



The importance of integrating basic and clinical research toward the development of new therapies for Huntington disease

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Huntington disease (HD) is a dominantly inherited neurodegenerative disorder that results from expansion of the polyglutamine repeat in the huntingtin (*HTT*) gene. There are currently no effective treatments for this devastating disease. Given its monogenic nature, disease modification therapies for HD should be theoretically feasible. Currently, pharmacological therapies aimed at disease modification by altering levels of *HTT* protein are in late-stage preclinical development. Here, we review current efforts to develop new treatments for HD based on our current understanding of *HTT* function and the main pathological mechanisms. We emphasize the need to enhance translational efforts and highlight the importance of aligning the clinical and basic research communities to validate existing hypotheses in clinical studies. Human and animal therapeutic trials are presented with an emphasis on cellular and molecular mechanisms relevant to disease progression.

Introduction

The broad spectrum of neurodegenerative diseases (NDDs) is characterized by the selective death of specific neuronal populations. Identification of the genes that cause the inherited forms of these diseases has led to a greater understanding of pathogenic mechanisms. Among the most common NDDs, the inherited forms are only a small subset of all cases, notable exceptions being spinal muscular atrophy, the spinocerebellar ataxias, and Huntington disease (HD). For instance, mutations in superoxide dismutase-1 in amyotrophic lateral sclerosis, of α -synuclein or the leucine-rich repeat kinase-2 in Parkinson disease (PD), or of the amyloid precursor protein in Alzheimer disease (AD) account for just 1%–5% of all cases in the general population (1–3). By contrast, although the prevalence of HD (5–10 per 100,000) (2) is much lower than for PD or AD, the complete penetrance of the HD mutation makes this one of the most common inherited NDDs. HD is unique in that allele carriers can be identified prior to the development of clinically meaningful symptoms, making it a model for the development of disease-modifying therapies with the potential to influence similar strategies – from scientific and regulatory perspectives – for other NDDs with more heterogeneous etiologies. Given the monogenic nature of HD, its prevalence and penetrance, and the existence of worldwide clinical networks (<http://www.euro-hd.net>), we stress that HD is a disease for which this ambitious goal might be achieved.

HD is an autosomal dominant disease exclusively caused by the expansion of a CAG repeat in the huntingtin (*HTT*) gene, which encodes a stretch of polyglutamines at the amino terminus (4). Expansion length (>35 CAGs) is negatively correlated with age of onset of clinical symptoms and accounts for 60%–70% of the variation (5). Clinically, HD is characterized by motor, cognitive, and psychiatric disturbances. These include deficits in movement control (chorea, dyskinesias), impairments in executive function, working

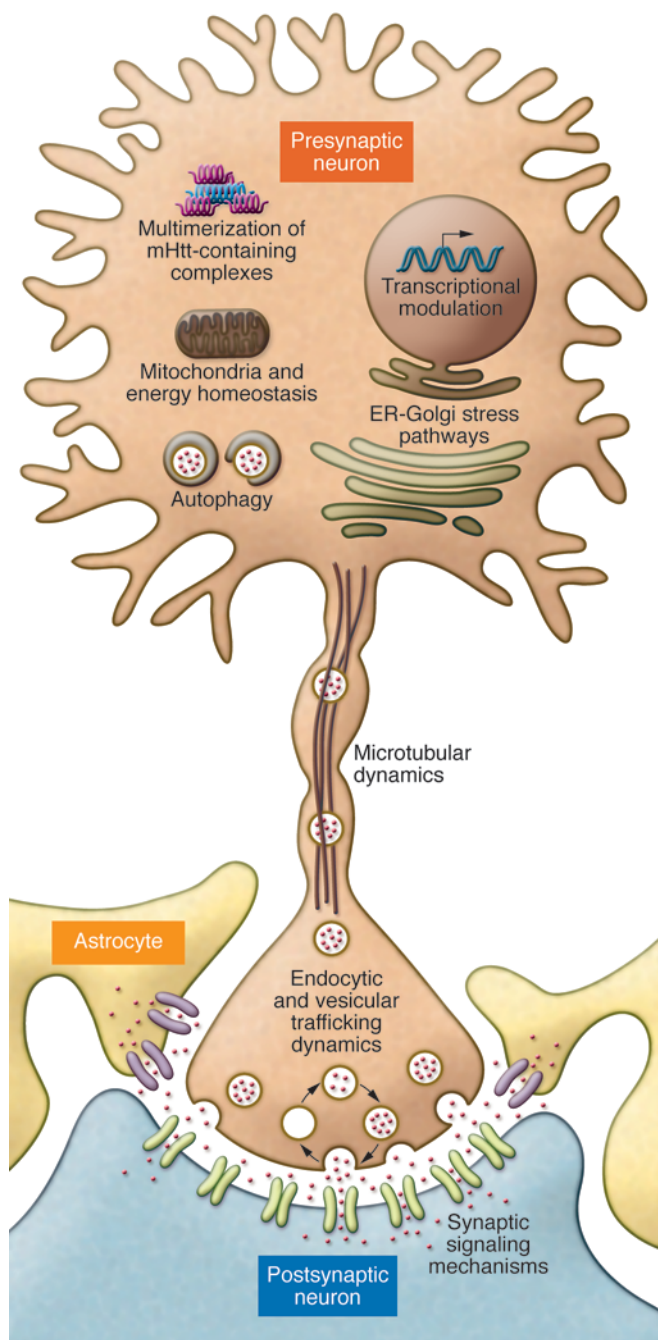
memory, attention, impulsivity, loss of motivation and self care, emotional lability, and a high incidence of depressive disorders (6–8).

Traditionally, therapeutic approaches to HD have included compounds developed for psychiatric indications based on the affected neuronal circuitry: the frontal and motor corticostriatal circuits (9, 10). None of these were initially developed for the treatment of HD. In this review we focus on the cellular and biological pathways affected by mutant *HTT* (mHTT) and the current status of associated drug discovery efforts (Figure 1). We also emphasize the need for further clinical research to validate existing hypotheses, which are mostly derived from animal studies and postmortem human tissues. It is generally accepted that most candidate therapeutics fail due to lack of efficacy in pivotal clinical studies. Leaving aside issues arising from inadequate clinical rating scales or trial design flaws, a simple explanation for this failure is that the pathogenic mechanistic hypotheses developed for a given indication, or the chosen intervention points within those mechanisms, the “targets”, are incorrect. The critical question for both the basic and clinical research communities is how we can work together more effectively to better define targets to maximize success. In this context, success is defined as developing therapies to slow the progression of HD, leading to significantly improved quality of life and extended functional lifespan. Although an ambitious goal, a disease such as HD represents a unique opportunity in which true disease modification should be attainable.

HD is characterized by the progressive degeneration of a subset of neurons in the corpus striatum, populations of cortical pyramidal neurons in the motor, frontal, and occipital cortices (8, 11–14), as well as neurons in other brain regions such as the hypothalamus (15). Current clinical diagnosis usually occurs in mid-life and is generally defined by the onset of motor symptoms. Intracellular inclusions of nuclear or neuropil *HTT* also contain other ubiquitinated proteins (4, 16). Many of these neurological and neuropathological features are, perhaps surprisingly, associated with other NDDs of different molecular etiology. Traditionally, NDDs have been defined by the cardinal symptoms that arise from the affected circuitry; for instance, the executive, attention, and plan-

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**Figure 1**

Cellular mechanisms implicated in HD pathogenesis. The major mechanisms associated with HD pathogenesis are depicted here. The schematic shows a presynaptic neuron and a postsynaptic neuron flanked by two astrocytes. HTT itself is depicted as a “solenoid,” based on the presumed folding due to its HEAT repeats. The mechanisms depicted are multimerization of mHtt-containing complexes, transcriptional modulation, ER-Golgi stress pathways, mitochondria and energy homeostasis, microtubular dynamics, endocytic and vesicular trafficking dynamics, autophagy, and synaptic signaling mechanisms. mHTT, mutant HTT protein.

that the progression was faster than in mice expressing full-length mHTT, supported the toxic fragment hypothesis (22). This theory postulates that the cleavage of HTT into N-terminal fragments is an early causative event in HD pathogenesis. Disease progression in the R6/2 mouse is rapid and recapitulates some of the pathological findings in postmortem HD tissues, including inclusion formation, some striatal and cortical neuronal death, ventricular enlargement, widespread white matter atrophy, and similar patterns of transcriptional dysregulation (21, 23–28). Other full-length models of HD include knockin mouse models (19, 26) and transgenic YAC and BAC mice and rats (20, 29, 30). These differ in mHTT expression levels, length of the CAG repeat, age of phenotype onset, rate of disease progression, extent of neuronal death, and the robustness of behavioral (cognitive, psychiatric, and motor) disturbances. Most of the mechanistic hypotheses driving the field have been identified or explored within these rodent models.

Although molecular changes observed in HD seem to be well conserved (26, 31–33), relatively minimal neuronal death occurs in rodents. Also, because frontal cortex anatomy is vastly different from rodents to primates, these models will likely only recapitulate some aspects of HD (34). Ideally, the clinical relevance of a particular intervention would be ascertained as rapidly as possible. In this regard, the main challenge in designing observational or exploratory interventional clinical studies is to gain insight into the exact nature of the deficits within complex biological mechanisms (in humans), which would support specific targets amenable to pharmacological intervention. It might only be possible to achieve this by “stressing” the system in a clinical context in order to uncover a statistically significant effect. For instance, an evaluation of energetic homeostatic responses (through direct measurements in muscle tissue) after an exercise stress paradigm might be necessary to uncover robust changes in energetic endpoints. To identify selective deficits that can be targeted therapeutically, an analysis of specific molecular alterations might only be possible through the use of peripheral tissues also affected in HD (35). Finally, to understand functional alterations in synaptic networks, or the involvement of specific neurotransmitter pathways, stressors might be applied to uncover these deficits prior to overt clinical symptoms (36, 37). Clinically available drugs such as sub-anesthetic doses of ketamine to probe the NMDA receptor system might be used to investigate the effects in cognition in HD patients. These specific approaches, coupled with imaging technologies, can be informative of specific alterations in HD.

In developing disease-modifying strategies, it is important to understand the link between initial pathogenesis related to mHTT function and compensatory mechanisms that develop over the extended disease course. For this reason, the importance of conducting longitudinal studies in pre-manifest individuals cannot be

ning deficits manifest in HD can be linked to dysfunction of frontostriatal circuits (8). Since all HD patients share the same mutation, a treatment aimed at a mechanism proximal to HTT might benefit all patients; this is in contrast to AD or PD, in which only a minority of cases arise from well-known molecular alterations.

Identifying mutations causative for a given disease enables the development of genetic animal models; there are now many rodent models of HD, and sheep and primate models have been engineered more recently (17–20). The R6/2 mouse is the most widely used and expresses an N-terminal fragment of the *HTT* gene under the control of the human *HTT* promoter (21). The finding that a fragment of HTT was sufficient to cause HD-like symptoms, and



Table 1
Ongoing therapeutic preclinical and clinical efforts

Molecule/target	Sponsor	Status
ACR16	Neurosearch	Phase III
AFQ056 mGluR5	Novartis	Phase II
Atomoxetine	University of Iowa	Phase II
Citalopram	NINDS	Phase II
CoQ10	NINDS	Phase III
Creatine	NCCAM/University of Rochester	Phase III
Latrepirdine	Medivation Inc.	Phase III
GDNF	Ceregene	Preclinical
HDAC4 inhibition	CHDI Foundation	Preclinical
HTT ASO	ISIS Pharmaceuticals	Preclinical
HTT siRNA	Alnylam and Medtronic	Preclinical
Improved CoQ10	Edison Pharmaceuticals	Preclinical
JNK3 inhibition	CHDI Foundation	Preclinical
KMO inhibition	CHDI Foundation	Preclinical
Lithium and divalproex	NINDS	Phase II
LNK-XXX	Link Medicine	Preclinical
P38 inhibition	CHDI Foundation	Preclinical
Memantine	UCSD	Phase IV
PDE inhibition	CHDI Foundation	Preclinical
PDHK inhibition	CHDI Foundation	Preclinical
Sirtuin-1 activation	CHDI Foundation	Preclinical
Sirtuin-1 inhibition	Siena Biotech	Phase I
TG2 inhibition	CHDI Foundation	Preclinical
TRKB modulation	CHDI Foundation	Preclinical

NCCAM, National Center for Complementary and Alternative Medicine;
NINDS, National Institute of Neurological Disorders and Stroke.

overemphasized. Most published clinical studies involve manifest HD patients (who may be on multiple psychiatric medications), are cross-sectional, and typically have a sample population that is too small to draw significant conclusions (see Supplemental Table 1; supplemental material available online with this article; doi:10.1172/JCI45364DS1). The continued support of physicians and individuals at risk is required to better understand the emergence of early HD-related changes and their correlation with onset and progression of clinically relevant symptoms. To achieve this, two studies – PREDICT-HD and TRACK-HD (6, 7, 38, 39) – are evaluating disease symptom progression in important clinical domains, as well as circuitry changes at and prior to clinical diagnosis. Similarly, developing optimal symptomatic therapies will also require an understanding of the heterogeneity in the manifestation and timing of symptoms.

Existing animal and clinical studies with an emphasis on mechanisms

Ongoing and completed HD therapeutic clinical trials (Table 1, Supplemental Table 1, and refs. 9, 10, 40) have largely focused on the mechanistic areas of synaptic transmission and energy homeostasis. A gene delivery tolerability study has been conducted with ciliary neurotrophic factor (41), minocycline was used to inhibit caspase-1 and modafinil was studied for its potential effects in cognition and alertness (42). The Cochrane Collaboration has systematically reviewed therapeutic intervention trials for both symptomatic treatments (10) and disease progression (40) in HD. Many of the symptomatic treatment trials included few patients, and the primary outcome measure was total functional capacity and/or

motor performance. Tetrabenazine is the only symptomatic treatment that has shown efficacy in reducing chorea in ambulatory HD patients (10) and has since been approved for clinical use. Most HD symptoms are currently treated ineffectively or not at all, and therefore this is an important area of clinical research. Ongoing symptomatic trials include a metabotropic glutamate receptor-5 (mGluR5) inhibitor (Table 1 and ref. 43) and latrepirdine (44). However, the development of disease-modifying treatments is the primary focus of HD therapeutic research and of this review. To date, no disease-modifying clinical efficacy trials have demonstrated treatment efficacy (40). A major limitation is that clinical assessment tools used as outcome measures lack sensitivity, meaning that the statistical power to detect improvement is poor even when hundreds of patients are tracked over two or three years. The generation and validation of improved assessment measures is a major focus of the European Huntington’s Disease Network and of the PREDICT-HD and TRACK-HD studies.

The discovery of the disease-causing mutation in *HTT* and the development of rodent models facilitated the investigation into potential pathogenic mechanisms through genetic manipulation as well as pharmacologic or molecular intervention (Supplemental Tables 2 and 3). Some notable recent pharmacological and molecular approaches include modulation of adenosine signaling (45), histone deacetylase (HDAC) inhibition (refs. 46 and 47 and Supplemental Table 3), phosphodiesterases (PDEs; refs. 48 and 49), kinase modulation (50, 51), CB2 cannabinoid receptor (52), and the growth factor pathways modulated by glial cell derived neurotrophic factor (GDNF), neurturin, and brain derived neurotrophic factor (BDNF) (53–57). Targets that have proved efficacious in genetic crosses notably include the involvement of caspases (22), HDAC4 (58), sirtuins (59), BDNF (54), p53 (60–62), and transglutaminase 2 (63, 64). In addition, deleterious effects associated with the genetic reduction of specific targets has highlighted the potential involvement of some mechanisms in the pathology of HD, notably CB2 (52), CREB1 (65, 66), mGluR-2 and -5 (43), Hsp70 (67), and PGC1 α (68).

Pathogenic mechanisms in HD and current approaches to intervention

HTT as a therapeutic target. The most expeditious way to modify the course of HD would be to prevent the expression or function of mHTT itself. Currently, mHTT is not a target for traditional pharmacologic modulation, since it has complex functions that remain incompletely understood. However, approaches to decrease HTT expression are in late preclinical development (Table 1 and ref. 58). One approach uses antisense oligonucleotides (ASOs) that function in vivo through an RNase-H mechanism to degrade the mRNAs of both alleles of *HTT* and is delivered through infusion into the ventricular or intrathecal spaces. The other uses siRNA therapeutics targeting both alleles via intraparenchymal administration. Both strategies aim to decrease the WT and mutant alleles of *HTT* and therefore share similar on-target mediated toxicity challenges. Significant loss of WT *HTT* expression is known to be detrimental both in developmental and adult contexts (69, 70). It is noteworthy that allele-specific therapies are being developed to mitigate on-target effects due to excessive lowering of WT HTT protein.

Currently, rodents are being used to determine the therapeutic window between efficacy due to decreased mHTT and adverse effects that might be triggered by insufficient WT HTT. There might be significant challenges associated with both approaches,



and given their different mechanisms of action, modality-dependent side effects might differ. Perhaps the most significant challenge is identifying markers sensitive to the reduction of HTT in the brain that could assess whether an adequate dose has been achieved within the predicted therapeutic window. The propensity of mHTT to oligomerize could possibly be used to assess dosage effects on the formation of these aggregates in vivo. In AD, imaging tools can now visualize plaque load and various species of TAU protein and A β peptides can be detected in rodent and human CSF (71), an approach that would be invaluable for the clinical development of HTT-lowering therapies. While HTT is an intracellular protein (like TAU protein), it might accumulate in CSF due to neuronal loss, a possibility that will be investigated once sensitive assays are optimized.

Transcriptional dysregulation is robustly correlated between HD animal models and human postmortem samples, suggesting a central role of mutant *HTT* in these molecular changes. Genes encoding neurotransmitter receptors are downregulated early in disease, including dopamine (D1 and D2; refs. 72 and 73), adenosine (A2a; ref. 74), and cannabinoid (CB1; ref. 75) receptors for which existing imaging tracers could potentially act as indirect markers of mHTT function in clinical studies. Energetic alterations in patients and animal models of HD (76–78) may be of relevance since energetic endpoints can be monitored non-invasively in vivo through imaging or MRS techniques (79, 80). Finally, it will be vital to identify degeneration-relevant markers, such as MSN or cortically expressed proteins found in CSF, which could be used to track degeneration longitudinally. Animal models will be invaluable in determining which measures are sensitive to decreased HTT levels (and which are reversible after loss of mHTT), that might guide clinical development.

The PREDICT-HD and TRACK-HD studies are evaluating longitudinal changes in premanifest HD and individuals with early-stage disease. Previous studies by Tabrizi et al. have identified robust cross-sectional changes (39), and currently this group is examining parameters that may be sensitive enough to track disease progression over a short time span (1–3 years). Such markers sufficiently sensitive for Phase II studies would warrant further investment for disease-modification trials. Given the widespread degeneration observed in the basal ganglia and cortical areas in manifest and advanced HD (12, 14, 38, 39, 79, 81–83), it is plausible that non-invasive techniques such as quantitative EEG (qEEG) could gauge progression. However, validating these approaches together with assessing sensitive tasks in functions important for quality of life of HD patients remains an important area of investigation for disease modification therapies.

HTT aggregation and protein homeostasis. In all NDDs, seemingly soluble proteins are mutated and form a multitude of oligomeric species and intracellular inclusions (16). The processes governing oligomerization and the mechanisms by which they cause cellular dysfunction are fundamental areas of investigation. Any strategy to rebalance the equilibrium of this process is a potential therapeutic approach. One possibility is to manipulate the cellular mechanisms that ensure correct protein folding (16, 84) or eliminate misfolded proteins: the ubiquitin proteasome system (85) and autophagy (84, 86–88). Autophagy induction can decrease aggregate load in various neurodegeneration models, including HD (88). To date, the main pharmacologic approach in clinical development to directly enhance autophagy is the inhibition of farnesyl transferase, a protein responsible for the farnesylation (a lipid modification) of a number of substrate proteins and implicated in autophagy

regulation (Table 1 and ref. 89). However, recent evidence from a knockin mouse HD model suggests that HD-specific alterations in autophagy might lead to a block in the trafficking or degradation of HTT (86). This could have implications for the exact therapeutic approach (that is, for which step in the autophagy cascade to target) and the disease stage at which a therapeutic intervention might be effective. For instance, as this block in the degradation of HTT exists in HD-derived lymphoblasts, we could use these cells in the development of autophagy-directed therapeutics. The main challenge for this area is to understand whether peripheral autophagy mechanisms are predictive of central modulation of autophagy, and to bypass the known adverse effects associated with chronic peripheral inhibition of mTOR signaling, such as ulcerative colitis, anemia, and neutropenia, among others (90).

Energetics. Mitochondrial dysfunction is implicated in most CNS disorders, and energetic disturbances in HD are well documented (27, 68, 76, 78, 91–93). The absence of mutations in the mitochondrial genome suggests indirect effects of mHTT on mitochondrial integrity (assuming nuclear-encoded mitochondrial genes are not affected specifically in HD). Abnormalities in the electron transport chain and the glycolytic machinery have been reported, but few define the precise lesion(s) that would suggest therapeutic strategies (93, 94). Many clinical trials have attempted to alleviate mitochondrial dysfunction (Supplemental Tables 2 and 3) using a variety of anti-oxidants and energetic supplements such as ethyl-EPA, idebenone (coenzyme Q₁₀ [CoQ₁₀]), or creatine without much success. These compounds suffer from poor pharmacokinetic properties or unclear correlation between brain exposure levels and their biological effects. A more potent CoQ₁₀ analog with improved tissue distribution is being developed to treat mitochondrial myopathies and HD (Table 1 and ref. 58). A comprehensive longitudinal investigation of central and peripheral mitochondrial and glycolytic function in HD patients is required to define the relationship between peripheral energetic changes and central and peripheral mechanisms (35, 78). Recently, modulation of sirtuin and its downstream targets – the transcription factors PGC1 α and PPR1 γ (76, 95–98, and Supplemental Tables 1 and 2) – has been shown to modulate the expression of genes important in mitochondrial function; the relevance for HD is supported by the association of PGC1 α polymorphisms with age of onset (99). Both SIRT1 and PPR1 γ appear tractable as therapeutic targets and, therefore, as validation of this mechanistic hypothesis.

Transcriptional changes. Transcriptional dysregulation has been extensively documented as a pathogenic mechanism in HD. The transcriptional changes that occur are robust and highly conserved between rodent models and HD postmortem brain (33). However, dysregulated transcriptional signatures have not been studied longitudinally in humans, and whether these can track disease progression (at least peripherally) is unclear. Altered expression of specific neurotransmitter receptors can be tracked in human imaging studies (73–75, 100) and likely influences the excitability of vulnerable neurons, rendering them susceptible to deregulated calcium signaling, leading to cell death. The role of mHTT protein in transcriptional processes modulated by Sp1, p53, REST/NSRF, and CREB is well documented (31, 32, 61, 62, 65, 66, 101–105). A feasible strategy to modulate CREB signaling in the brain through the modulation of PDEs is in place. Rolipram, a PDE4 inhibitor, has been shown to modify some of the symptoms in HD models (striatal death, survival, motor deficits; Supplemental Table 2 and refs. 48, 49), and other selective PDE inhibitors such as PDE10 are being



investigated (106). Similarly, the beneficial effects of non-selective HDAC inhibitors such as SAHA (46, 47, 107–109) prompted the genetic investigation of individual HDACs in the R6/2 mouse (Supplemental Table 3). Based on these findings, class II HDAC-selective inhibitors are in preclinical development. The Sirt proteins regulate many pathways that are significant in HD pathogenesis, and both activation and inhibition of SIRT1 has been reported to be beneficial in HD models. Resveratrol improved peripheral glucose levels but did not affect survival or striatal pathology in HD mice (Supplemental Table 3; refs. 58, 59). This target requires further investigation with selective brain-penetrant compounds.

Synaptic biology. Circuitry changes (neuronal death, white matter alterations, retraction of processes, and synaptic dysfunction) directly underlie alterations in symptomatic functional domains. The release of GABA by MSNs and their vulnerability in HD led to the initial investigation of GABAergic agents to treat HD, although these therapies proved ineffective (see references in Supplemental Table 1). Other neurotransmitters that have been investigated include glutamate (the major afferent transmitter modulating the firing of the MSNs), acetylcholine, and dopamine (the basal ganglia being the major target of substantia nigra projection neurons). Dopamine agonism has been shown in animal models to be detrimental to HD rodent models, whereas D2 antagonism is associated with improved motor performance in patients (9, 72, 110–113). The only approved drug for HD is tetrabenazine, a vesicular monoamine transporter-2 (VMAT2) inhibitor that lowers extracellular dopamine and norepinephrine (9, 10, 113). However, despite beneficial effects on chorea and motor subscores, tetrabenazine fails to improve the cognitive and psychiatric deficits, or to slow disease progression. Cholinergic modulation with galantamine has been shown to have potential beneficial effects (114) but a larger clinical trial to demonstrate efficacy has not been conducted.

The major hypothesis driving HD synaptic research is that of the excitability of MSNs. In this regard, approaches to reduce extrasynaptic glutamate signaling have been explored and include modulation of NR2B signaling (115), lowering glutamate receptor activation with NMDA receptor antagonists (ketamine and memantine; Supplemental Table 1), modulating the interplay of glutamate and dopamine on MSNs (72), and recently with mGluR5 antagonists (43). Currently there is conflicting evidence to support the inhibition of glutamate receptors as a disease-modifying strategy in HD (10, 21, 43, 96, 110, 116–118). Despite potential elevated glutamate signaling early in the disease course in rodent models, extensive deafferentation occurs at later stages, decreasing cortical and thalamic input to the basal ganglia (80, 119) and affecting regulated MSN firing. Biphasic changes in glutamate and dopamine transmission may explain why decreasing extrasynaptic signaling via NR2B appears effective in the YAC128 (a mouse model expressing human mHTT with 128 CAGs; refs. 29, 110), but not in the faster-developing R6/2 HD model (120, 121). The re-uptake of synaptically released glutamate by astrocytes occurs through the EAAT2 transporter, a target that is downregulated in HD (refs. 122, 123, and Figure 1). This downregulation leads to enhanced extracellular glutamate; the pharmacologic upregulation of EAAT2 is currently being explored preclinically. As in PD, electrical modulation of the output nuclei (in PD, the subthalamic nucleus; in HD, the globus pallidus) might confer significant motor relief, a hypothesis currently being tested clinically (124, 125).

Insights into neurotransmitter alterations in HD individuals have been gained through imaging studies that provide a static

and nonfunctional window into disease pathophysiology. Other techniques — such as qEEG, electrical stimulation, and fMRI monitoring of activity changes during functional tasks compromised in HD — have only recently been explored and, so far, only cross-sectionally (36, 80, 119). The most challenging goal is to understand system-wide changes in neural connectivity and the responsiveness of the affected circuitry to specific stimulations. The evaluation of selective agents aimed at neurotransmitter signaling components which control the excitability of affected neuronal populations in HD is needed to assess their potential effectiveness as symptomatic treatments. For instance, the identification of the earliest molecular mechanisms which contribute to the enhanced excitability of indirect pathway neurons will be critical to define novel intervention strategies. This should involve an understanding of firing properties of cholinergic and fast-spiking interneurons in an HD context, as well as a detailed investigation of membrane conductance alterations during disease progression. A greater emphasis on pallidal and subthalamic activity will be an important area to explore pharmacologically, as the loss of the MSNs has a significant effect in the activity of these output nuclei. Whether symptomatic agents will also modify disease progression is hard to predict (and therefore should be pursued) in the absence of a better understanding how mHTT regulates the synaptic properties of vulnerable neurons.

Concluding remarks

Fundamental change is required in the clinical exploration of HD biology in humans. Rather than cross-sectional alterations, an understanding of changes over time — from pre-manifest to early manifest disease — that includes investigation of disease-specific molecular alterations is essential. In order to uncover early changes, experimental medicine and interventional trials that stress a given cellular mechanism might be useful. Most pathogenic mechanism hypotheses are developed from animal models that are amenable to experimental or genetic manipulation; clinical researchers will have to devise experimental, non-invasive approaches that can query specific mechanisms and targets in humans to either validate or invalidate these hypotheses. This must not involve multi-year trials that recruit hundreds of patients, the most precious asset in a rare disorder.

Perhaps the most critical component of observational studies will be the standardization of best practice to ensure that small-sample studies can be meaningfully compared. This is particularly true of biofluid analyses (e.g., plasma and CSF) for which collection, shipment, and storage practices must be standardized to ensure high-quality data. In addition, an understanding of the longitudinal change in particular parameters will be critical to validate the role of specific mechanisms in disease progression, and possibly in patient selection for therapeutic trials. The reviews in this series explore in greater detail the recent advances in understanding of the synaptic changes and energetic dysfunction characteristic of HD (126, 127), as well as the development of oligonucleotide strategies for HTT reduction (128).

To conclude, the wider medical community should know that significant advances have been made in understanding the etiology of HD and in approaches to its treatment. Current efforts toward disease modification are at least as advanced as for any other neurological indication. The hope that effective treatments will be developed is realistic, and this message needs to be communicated to the patient community to encourage enrollment in clinical studies.



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