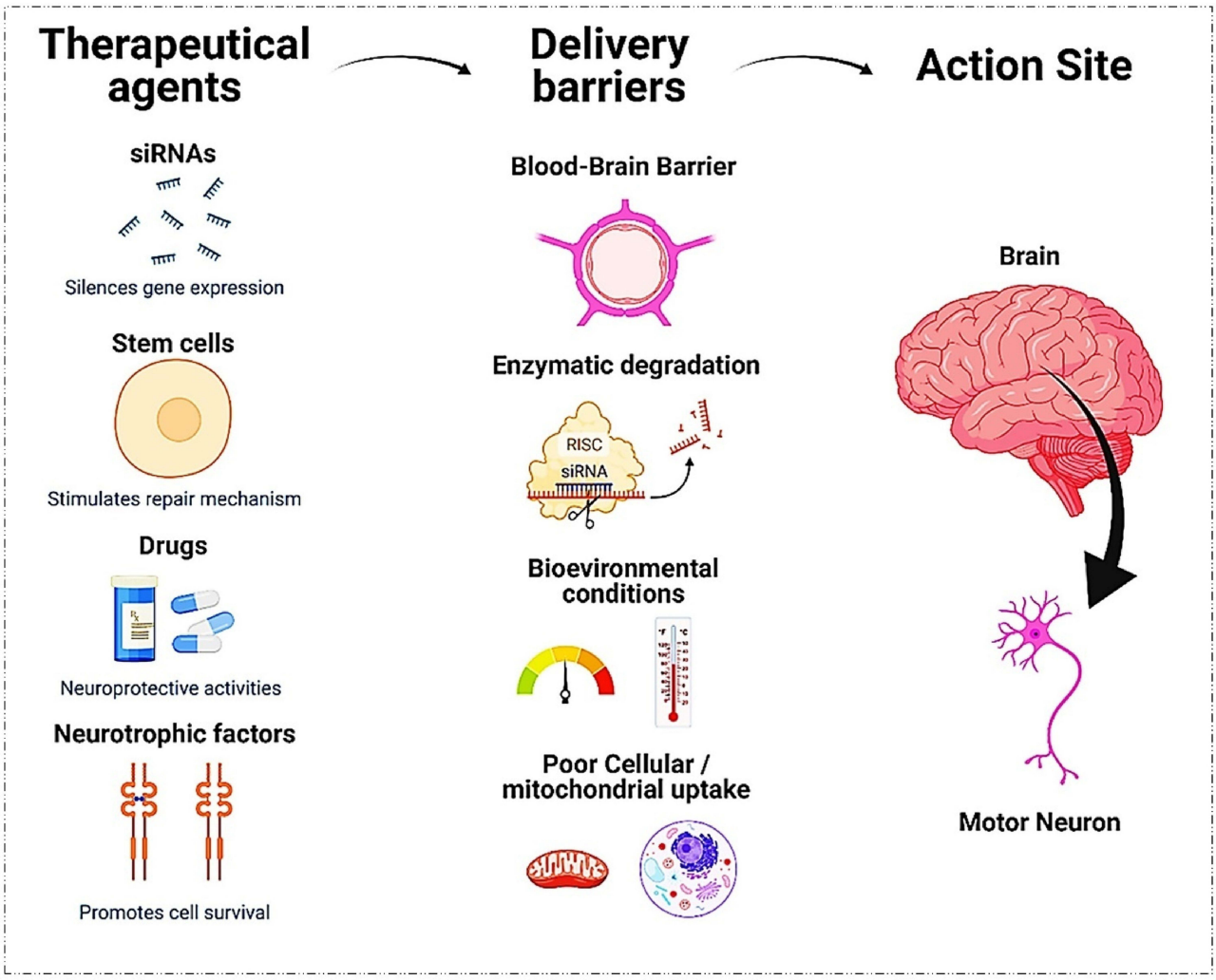

Figure 5 The figure highlights therapeutic targets such as RNA interference, neurotrophic factor delivery, and drug-based modulation. It also depicts the main delivery challenges, including the blood-brain barrier, enzymatic degradation, and cellular uptake limitations. Reproduced with permission from reference.[24]

affected neurons in the central nervous system (CNS) remains a significant challenge in managing Huntington's disease. While nanoparticles (NPs) can enhance drug bioavailability and targeting within the CNS, optimizing their size, shape, and surface properties to effectively penetrate the BBB while minimizing toxicity.[74]

Betzer et al[75] investigated the impact of the size of nanoparticles (20 nm, 50 nm, and 70 nm) on biodistribution and retention in Balb/C mice using insulin-coated gold nanoparticles (INS-GNPs). It was found that the greatest accumulation of the brain occurred with 20 nm INS-GNPs, which lasted longer in the body in comparison to 50 and 70 nm. Despite the fact that the research was conducted on retention and clearance, it also offered a clue on the potential of BBB penetration, where smaller nanoparticles (approximately 20 nm) passed the BBB more efficiently compared to the bigger ones. This implies that the size plays a crucial role in the accumulation and systemic retention of the brain. However, to improve the therapeutic efficacy of such diseases as Huntington additional studies on nanoparticles functionalization and region-specific targeting would be required.

Although the retention and clearance of nanoparticles at the systemic level is highlighted by Betzer, the penetration into the brain through the blood-brain barrier depends on the size of the particles and the functionalization of their surface. More recent literature also supports the fact that smaller sizes of NPs (approximately 20 nm) have more chances of entering the BBB.[76] Also, Zha et al[77] indicated that the functionalized nanoparticles based on gold nanoparticles

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effectively crossed the BBB and showed specific delivery to neuronal tissues, which is indicative of the significance of size and functionalization in enhancing brain cell penetration in brain degenerative disease treatments.

The primary barrier preventing nanoparticles (NPs) from reaching the brain is the BBB. Figure 3 illustrates key therapeutic targets and delivery challenges in HD treatment. The BBB is composed of endothelial cells lining the blood vessels, closely associated pericytes (PCs), and astrocytes (ACs) that extend their end-feet to the abluminal side of the vessels. This specialized architecture tightly regulates molecular transport outside the BBB. Tight junctions between ECs restrict paracellular transport, while a reduction in vesicular transport limits transcellular movement. Efflux pumps expressed on BBB endothelial cells actively expel small molecules, preventing their diffusion. This highly selective barrier protects the brain from pathogens and toxins but also hinders the delivery of drugs, nutrients, and therapeutic agents.[78]

Therapies for HD must selectively target mHTT while sparing normal HTT and other cellular components. This requires engineering nanoparticles with ligands, such as aptamers or antibodies, that bind specifically to mHTT. However, achieving high specificity and biocompatibility remains challenging, as some nanoparticles can induce oxidative stress and inflammation. Moreover, studies have shown low-cytotoxicity nanoparticles, such as hematite iron oxide, nickel oxide synthesized from Callistemon viminalis, and iron oxide from Coriandrum sativum, exhibit high cell viability and minimal hemolysis, supporting their potential for safe use in nanomedicine.[79] Cr_2O_3 nanoparticles synthesized using *Abutilon indicum* leaf extract showed higher biocompatibility (93.63%) than those made chemically (88.50%). Similarly, iron oxide NPs made with green tea extract and loaded with doxorubicin showed 90% cell viability at 30 μg/mL, supporting the potential of green-synthesized NPs for neurodegenerative disease treatment.[80,81] HD therapies like protein degradation, RNA interference, and gene therapy face stage-specific challenges. Multifunctional, stable nanoparticles are essential for effective integration and delivery in vivo.[82] To maximize efficacy and minimize off-target effects, drug release must be precisely controlled at the target site.[83]

Nano-Systems for Targeted Treatment of Huntington's Disease

Various nanosystems alleviate HD pathophysiology by targeting histone methylation, autophagy, apoptosis, mitochondrial dysfunction, and mHTT at the DNA, RNA, and protein levels. Some nano systems are briefly discussed in Table 1, whereas Table 2 contains the recent research on nanoparticle-based therapies for Huntington's disease, highlighting key studies, therapeutic approaches, and methodologies. The following sections explore these approaches, highlighting the potential of multifaceted nanotherapies in managing HD's complexity.

Table 1 Nano-Systems That Target Huntington's Disease

Sr.No.	Study	Nanosystem	HD Model	Method of Preparation	Therapeutic Outcome/Mechanism of Action	Ref
1	In Vivo	Chitosan-based NPs	HD mouse model	Evaporation by centrifugation	Targets HTT mRNA, resulting in decreased expression by 50% direct HTT gene-silencing effect	[84]
2	In Vitro	Peptide-loaded PLGA NPs	PC12 cells, neuro 2A cells (HD Q74), MDCK cells	Nanoprecipitation	Reduced polyQ aggregation. Suppression of mHTT-mediated toxicity	[85]
	In Vitro		Neuro 2A and PC12 cell lines Drosophila model of HD		Dose-dependent inhibition of polyglutamine aggregation. Larvae's crawling and climbing activities in adult flies were substantially enhanced attenuation of mutant huntingtin aggregation	[86]
3	In Vitro	Iron Oxide Nanoparticles	HEK-293 cells	Co-precipitation method	Reduced huntingtin protein levels direct modulation of HTT protein load	[87]

(*Continued*)

Table 1 (Continued).

Sr.No.	Study	Nanosystem	HD Model	Method of Preparation	Therapeutic Outcome/Mechanism of Action	Ref
4	In Vivo	(Poly)Trehalose-coated iron oxide NPS	Transgenic R62 mice and HD150Q cell lines	Reversed micelle and polymerization under a nitrogen atmosphere	HTT protein de-aggregation. Restoration of proteostasis	[73]
5	In Vivo	Epigallocatechin-3 Gallate PEGylated poly (lactic-co-glycolic) acid NPs with ascorbic acid	PC12 cells 3-NP induced C57BL/6 mice	Double emulsion nanoprecipitation method	Eliminated free radicals, a decrease in depressive-like behavior, and motor disturbances reduces oxidative stress associated with mHTT pathology	[88]
6	In Vitro	TiO2 NPs	Htt NTQ10 synthetic peptide	Sol-Gel technique	Arrests aggregation of mutant Huntingtin protein prevents mHTT fibril formation	[89]
7	In Vivo	Thymoquinone (TQ)-SLNs	HD Albino male rats	Molten stearic acid is mechanically stirred with lecithin, taurocholate, and thymoquinone.	NF-KB's nuclear translocation is inhibited by TQ-SLNs. Significantly reduces anxiety by blocking NO and GABA. Modulates inflammation linked with mHTT toxicity	[90]
8	In Vivo	Curcumin encapsulated solid lipid nanoparticles	3 NP intoxicated female Wistar rats	Nano-emulsion	Significant enhancement in mitochondrial function and antioxidant activity via Nrf2, with reduced oxidative stress and cellular damage in rats protects against mHTT-associated mitochondrial dysfunction	[91]
9	In Vivo	Rosamarinic acid SLNs	HD Male Wistar rats	Hot homogenization method	Reduces oxidative stress and boosts cellular antioxidant defences through NRF2 pathway activation counteracts mHTT-induced oxidative damage	[92]
10	In Vitro	Nanoquercetin	HD150Q cells	Quercetin encapsulation into polymer NP involving the addition of DMSO	Upregulation of autophagy promotes autophagic clearance of mHTT aggregates	[93]
11	In Vivo	MnFe2O4 NPs	Neuronal (2A) cell line	Ultrafiltration and ultrasonication	Proteasome clearance of GFP-Htt (Q74) by Ubiquitin enhanced degradation of mutant HTT	[94,95]
12	In Vivo	VOR Hydroxy Propyl β-CDs	R6/2 HD mice	VOR solubilized in HOP-β CD	Enhanced rotarod performance and reduced striatal atrophy ameliorates behavioral deficits driven by HTT pathology	[96,97]
13	In Vivo	Mithramycin-loaded PLGA NPs	R6/2 HD mice	Single/double emulsion and nanoprecipitation technique	Reduces Histone H3 hypermethylation and restores expression of genes essential for neuronal function and survival HTT-related gene repression	[98,99]
14	In Vivo	Cholesterol-loaded PLGA NPs (g7 modified)	HD mouse mo (R6/2 120Q; transgenic)	Gel filtration chromatography	NMDARs and PSD95 were elevated. Normalized GABAergic and partially glutamatergic synaptic responses. Restores HTT-dysregulated neurotransmission Improved locomotor activity was observed in the rotarod and OFT.	[100]
15	In Vivo	GDNFp-LPs focused ultrasound microbubbles	HD (R6/2 mouse mo 120Q; transgenic)	Transfection	GDNF overexpression reduces polyglutamine aggregates, oxidative stress, and apoptosis while enhancing neurite outgrowth and neuronal survival counteracts mHTT-driven neuronal degeneration	[101]

(*Continued*)

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Table 1 (Continued).

Sr.No.	Study	Nanosystem	HD Model	Method of Preparation	Therapeutic Outcome/Mechanism of Action	Ref
16	In Vivo	Selenium Nanoparticles (SeNPs)	Transgenic HD models of C. elegans	Chemical Reduction	Reduced oxidative stress, prevents huntingtin protein aggregation, and decreases mRNA expression of the histone deacetylase family.	[102]

Table 2 Summary of Recent Research on Nanoparticle-Based Therapies for Huntington's Disease

NP Type / Therapeutic Cargo	Model System / Delivery Route	Major Findings	Advantages	Limitations	References
Chitosan-based NPs encapsulating anti-HTT siRNA	YAC128 transgenic mouse; intranasal delivery	> 50% lowering of HTT mRNA in multiple brain regions at 48 h	Non-invasive nose-to-brain route; effective gene-silencing	Short-term: protein reduction, functional outcomes limited; translation issues	[84]
Modified β-cyclodextrin NPs + siRNA targeting HTT	In vitro BBB model + HD cellular lines	Demonstrated protection and delivery of siRNA; knock-down of HTT mRNA in cells	Good siRNA protection, BBB model demonstration	In vitro only; lacks in vivo functional/behavioural data	[55]
Hybrid nanocarrier combining siRNA + anti-inflammatory agent	HD model (preclinical)	Both HTT knock-down and reduction of inflammatory markers	Combination therapy addressing gene and inflammation	Early stage; long-term in vivo efficacy, toxicity data limited	[103]
PLGA NPs modified with g7 peptide + cholesterol	R6/2 HD mouse model	Improved synaptic markers, cognition and locomotor outcomes	Targets cholesterol dysregulation (non-gene) pathway	Low loading (~1%); delivery efficiency modest, older study	[100]
Selenium nanoparticles (Nano-Se)	Transgenic or non-mammalian HD model	Reduced aggregation and oxidative stress; improved phenotypes	Novel material; addresses oxidative stress and aggregation	Early stage; mammalian efficacy and safety pending	[102]
PEGylated PLGA NPs co-encapsulating EGCG + ascorbic acid	3-NP induced HD model in mice	Improved motor deficits, reduced neuroinflammation and neuronal loss	Enhances bioavailability of natural compounds; brain delivery	Toxin model, not genetic HD; specificity for the HTT pathway is limited	[88]
Solid lipid nanoparticles (SLNs) with rosmarinic acid; intranasal route	3-NP treated Wistar rats	Improved motor coordination and antioxidant markers	Non-invasive delivery; antioxidant pathway targeting	Toxin mo older study; direct HTT-targeting not shown	[92]
PEI-derived lipopolymers + siRNA against mHTT	Neuronal mutant HTT-GFP cell lines	Demonstrated mHTT transcription and aggregation reduction in vitro	High specificity; good in-cell proof of concept	In vitro only; lacks in vivo data; PEI toxicity potential	[104]

Targeting Mutated HTT RNA

Targeting RNA disrupts protein synthesis by blocking a key intermediate. Traditional methods like duplex RNAs and antisense oligonucleotides (ASOs) suppress mHTT mRNA. ASOs recruit RNase-H to degrade mRNA, and ongoing research aims to improve their potency, specificity, and resistance to nucleases.[105] Despite progress in nucleic acid therapies, RNA delivery faces major hurdles; its size, charge, and instability lead to rapid degradation and an immune response. The blood-brain barrier further restricts brain access, and cellular uptake is limited. ASOs require lifelong lumbar punctures (about six annually), which may cause side effects like headaches, infections, arachnoiditis, radiculopathy, and hemorrhage.[106] To overcome these challenges, polymeric nanoparticles, particularly glucose-coated nanoparticles, have been developed for intravenous administration, enabling brain targeting via the GLUT1 transporter. These nanocarriers rapidly accumulate in brain tissue, particularly in the cortex and hippocampus, and effectively knock down target long non-coding RNAs. Preclinical studies in murine models demonstrated a significant reduction in RNA expression and associated toxic protein aggregates. Glycemic control can further aid BBB crossing. However, off-target effects remain a concern due to GLUT1's presence in peripheral tissues.[107–110] Chitosan-based nanoparticles designed for intranasal delivery have shown promise in bypassing the BBB and transporting siRNA and ASOs directly to

the brain via the olfactory epithelium. This nose-to-brain route offers non-invasive access to target sites such as the striatum and cerebral cortex, critical regions in HD pathology. Experimental models using chitosan-siRNA complexes have reported suppression of HTT expression and partial restoration of motor function.[21,84,111] These findings demonstrated the carriers' capacity to shield the RNA payload and stop its premature release when ions and enzymes are present.

Nanocarriers Coated with siRNA and miRNA for Targeting the Mutated HTT RNA

RNA interference (RNAi) has emerged as a promising strategy for reducing mHTT expression in Huntington's disease. This endogenous post-transcriptional mechanism silences specific mRNAs by degrading them or blocking translation. It involves processing primary miRNAs into functional forms via the Dicer enzyme. However, RNAi therapies require frequent dosing and often produce off-target effects, with potential liver and kidney toxicity.[112]

In HD, mHTT sequesters the CREB-binding protein (CBP), leading to histone hypermethylation and decreased acetylation, which disrupts neuronal transcription. miR-22, a neuroprotective microRNA, inhibits histone deacetylases (HDACs), improving disease phenotypes in HD animal models. It also downregulates pro-apoptotic genes such as Trp53inp1 and MAPK14/p38, reducing apoptosis.[113] miR-22 modulates Rgs2 expression, enhancing ERK activation, which offers further neuroprotection. Despite its therapeutic potential, miRNA use in vivo is limited by rapid degradation, lack of tissue specificity, and immunotoxicity. To overcome delivery challenges, engineered exosomes were developed as natural nanocarriers, encapsulating miR-22 and modified with RVG peptide on Lamp2b protein to target acetylcholine receptors in neurons. These exosomes were administered intravenously, achieving targeted delivery to cortical and striatal neurons. In mouse models, this strategy demonstrated efficient brain uptake and a significant reduction in mHTT levels.[114–116] To achieve brain-specific targeting, a FLAG tag and the RVG peptide, which binds to acetylcholine receptors, were fused to the exosomal membrane protein Lamp2b. Dendritic cells were transfected with this fusion construct, and therapeutic miR-22 was loaded into the exosomes through electroporation. Separately, a therapeutic miRNA expression cassette was incorporated into an adeno-associated virus (AAV) vector. The AAV-miRNA enters target cells via self-endocytosis, expresses mature miRNA in the nucleus, and reduces mHTT protein levels by binding to HTT mRNA.[117,118]

Gene and RNAi delivery into neurons is challenging due to their post-mitotic nature and unique membrane properties. To enhance genetic material transfer, both viral and non-viral delivery methods have been extensively studied. Viral vectors, particularly lentiviruses and adeno-associated viruses (AAV), are commonly used in the CNS because they efficiently transduce non-dividing cells and have low immunogenicity. However, viral vectors carry risks of immune reactions, which can be severe, and have limited cargo capacity. This has driven research into safer, non-viral carriers. Modified cyclodextrins (CDs), natural oligosaccharide-based molecules, have emerged as promising nucleic acid carriers that can complex with siRNA and protect it from enzymatic degradation.[119] With the hydrophobic sides facing inward, CD molecules are doughnut-shaped and may form a compound with small hydrophobic molecules that fit into the central cavity. Because the hydrophilic surfaces of the cyclodextrins face outward, the complexes gained aqueous solubility. Other benefits of employing cyclodextrins include lowering the toxicity of the drug at the site of administration, concealing negative reactions, and altering the pharmacokinetic characteristics of a drug, which lengthens its half-life.[96]

The utilization of self-assembling modified β-CDs as vectors for neuronal siRNA delivery was demonstrated in a study.[120] In contrast to conventional cationic lipid- or polymer-based vectors, CD-based vectors have recently been viewed as appealing gene delivery vectors because of their enhanced toxicity profiles.[121] The ST14A-HTT120Q rat striatal cell line, human primary fibroblasts naturally harbouring the human mutant HTT gene, and the most widely used in vivo, R6/2 mouse HD model were among the in vivo models to which HTT-targeted siRNAs were delivered using modified β-CDs.[120] These modified β-CDs engage electrostatically with polyanionic siRNAs to produce nucleic acid condensation and NP production.[122] In a study, it was demonstrated that the CD-siRNAs combination reduced HTT gene expression in R6/2 mice by 85% in just 4 hours, and that these effects persisted for up to 7 days after injection.[120] In another reported study, magnetic nanoparticles (10–20 nm) were synthesized via co-precipitation, showing stable size and dispersion. Oleic acid-coated MNPs, cross-linked with polyethyleneimine, efficiently delivered siRNA into HEK-293 cells under a magnetic field with low toxicity. They successfully reduced huntingtin protein levels, suggesting potential

for HD therapy.[87] Although RNA therapies modulate downstream gene expression, their mechanism is distinct from autophagy or apoptosis-targeting strategies discussed in later sections. This section primarily focuses on post-transcriptional silencing of mutant HTT RNA through exogenous siRNA or miRNA delivery.

Nanoparticles for Targeting mHTT Protein

PolyQ Peptides and HD Pathogenesis

A modular amphiphilic peptide has been engineered to specifically target mutant huntingtin aggregates by using a dual-domain strategy. The design includes a polyglutamine (polyQ) segment that enables selective interaction with the expanded polyQ tract in mHTT, and a polyarginine segment, which enhances peptide solubility and cellular uptake. PolyQ (Polyglutamine) peptides, which are composed of repetitions of glutamine residues, are the key feature of the HD pathogenesis. PolyQ repeats that are formed in the N-terminal region of the huntingtin (HTT) protein cause aggregated structures, which are toxic to neuronal cells and cause neurodegeneration in the HD brain. PolyQ peptides present major therapeutic intervention targets because their aggregation is the disease pathology of HD. Many peptide-based approaches have been designed to prevent the aggregation process, including PolyQ binding peptides (QBP1) and modified PolyQ peptides, which could potentially alleviate the progression of the disease.[123] The peptides demonstrate potential in addressing the initial phases of HTT aggregation, which means that they are the most logical ones to be used in nanoparticle-based drug delivery systems designed to overcome the BBB.[85,124]

Moreover, the positively charged arginine residues introduce electrostatic repulsion that can potentially hinder further aggregation of mHTT–peptide complexes. This approach provides a targeted and biophysically informed method to disrupt early aggregation events implicated in HD.[82] The inhibition of HTT aggregation via peptides and nanoparticles in this section targets early nucleation and elongation phases of protein aggregation, which are mechanistically distinct from downstream autophagic or apoptotic clearance pathways.

In vitro studies with PolyQ peptides reveal a two-step aggregation process: nucleation followed by elongation, resulting in amyloid-like beta-sheet fibrils. In cell and animal models expressing mHTT N-terminal fragments, the Nt17 region adjacent to the PolyQ tract promotes aggregation by forming tetrameric helices that evolve into oligomers, protofibrils, and mature fibrils. Although monomeric Nt17 and Httex1 peptides lack stable secondary structure overall, certain segments show helicity. During oligomerization and fibril formation, Nt17 adopts more stable helical conformations, indicating its structural role and molecular interactions are crucial for stabilizing intermediate and mature aggregates.[125,126]

PolyQ peptides have the potential; however, their stability in vivo is a key issue. These peptides tend to disintegrate easily and lose their effectiveness in animals. Moreover, effective delivery in the BBB is still a major issue that does not provide them with much therapeutic scope. More so, the chronic toxicity and teratogenicity of such peptides upon their chronic administration have not been sufficiently examined in animal models.[124,127]

Nt17 and Its Role in Aggregation Inhibition

By disrupting Nt17-mediated oligomer formation, isolated or monomeric Nt17 fragments prevented the establishment of the aggregated Httex1 sequence. Since fully formed helical Nt17 cannot trigger mutual helical conformation in neighboring Nt17, its aggregation inhibitory effects are significantly reduced.[128] The Nt17 sequence was found to co-localize inside the helical bundles of N-terminal repeats by covalently binding to PolyQ to stop it from aggregating.[129] Since PolyQ aggregates can add monomers that are blocked, several peptide-based inhibitors are created that decrease the elongation step of PolyQ aggregation.[130]

Nt17 aggregation inhibitory effects are also dramatically impaired during the aggregation of Nt17 when it acquires a fully helical conformation and loses the ability to inhibit the subsequent aggregation. This leads to decreased efficacy of Nt17 at late stages of aggregation. Moreover, the long-term functionality of isolated Nt17 fragments in vivo remains untested, and its capacity to get to the involved brain areas in HD models is doubtful.[131]

PGQ9 Peptides as Aggregation Inhibitors

Aggregation of PolyQ is reduced by the peptides PGQ9[P^2] and PGQ9[$P^{1,2,3}$].[132] Nt17 PGQ9 [$P^{1,2,3}$] is a hybrid inhibitor that was created to prevent HTT aggregation in both its nucleation and elongation phases.[132] Furthermore, it has been discovered that PGQ9[P2] inhibitors shield PC12 cells from the exogenous toxicity of PolyQ aggregates. Since the HTT protein has an attachment point for proteins, several peptide-based treatments such as QBP1 (Poly Q binding peptide), p42, ED11, Exendin4, and BIP have been utilized to treat HD.[133] It is thought that polyQ protein aggregation results from QBP1's binding to polyQ, which modifies the expanded polyQ stretch's fictitious hazardous configuration.[134] Bioactive peptides typically degrade and become inactive in vivo.[135] The BBB prevents any external molecule from entering the brain.[65] As a result, inhibitory aggregation peptides were employed in many drug delivery systems as promising therapy possibilities for HD. Several delivery vector techniques were used to effectively distribute PGQ9[P2] peptides to the brain.[85,86]

Although they can prevent aggregation, the life span of the PGQ9 peptides is low in vivo, thus restricting their use in treating ailments in the long run.[85] These peptides face a significant challenge in bioavailability to the brain because of the BBB, and their stability over long periods of time and possible immunogenicity need to be studied further. Similarly, peptide-based drugs do not usually have the efficacy they retain because of high rates of metabolism and excretion.

PLGA Nanoparticles for Peptide Delivery

PLGA NPs were the main drug delivery vector that was selected. By dissolving fixed amounts of peptide and PLGA in DMSO, a nanoprecipitation technique was used to create PLGA NPs loaded with PGQ9[P2] peptide. Following the disaggregation technique, PGQ9[P2] is readily soluble in DMSO. Increased encapsulation and solubility are thought to be caused by DMSO and PLGA's propensity to establish hydrogen bonds as well as PLGA's contact with the peptide through hydrophobic and ionic interactions, making it a viable nanocarrier for peptide transport across the BBB.[136] Ninety percent of these NPs are less than 190 nm, according to dynamic light scattering measurements.[137] Particles around 200 nm tend to activate the reticuloendothelial system (RES) or undergo splenic filtration, reducing their in vivo half-life [91]. Approximately 23% peptide loss to the aqueous medium occurred near the nanoparticles, primarily due to peptide hydrophilicity and limited PLGA encapsulation capacity.[138,139] Future approaches, therefore, seek to improve the therapeutic efficacy of the peptide inhibitor by developing a medication delivery method with consideration for the problems associated with peptide loss. To overcome these limitations, PLGA nanoparticles were employed as the nanocarrier, synthesized via nanoprecipitation with carbodiimide cross-linking and coated with polysorbate 80 to enable blood–brain barrier penetration, providing an intravenous delivery route. These PLGA NPs targeted key brain regions implicated in HD pathology and in preclinical Drosophila and neuronal cell line models, demonstrated improved motor function, and significantly reduced mHTT aggregation.[86]

Although a better delivery is observed with PLGA NPs, they are not resistant to nanoparticle degradation and peptide loss. The percentage loss of the peptide in the aqueous medium is about 23% because the peptide is hydrophilic and the encapsulation ability of PLGA is not high.[140] Moreover, 200 nm-sized particles may trigger the reticuloendothelial system (RES), splenic filters, and shorten their half-life in vivo. The stability and safety of these nanoparticles in the long term in larger animal models remains an issue.

Trehalose Nanoparticles for mHTT Aggregation

By scavenging ROS and blocking the expression or synthesis of inducible nitric oxide synthase, trehalose may have significant anti-inflammatory and antioxidant effects in vivo and decrease mHTT aggregation.[141] Trehalose therapy improves mHTT protein elimination in vitro cell culture assays by raising autophagic flux in various mammalian cells, such as Neuro2A and CHO cells.[142] Trehalose may directly bind to enlarged polyglutamine since it prevents the aggregation of two distinct proteins that contain polyglutamine, namely, Mb-Gln35 and truncated huntingtin.[143] In an HD transgenic mouse model, trehalose showed neuroprotective effects independent of glucose, improving motor function, reducing brain atrophy, increasing lifespan, and decreasing polyglutamine aggregation. Since trehalose is a disaccharide broken down into glucose, encapsulation into polymeric nanoparticles (NPs) was used to prevent

catabolism and enable effective CNS delivery to inhibit protein fibrillation. Poly(trehalose) nanoparticles with a 6 nm iron oxide core and zwitterionic polymer shell were administered via intraperitoneal injection, demonstrated efficient crossing of the BBB and showed up to 1000-fold greater inhibition of mHTT aggregation compared to free trehalose in HD mouse models.[144]

The primary limitation of this method lies in the fact that trehalose is a disaccharide that is metabolized into glucose in vivo, which restricts its stability and the therapeutic opportunities in the long term. Also, loading nanoparticles can lead to the loss of peptides during delivery and unpredictable efficacy in the long term. The long-term neurodegeneration progression action of trehalose has not been studied.

Catechin-Loaded Trehalose Nanoparticles

Catechin, a fragrant polyphenol with antioxidant and anti-amyloidogenic properties, reduces intracellular reactive oxygen species (ROS), enhancing cell survival. Studies show that catechin-loaded trehalose-conjugated polylactide nanoparticles (NPs) improve neuroprotection against intracellular polyglutamine aggregation in HD. In this NP system, hydrophilic trehalose, arginine, or dopamine decorate the surface: trehalose facilitates binding to aggregated proteins, arginine's positive charge promotes cellular uptake, and dopamine targets neurons via dopamine receptor interaction. The hydrophobic polylactide core enhances catechin delivery and anti-amyloidogenic activity, illustrating how phytochemicals can aid neuroprotection in neurodegenerative diseases.[145]

The lack of bioavailability and stability of catechin in vivo is a serious limitation to the clinical use of this chemical. The hydrophilicity of catechin and its rapid degradation by biological systems are obstacles to successful use in biological therapies of neurodegenerative diseases. The nanoparticle formulation has to be optimized further to enhance long-term solubility and efficacy.

EGCG Nanoparticles for HD Treatment

Epigallocatechin-3-gallate (EGCG), the main polyphenol in green tea (Camellia sinensis), has gained significant interest in HD treatment. In vitro studies show EGCG potently inhibits mutant HTT exon 1 protein aggregation. It also modulates protein misfolding, oligomer formation, toxicity, and aggregation in yeast and fly HD models. However, EGCG's multiple hydroxyl groups and aromatic rings enhance its antioxidant activity but cause poor physicochemical stability, resulting in low bioavailability and limited intestinal absorption, which restricts its therapeutic potential.[146,147] To address this, PEGylated poly(lactic-co-glycolic acid) NPs co-encapsulating EGCG and ascorbic acid (AA) were administered systemically, improving delivery to the striatum and cortex and significantly reducing motor deficits, neuroinflammation, and neuronal loss in a mouse HD model.[88]

EGCG has low bioavailability and is unstable in vivo, limiting its therapeutic applications despite its antioxidant properties. Besides, PEGylated PLGA nanoparticles employed to improve EGCG delivery should be optimized further to enhance stability and surmount inadequate intestinal absorption in clinical practices.

TiO_2 Nanoparticles for Aggregation Inhibition

TiO_2 nanoparticles (NPs) inhibit huntingtin exon 1 peptide aggregation by catalyzing the selective oxidation of methionine 7 to sulfoxide (Met7O). NMR studies show TiO_2 interacts with httNT and httNTQ10 peptides, reducing the concentration of aggregation-prone, native httNTQ10 and blocking fibril formation. Photo-excited TiO_2 NPs further decrease aggregation, although at 5 $g \cdot L^{-1}$ they can induce rapid aggregation and polymorphic fibril formation in short peptides like httNTQ10. The photocatalytic activity of TiO_2 NPs, which generates reactive oxygen species under UV exposure, presents both therapeutic potential and challenges.[89,148] As a result, future studies might concentrate on improving TiO_2 NPs' characteristics to increase their use as a tool for HD management.

The high concentrations of TiO2 nanoparticles can cause quick aggregation and polymorphic formation of fibrils, which may undermine their therapeutic application. The potential of toxicity and safety concerns of the long-term exposure to TiO 2 NP has to be thoroughly assessed in future research.

Nanoparticles Targeting Mitochondrial Dysfunction

Delivering drugs to mitochondria requires crossing the outer and inner membranes, with the inner membrane blocking polar, positively charged molecules. Thymoquinone (TQ) from black cumin has antioxidant and anti-inflammatory effects, but poor solubility limits its use. Encapsulating TQ in solid lipid nanoparticles (SLNs) improves delivery and effectiveness. In an HD rat model, TQ-SLNs (10–20 mg/kg, administered systemically) improved motor function, memory, and reduced oxidative stress and mitochondrial damage compared to free TQ.[149] While oxidative stress may indirectly influence apoptotic and autophagic responses, the primary focus of this section is on preserving mitochondrial function and reducing ROS production, differentiating it from direct modulation of autophagy or programmed cell death. Curcumin, a potent antioxidant and anti-inflammatory agent, alleviates HD effects but suffers from poor oral absorption due to low water solubility. To improve brain delivery, curcumin was encapsulated in solid lipid nanoparticles (C-SLNs).[150] In 3-NP-induced HD rats, oral C-SLNs (40 mg/kg) for 7 days enhanced glutathione and superoxide dismutase via the Nrf2 pathway, while significantly reducing reactive oxygen species, lipid peroxidation, protein carbonyls, and mitochondrial edema.[91] Rosmarinic acid (RA), a phenolic diterpene antioxidant, protects neurons from oxidative stress by reducing ROS, inhibiting calcium overload, and suppressing c-fos production. RA's antioxidant effects also involve carnosic acid and rosemary, which activate the Nrf2 pathway. RA conjugated to SLNs and administered via the intranasal route bypasses the BBB through nasal mucosa absorption, enhancing brain delivery non-invasively. In 3-NP-treated male Wistar rats, intranasal RA-SLNs improved body weight, motor coordination, and reduced striatal oxidative damage.[92]

Nanocarriers Promoting Autophagy in HD

Autophagy is a catabolic process that delivers intracellular components to lysosomes for degradation. In HD, mHTT disrupts autophagy, impairing aggregate clearance. This dysfunction is linked to the AMPK pathway, a key energy sensor that inhibits ATP-consuming growth processes and promotes catabolism. AMPK induces autophagy by inhibiting mTORC1 and phosphorylating ULK1 (ATG1 homolog). Resveratrol, a stilbene compound, activates AMPK by raising pAMPK levels and SIRT1 activity, enhancing neuronal autophagy alongside neuroprotective, anti-inflammatory, and antioxidant effects. It increases the AMP/ATP ratio by inhibiting mitochondrial ATP synthase and modulates intracellular calcium via CaMKK signaling. Normally, mTOR suppresses autophagy by inhibiting the ULK1/ATG13/FIP200 complex; AMPK activation inhibits mTORC1 through Raptor phosphorylation, promoting autophagy.[151] Although some compounds discussed here, such as resveratrol and quercetin, may also exhibit anti-apoptotic properties, the primary mechanism emphasized in this section is the activation of AMPK and inhibition of mTORC1 to promote autophagic clearance of mutant huntingtin aggregates. Resveratrol faces challenges like poor water solubility, chemical instability, and sensitivity to heat, pH, UV light, and enzymes. To address these issues, Resveratrol was formulated into polycaprolactone (PCL) micelles (~100 nm size), coated with polyethylene glycol (PEG), enabling improved BBB penetration and systemic administration, resulting in enhanced neuronal autophagy and neuroprotection in preclinical models.[152] Apolipoprotein E (ApoE) is used to functionalize resveratrol-loaded SLNs to prevent degradation and enable brain delivery. These ApoE-SLNs cross the BBB by mimicking lipoprotein particles and interacting with low-density lipoprotein receptors (LDLR). Two ApoE functionalization methods were developed, including biotinylation of ApoE followed by avidin binding to the SLN surface, ensuring a rapid and stable attachment.[153] Two ApoE-functionalized SLNs—SLN-DSPE-ApoE and SLN-Palmitate-ApoE were created by binding avidin-conjugated nanoparticles to biotinylated ApoE. These NPs measured 100–200 nm with no aggregation. ApoE enabled active targeting by specifically binding SLNs and enhancing their transport across the BBB with increased permeability.[154] Quercetin, a flavonoid with antioxidant, anti-inflammatory, and autophagy-promoting effects, shows strong neuroprotection in HD models. To improve BBB crossing, it's encapsulated in polyaspartic acid micelles as nanoquercetin, which is colloidally stable and enhances autophagy and anti-amyloid activity at lower doses.[93] Quercetin NPs are synthesized by coupling polysuccinimide (PSI) with cholesterol and ethylenediamine for brain targeting, achieving 40 to 50% quercetin conjugation via Schiff base formation. Nanoquercetin enhances autophagy (LC3 II/LC3 I ratio) with sustained release of about 45% in 24 hours and 5 to 8% over 72 hours, and an optimal size for high cellular uptake against mutant huntingtin.[93]

A zwitterionic-lipophilic surface and particle size under 100 nm enable nanoquercetin's superior cellular uptake via endocytosis. Its sustained quercetin release ensures prolonged intracellular availability and enhanced autophagy, unlike molecular quercetin, which shows poor solubility, cytotoxicity, and uncontrolled autophagy at high doses.[93] $MnFe_2O_4$ superparamagnetic nanoparticles exhibit bioactivities like oxygen evolution and nuclease/oxidase-mimicking, aiding HD treatment by accelerating LC3-I to LC3-II conversion and enhancing K48-linked ubiquitination of mutant huntingtin (GFP-Htt-Q74) in Neuro 2A cells. Their clearance effect relies on the ubiquitin-proteasome system, as shown by PYR-41 inhibition, and they demonstrate minimal toxicity.[94]

Histone Methylation Regulation Mediated by Nanocarriers in HD

Histones, rich in lysine and arginine, package DNA, and in HD models, increased H3K9me2 and SETDB1 methyltransferase (targeting H3K9me3) are linked to pathological gene suppression. mHTT reduces histone H4 acetylation by interacting with acetyltransferase domains, while CBP acetyltransferase is sequestered in HTT aggregates, contributing to epigenetic dysregulation in HD.[155,156] Histone hypoacetylation has been demonstrated in the R6/2 and HD-N171-82Q mouse models.[157] HDAC inhibitors are useful therapeutic drugs for HD because they increase histone acetylation, which in turn promotes transcription of suppressed genes.[158,159] MAPKs sustain a variety of neuronal functions linked to HD pathogenesis, such as release of glutamate, apoptosis, generation of synaptic vesicles, and outgrowth and maintenance of neurites. However, systemic toxicity, issues with drug stability, pharmacokinetic properties, off-target effects, diffusion into tumor tissues, and oral delivery are some of the disadvantages of using HDAC inhibitors.[160,161] SAHA-loaded PLGA nanoparticles improve the delivery of HDAC inhibitors by addressing solubility and toxicity challenges. Complexation with 2-hydroxypropyl-β-cyclodextrin enhances oral bioavailability and reduces motor impairment in R6/2 HD mice. Encapsulation in PEO-PLA copolymers further optimizes solubility and pharmacokinetics, enabling selective modulation of HDAC isoforms in the brain without affecting global gene expression.[162,163]

Mithramycin, a natural antibiotic, epigenetically regulates HD by binding GC-rich DNA minor grooves, reducing H3K9 hypermethylation via downregulating ESET, and significantly improving behavior and survival in R6/2 HD mice. Due to its high water solubility and poor CNS penetration, mithramycin requires large doses, prompting its encapsulation in PLGA nanoparticles for targeted brain delivery.[98] Valproic acid (VPA), an HDAC class I/IIa inhibitor, reduces myoclonic hyperkinesia in HD but is effluxed by BBB transporters; thus, VPA-loaded nanostructured lipid carriers (NLCs) were developed for enhanced CNS delivery, particularly via intranasal administration. Preconditioning MSCs with VPA and lithium before transplantation in HD models improves stem cell survival, reduces huntingtin aggregates, and enhances motor function, with further brain-targeting improved by coating MSCs with vascular binding peptide (VBP) conjugated to hyperbranched polyglycerol (HPG) to enhance nasal uptake.[164]

Targeting Cholesterol Dysregulation in the HD Brain

HD features disrupted brain cholesterol homeostasis, evidenced early by reduced 24S-hydroxycholesterol levels and decreased cholesterol synthesis linked to mutant HTT's impairment of SREBP-regulated genes in astrocytes, leading to deficient neuronal cholesterol supply and synaptosomal sterol depletion (Elaborated in Figure 6). Since cholesterol cannot cross the BBB, biodegradable PLGA nanoparticles modified with glycopeptide g-7 have been developed for systemic delivery; these NPs show 0.7 ± 0.1 mg/100 mg loading capacity, 68% encapsulation efficiency, and sustained cholesterol release of ~35% over 72 hours, enhancing brain cholesterol replenishment.[100] Cholesterol-loaded g7-PLGA NPs improve memory in R6/2 mice by restoring synaptic activity, but have low cholesterol loading (~1%) and degrade easily. Increasing cholesterol content and using intranasal deuterium-labeled cholesterol liposomes boosts brain delivery and offers sustained release with higher uptake.[165]

The two studies regarding the treatment of cholesterol imbalances in HD brain adopt various modes of delivery. The former one applies a systemic delivery of cholesterol through glycopeptide g-7-modified PLGA nanoparticles, which can increase memory and synaptic activity in R6/2 HD mice. But it has drawbacks because of low loading of cholesterol (less than 1%) and quick degradation of the nanoparticles. The second study used deuterium-labeled cholesterol liposomes by intranasal delivery, which is superior to earlier delivery methods due to its better delivery and longer release; however, it has not shown long-term

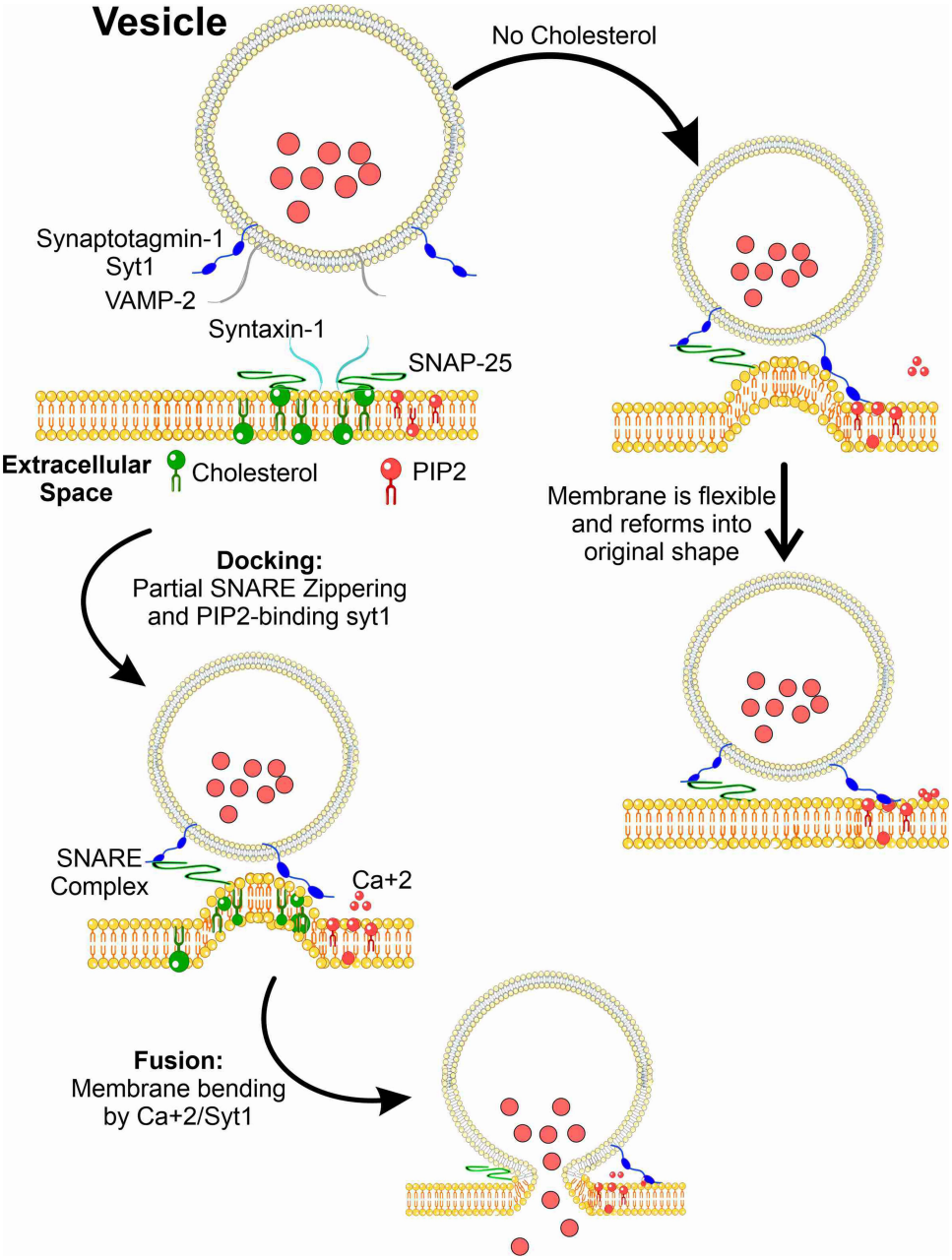

Figure 6 Cholesterol plays a vital role in maintaining synaptic integrity and neuronal communication by modulating membrane fluidity and curvature essential for Ca^{2+}-dependent vesicle fusion. In Huntington's disease, disrupted cholesterol homeostasis impairs synaptotagmin–1–mediated membrane deformation, compromising synaptic transmission and contributing to cognitive decline. The figure is drawn by the authors themselves.

efficacy and raises questions of stability and biocompatibility. Both methods are promising, yet some challenges require greater refinement.

Apoptosis Targeting in a GDNF-Dependent Way

Glial cell line-derived neurotrophic factor (GDNF), a natural neuroprotective factor, promotes neuron survival by activating mitogen-activated protein kinase (MAPK) and inositol trisphosphate (IP3) pathways and inhibiting apoptosis via Akt. Traditional invasive delivery posed risks and required frequent injections, but AAV-mediated GDNF gene transfer offers sustained, non-invasive expression in HD mouse striatum, improving motor function and neuron preservation for up to 11 weeks after a single injection.[166] GDNF binds to its glial cell line-derived neurotrophic factor

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receptor α1 (GFR α1)/Ret receptor, activating MAPK and IP3 signaling cascades and inhibiting caspases 3 and 9 via protein kinase B (Akt) to promote neuronal survival. While the Akt pathway activated by GDNF may interact with mechanistic target of rapamycin (mTOR) signaling and affect autophagy, this discussion specifically focuses on its role in inhibiting caspase-mediated apoptosis, distinguishing it mechanistically from autophagy-related processes. Due to risks with invasive delivery, adeno-associated virus 2 (AAV2) vectors carrying GDNF under a hybrid cytomegalovirus (CMV)-chicken β-actin (CAG) promoter enable sustained striatal expression in N171-82Q HD mice, improving rotarod performance, reducing clasping, and preserving neurons for up to 11 weeks after a single 2 μL injection.[167] GDNF-encoding plasmids encapsulated in 150 nm liposomes cross the BBB more efficiently when combined with focused ultrasound and microbubbles, which induce acoustic cavitation. In R6/2 HD mice, this method reduces mutant HTT aggregates in the cortex and striatum by 80–90%, demonstrating effective non-invasive gene delivery.[101]

Surface-Engineered Nano-Systems for Targeted Brain Delivery

Surface engineering of nanosystems constitutes a pivotal advancement in nanomedicine, enabling enhanced delivery of therapeutic agents across the BBB for neurodegenerative disorders such as Huntington's disease. This approach involves the functionalization of nanoparticle surfaces with specific ligands such as transferrin, lactoferrin, apolipoproteins, antibodies, and cell-penetrating peptides that facilitate receptor-mediated transcytosis, a key mechanism allowing selective transport across the BBB. Further, surface modification with hydrophilic polymers like PEG confers "stealth" properties, minimizing opsonization and subsequent clearance by the mononuclear phagocyte system, prolonging systemic circulation time and improving bioavailability.[168–170]

Recent studies highlight the incorporation of stimuli-responsive moieties into nanosystems, enabling controlled and site-specific drug release in response to microenvironmental cues such as acidic pH, elevated enzyme activity, or redox gradients characteristic of pathological brain regions. For instance, pH-sensitive linkers can exploit the slightly acidic environment of diseased neural tissue to trigger drug release selectively, enhancing therapeutic index while minimizing off-target effects.[171,172] Emerging materials such as dendrimers and solid lipid nanoparticles have been surface-engineered to incorporate targeting ligands and responsive linkers, demonstrating improved BBB penetration and neuronal uptake in preclinical models. These engineered nanosystems not only protect therapeutic cargos from enzymatic degradation but also facilitate intracellular delivery, addressing intracellular pathological pathways implicated in HD pathogenesis, including mutant huntingtin aggregation and mitochondrial dysfunction.[173,174]

Challenges and Future Prospects

Despite the considerable advancements in the design and application of surface-engineered nanosystems for the treatment of HD, several critical limitations continue to impede their successful clinical translation. A major challenge lies in the unpredictable interactions between nanoparticles and biological systems, particularly the formation of the protein corona upon systemic administration. This dynamic layer of adsorbed plasma proteins can alter the physicochemical properties of nanoparticles, leading to changes in biodistribution, cellular uptake, immunogenicity, and targeting efficiency. In the context of HD, such variability compromises the ability of nanoparticles to cross the BBB and deliver therapeutic payloads to affected brain regions with precision.[175,176] Furthermore, the body's innate clearance mechanisms, particularly those mediated by the mononuclear phagocyte system in the liver and spleen, can rapidly eliminate nanoparticles from systemic circulation, reducing their bioavailability and therapeutic efficacy.[177] The BBB itself remains a significant obstacle. Although functionalization strategies such as ligand conjugation have shown potential in enhancing nanoparticle transport across the BBB via receptor-mediated transcytosis, the heterogeneous nature of BBB integrity in HD patients, especially at different stages of disease progression, introduces variability in treatment outcomes. Similarly, there is an inherent risk that certain nanoparticles may inadvertently disrupt tight junctions within the BBB, potentially leading to neuroinflammation or off-target effects.[178] Another major limitation involves the scalability and reproducibility of nanoparticle synthesis under Good Manufacturing Practice (GMP) conditions. The complex surface modifications required for brain-targeted delivery often lead to batch-to-batch variability, and maintaining consistency in size, charge, surface ligand density, and stability over time remains a formidable task for industrial production.[179]

On the regulatory front, there is a significant gap in standardized frameworks tailored specifically to nanotherapeutics. Current drug approval processes are often not well-equipped to assess the multifaceted behaviors of nanosystems in vivo, resulting in delays and uncertainty in regulatory pathways. Moreover, the majority of preclinical evidence for HD nanotherapies comes from transgenic rodent models, which, while informative, fail to fully replicate the pathophysiological complexity of human HD. Differences in species-specific BBB permeability, immune responses, and nanoparticle clearance limit the extrapolation of preclinical findings to human applications. There is also a scarcity of robust, human-relevant in vitro models of the BBB and validated biomarkers to guide clinical translation.[180–182] Recent studies emphasized surface-engineered nanosystems particularly ligand-functionalized polymeric nanoparticles, biomimetic cell-membrane-coated carriers, and hybrid organic–inorganic nanostructures for enhancing therapeutic precision in neurodegenerative disorders; however, their direct application to HD and HTT biology is still evolving. Surface modifications (transferrin, lactoferrin, RVG-peptide, and exosome-mimetic coatings) have shown to improve BBB penetration and reduce systemic clearance, mechanisms that are especially relevant for HD where widespread striatal and cortical degeneration demands efficient brain-wide biodistribution.[183,184] Nanoparticles can modulate pathways dysregulated in HD, including autophagy, oxidative stress, mitochondrial dysfunction, and neuroinflammation which are key pathological processes linked to mHTT aggregation. Nano delivery of gene-silencing molecules (siRNA, ASOs, CRISPR components) represents promising strategies for lowering HTT expression, and surface-engineered carriers substantially enhance their stability, endosomal escape, and neuronal uptake.[58,185] HD-specific nanoparticle studies remain limited, however, neurodegenerative research demonstrates that optimized size, charge, and surface ligand density can facilitate targeted neuronal delivery, reduce off-target accumulation, and improve therapeutic index principles directly translatable to HTT-lowering approaches.[186] Together, this expanding literature underscores that surface-engineered nanosystems are not only capable of supporting targeted HTT/mHTT modulation but also offer a versatile platform for addressing multiple pathological mechanisms in HD, thereby reinforcing their future potential as next-generation therapeutic tools.

Conclusion

Huntington's disease remains among the serious treatment problems as it does not respond to disease-modifying therapies, the drug bioavailability is limited, and it does not fully penetrate the blood-brain barrier. There is a promising solution in nanotechnology-based drug delivery systems such as polymeric particles, lipid carriers, and micelles, which tend to deliver therapeutic agents to specific areas of the brain with precision, control, and high efficiency, and with minimal side effects. Desirable preclinical model effects have been demonstrated using these systems in mutated HTT RNA (siRNA and miRNA), mHTT protein, mitochondrial dysfunction, autophagy, cholesterol dysregulation, and GDNF-dependent apoptosis targeting. These methods have been demonstrated to decrease the accumulation of toxic proteins, decrease oxidative stress, enhance cellular recycling of proteins, and recover altered gene activities. Peptide-based formulations made in the presence of biodegradable polymers have shown, in specific instances, to be highly compatible with the brain tissue and also deliver drugs across the protective barrier of the brain. Though such innovations have enormous potential, these delivery systems require additional research and development so that they can be optimized for use in the treatment of HD.

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