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Review

Huntington's disease: pathogenesis to animal models

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Abstract:
Huntington's disease (HD) is an inherited genetic disorder, characterized by cognitive dysfunction and abnormal body movements called chorea. George Huntington, an Ohio physician, described the disease precisely in 1872. HD is a dominantly inherited disorder, characterized by progressive neurodegeneration of the striatum but also involves other regions, primarily the cerebral cortex. The mutation responsible for this fatal disease is an abnormally expanded and unstable CAG repeat within the coding region of the gene encoding the huntingtin protein. Various hypotheses have been put forward to explain the pathogenic mechanisms of mutant huntingtin-induced neuronal dysfunction and cell death. None of these hypotheses, however, offers a clear explanation; thus, it remains a topic of research interest. HD is considered to be an important disease, embodying many of the major themes in modern neuroscience, including molecular genetics, selective neuronal vulnerability, excitotoxicity, mitochondrial dysfunction, apoptosis and transcriptional dysregulation. A number of recent reports have concluded that oxidative stress plays a key role in HD pathogenesis. Although there is no specific treatment available to block disease progression, treatments are available to help in controlling the chorea symptoms. As animal models are the best tools to evaluate any therapeutic agent, there are also different animal models available, mimicking a few or a larger number of symptoms. Each model has its own advantages and limitations. The present review deals with the pathophysiology and various cascades contributing to HD pathogenesis and progression as well as drug targets, such as dopaminergic, γ-amino butyric acid (GABA)ergic, glutamate adenosine receptor, peptidergic pathways, cannabinoid receptor, and adjuvant therapeutic drug targets such as oxidative stress and mitochondrial dysfunction that can be targeted for future experimental study. The present review also focuses on the animal models (behavioral and genetic) used to unravel pathogenetic mechanisms and the identification of novel drug targets.

Key words:
excitotoxicity, gait abnormalities, Huntington's disease, memory, oxidative stress

Introduction

Huntington's disease (HD) is an inherited neurodegenerative disorder, characterized by progressively worsening chorea, cognitive and psychiatric disturbances involving the basal ganglia and cerebral cortex [60]. The degenerative process primarily involves medium spiny striatal neurons and, to a lesser extent, cortical neurons. γ-amino butyric acid (GABA)ergic and enkephalin neurons of the basal ganglia are the most vulnerable in HD [77], and their early dysfunction is responsible for chorea development. HD is caused by the expansion of a polymorphic CAG trinucleotide repeat encoding a polyglutamine tract within the huntingtin (htt) protein (The Huntington's Disease

Collaborative Research Group, 1993). The mechanisms responsible for mutant htt pathogenicity are still largely unknown, as is the reason why striatal medium spiny neurons are most vulnerable in HD despite ubiquitous expression of mutant and normal htt. Normal htt has been shown to be anti-apoptotic [30, 91, 95] and essential for normal embryonic development [31, 81, 113].

HD has a rich historical literature, stretching back well over a century and involving some of the most prominent figures in medicine and neurology. The description of the disease by George Huntington in 1872 is one of the most remarkable in the history of medicine [57, 90]. Until recently, the history of HD research has been one of gradual progress rather than of sudden leaps. Initial development in this area arose from the illness of Woody Guthrie, the American folk singer, who suffered from HD symptoms beginning around 1952 and died in 1967 at the age of 55. His widow Marjorie devoted the later part of her life to promoting all aspects of HD research. Currently, a number of HD research groups are working in this area. HD is prevalent in many different countries and ethnic groups around the world [60, 93]. HD has a worldwide prevalence of 5 to 8 per 100,000 people, with no gender preponderance. The highest frequencies of HD are found in Europe and countries of European origin. The lowest frequencies are found in Africa, China, Japan, and Finland. The prevalence rate in the US is approximately 4.1 to 8.4 per 100,000 people [48]. A recent study regarding the distribution of C-A-G repeats in the normal population suggests a higher prevalence of HD in India, closer to the prevalence seen in Western Europe. Haplotype analysis indicates the presence of a founder mutation in a subset of families and provides evidence for multiple, geographically distinct origins of the HD mutation in India. A study conducted on 124 (94 male and 30 female) elderly patients (more than 60 years of age) in a teaching hospital reported that 2.4% of patients had HD or Parkinson's disease in India [58].

Genetics

The disease is caused by a mutation encoding an abnormal expansion of CAG-encoded polyglutamine repeats in a protein called htt. The HD gene is localized on chromosome 4p16.3 and comprises 67 exons and 3144 amino acids. The protein htt consists of a series of CAG repeats coding for glutamine residues (polyQ) followed by two short stretches of prolines. There are normally 10–29 (median, 18) consecutive repeats of the CAG triplet that codes for glutamine. By contrast, HD patients have expanded numbers of CAG repeats, from 36 to 121 (median, 44). The length of the CAG/polyglutamine repeat sequence is inversely correlated with the age of disease onset [64]. Therefore, increased CAG expansion causes earlier onset, whereas patients with less expansion show the first symptoms late in their lives. Disease progression is rapid in patients with more CAG expansion. In transgenic mice expressing human huntingtin with an expanded CAG/polyglutamine, a progressive syndrome develops, which is characteristic of human HD [83]. The protein htt is widely expressed within the central nervous system and in extraneural tissues. Huntingtin is expressed more intensely in neurons than in glial cells. Accumulation of proteolytic htt fragments and their aggregation trigger a cascade that leads to increasing neuronal dysfunction through oxidative injury, transcriptional dysregulation, glutamate excitotoxicity [56, 69], apoptotic signals, mitochondrial dysfunction and energy depletion [6], as shown in Figure 1.

These changes are accompanied by neurochemical alterations, which involve not only glutamate receptors but also other receptors, such as the dopamine (DA) and adenosine receptors involved in motor functions [36, 84, 106]. HD is a classic example of an autosomal dominant disease. The age of onset and disease severity are dictated by the extent of the HD gene mutation and by the sex of the patient. However, environmental factors and genetic modifiers can modify the variability of clinical expression.

Behavioral aspects

HD is an inherited neurodegenerative disease that damages specific areas of the brain, resulting in movement difficulties as well as cognitive and behavioral changes [61]. Movement difficulties are associated with both involuntary and voluntary movement, which progressively worsen over time. The most common clinical manifestation of HD is chorea. Chorea is defined as quick, vermicular movement, which may be superimposed on a purposeful act [25]. Cho-

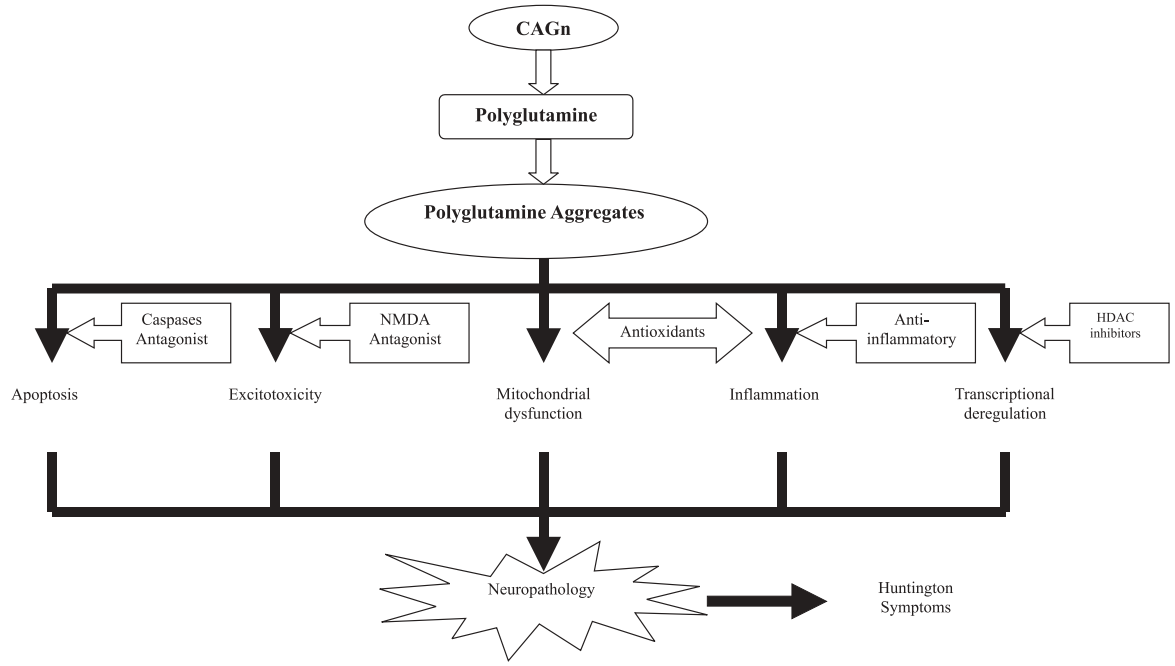

Fig. 1. Pathology of Huntington disease and different drug targets. HDAC: Histone deacetylase

rea is more prominent in the orofacial regions and the distal musculature of the hands and feet. In patients with untreated chorea, the symptoms lead to severe voluntary and goal-directed motor dysfunction [26, 37, 89]. More subtle abnormal voluntary movements are also present and may include bradykinesia, evident in slowed initiation and execution of poorly coordinated movements. The voluntary movement disorder is particularly apparent in disruptions of gait, reaching behavior and manual dexterity [42, 80]. Voluntary eye movement disruptions are evident in diminished velocity on ocular pursuit and an occasional nystagmus [67].

Prevalent psychiatric disturbances may appear before the onset of motor impairment [38, 100, 108]. Affective disorders are the most commonly prevalent psychiatric disorders in HD, with documented rates of major depression as high as 50% [50] and mania or hypomania as high as 12% [38, 86]. The affective component is of particular concern, in light of the risk of suicide associated with HD, which has been estimated to be as high as 7% [92]. Psychiatric symptoms associated with putative subcortical dementias, such as apathy, irritability and impulse control problems, have also been observed in HD patients [15, 19, 28]. There may also be a relatively high rate of violent behavior and criminality [27], explosive disorder [108] and a schizophrenia-like psychosis.

The cognitive changes in HD have traditionally been referred to as dementia. People with HD have specific and characteristic cognitive difficulties. Cognitive deficits appear with abnormal movements and progressive, unremitting exacerbation [16]. General intellectual abilities show a mild diffuse impairment within the first year of onset of overt motor signs, with a robust impairment in memory for new learning, visuoperceptual abilities and visuomotor functions [7, 16, 79]. More subtle early impairment may be observed regarding sustained attention, problem solving and verbal fluency along with memory deterioration over time relative to other abilities [11, 18]. Aside from dysfunction of the vocal apparatus, expressive and receptive language abilities may remain relatively stable or show only minimal disruption over the first few years of the disease [71]. Anomia and aphasia, for example, are rare in early stages; the disease generally spares language functions, including comprehension, vocabulary and general knowledge [16, 89]. As the disease progresses, language abilities begin to decline and combine with more severe exacerbation of early impairments to produce a general intellectual state that further causes mental retardation [11, 16, 59].

Another behavioral alteration of HD is altered sexuality; the possible cause may be a delicate imbalance of hormones in the brain. Most commonly, people with

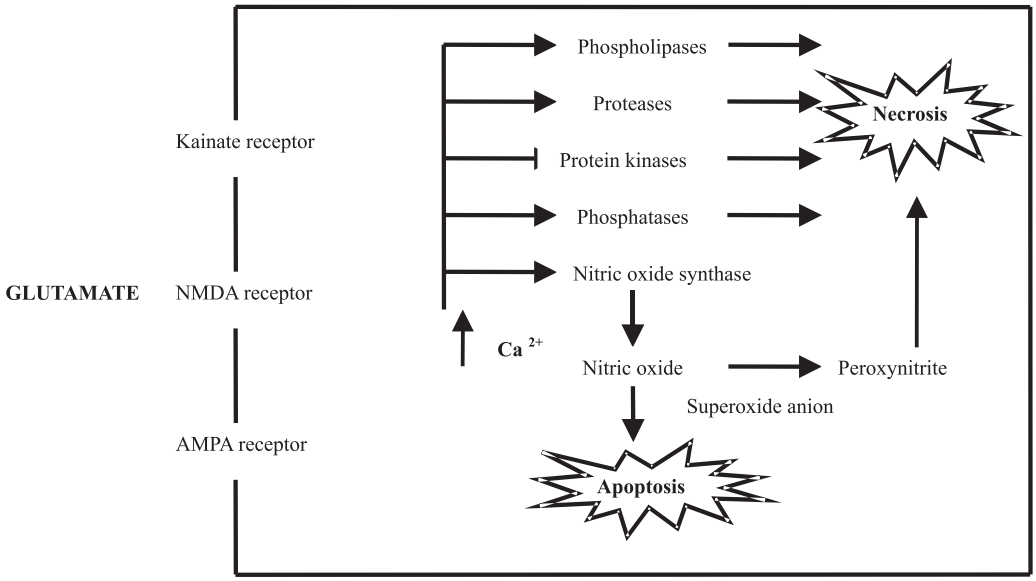

Fig. 2. Different neuronal circuits expressing various pathways

HD suffer from decreased sex drive. However, increased sex drive and inappropriate sexual behavior are less common alterations among HD patients [25].

Neurochemistry

Alteration of neurotransmitter levels, especially those of glutamate, GABA and DA receptors, is another hallmark of HD [22]. Altered expression of neurotransmitter receptors precedes clinical symptoms in transgenic mice and contributes to subsequent pathology [21]. Inhibition of caspase activation prevents downregulation of the receptor, suggesting that caspases are mediators not only for cell death but also for cell dysfunction [83]. There are several important unresolved questions concerning progressive neuronal degeneration in HD, including and understanding of the sequence of events that leads to neuronal degeneration and cell death and the reason for the selective vulnerability of specific neuronal types within the striatum.

A variety of cellular insults may intersect, leading individually or in concert to neuronal degeneration, neuron death and ultimately amyotrophic lateral sclerosis. A faculty gene (1) and excess glutamate (2) may lead to damaging free radicals (3), which can harm the DNA of the nerve cell. Glutamate also may lead to detrimental calcium production, which can churn out its own supply of DNA-damaging free radicals. The free radicals also may injure neurofilaments (4), proteins that serve as the skeleton of the cell. In addition, the immune system (5) may be involved in damaging neurons.

Because the key neuronal structures that display dysfunction and degeneration in HD are interconnected *via* long circuit loops (corticostriatal connections, striatal outputs to globus pallidus (GP) and substantia nigra, substantia nigra and globus pallidus projections to thalamus and thalamic projections back to the cortex), there are many synaptic interactions that can contribute to the functional alterations observed in HD. Since the pioneering studies by Wong [110], which showed perturbations in the synthesis of glutamate by corticostriatal neurons in HD, investigations of this pathway have been at the core of multiple attempts to understand the mechanisms of HD pathology.

Glutamate

Excitotoxicity can be defined as cell death ensuing from the toxic actions of excitatory amino acids [96]. Glutamate is a major excitatory neurotransmitter in the mammalian CNS [32, 50]. Neuronal excitotoxic-

ity usually refers as neuronal death arising from prolonged exposure to glutamate and the associated excessive influx of calcium ions and water into the cell.

The resulting calcium overload is particularly neurotoxic, leading to the activation of enzymes that degrade proteins, membranes and nucleic acids, as shown in Figure 2 [8]. One hypotheses that attempts to explain the exquisite vulnerability of the medium spiny projection neurons of the striatum to degeneration in HD is the 'excitotoxicity hypothesis'. In the context of HD, this hypothesis stipulates that excessive activation of glutamate receptors, increased glutamate release from cortical afferent, reduced uptake of glutamate by glia or hypersensitivity of postsynaptic glutamate receptors on striatal projection neurons, causes an alteration in intracellular calcium homeostasis and mitochondrial dysfunction, resulting in neuronal dysfunction and death of striatal medium spiny neuron's [29, 102]. Support for the excitotoxic hypothesis came in part from radioligand binding studies in *post-mortem* HD brain tissue, which showed a disproportionate loss of NMDARs from the striatum of patients in early symptomatic and, in a few cases, pre-symptomatic stages of the disease [2, 112]. These studies suggest that striatal neurons with high NMDAR expression are the most vulnerable and are lost early during disease progression. Since NMDA receptors are intimately associated with excitoxicity, they were one of the first glutamate receptors studied in mouse models of HD.

GABA

GABA is an inhibitory neurotransmitter with a postulated link to the inhibition of spontaneous involuntary movements [86]. In the striatum, 90% of neurons are medium spiny neurons, GABA-containing projection neurons that are preferentially lost in HD [33, 63]. Early evidence suggests a decreased level of GABA and its synthetic enzyme glutamic acid decarboxylase (GAD) in *post-mortem* HD brains [48, 52, 92]. Whereas larger aspiny interneurons are unaffected in the early stages of HD, spiny neurons are severely diminished [34]. The loss of striatal GABA receptors probably represents the loss of striatal neurons. However, the increase in GABA receptors in the GP external (GPe), an area that normally receives synaptic input from striatal projections, probably represents a measure of denervation supersensitivity [43]. Disruptions in GABA systems are not limited to the striatum. Reynolds and Pearson [94] have shown decreased GABA levels in the hippocampus and cerebral cortex as well as reduced levels of the synaptic enzyme GAD throughout the brain. Different neuronal circuits expressing various pathways are shown in Figure 3. Glutamate release can be regulated by GABA receptors located on corticostriatal terminals [23, 65]. Activation of these receptors exerts a significant inhibitory effect [20, 82]. Although a specific link between a particular biochemical abnormality and HD patho-

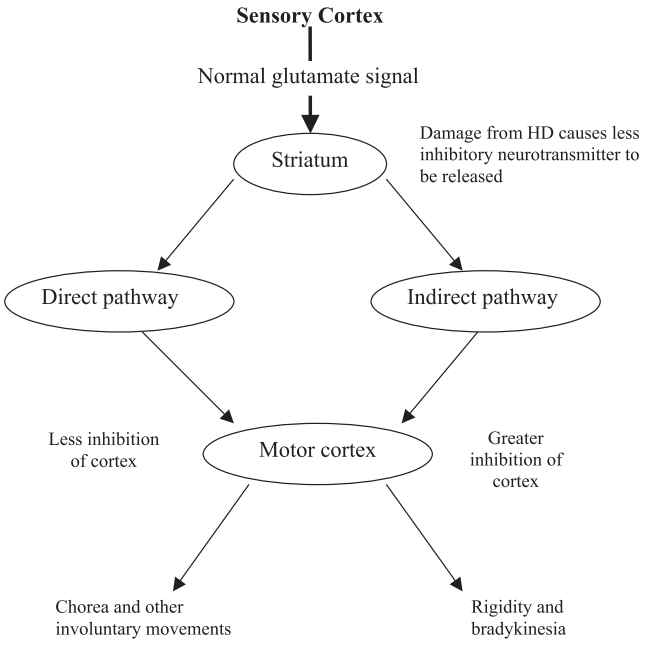

Fig. 3. Schematic diagram of circuitry and neurotransmitters of the basal ganglia-thalamo-cortical circuitry, indicating the parallel direct and indirect pathways from the striatum to basal ganglia output nuclei

genesis has yet to be found, neuropathological studies have underscored the role of small-to-medium-sized striatal spiny neurons that contain GABA [35]. As shown in Figure 3, indirect pathways involved in the pathophysiology and expression of HD symptoms (such as chorea and other involuntary movements) are due to an imbalance between inhibitory neurotransmitters and excitatory neurotransmitters.

In particular, increased inhibition of enkephalin-positive GABAergic neurons would reduce striatal output along the indirect pathway, similar to a functional ablation. This may lead to disinhibition of the GPe and could explain why lesions ameliorate HD symptoms in this area [20, 82].

DA

The neostriatum is densely innervated by dopaminergic fibers that originate in the substantia nigra. Despite the high concentrations of DA in the striatum [91], there is increasing evidence that DA or one of its metabolites might be neurotoxic. Dopaminergic and glutamatergic systems interact closely at the level of medium spiny neurons. Dopaminergic nigrostriatal neurons synapse mainly onto the necks of dendritic spines of medium spiny projection neurons, whereas glutamatergic cortical afferents synapse specifically on the heads of the same dendritic spines [104]. In addition, recent studies suggest that DA may also modulate striatal interneuron activity. Since the activity of medium spiny neurons is also finely regulated by interneurons, by modulating the activity of these interneurons, DA exerts indirect but potent control over striatal output neurons [10, 21]. There are compelling data suggesting that DA or its metabolites (or both) can generate ROS. In rodents, DA is metabolized *via* monoamine oxidase to 3,4-dihydroxyphenylacetaldehyde (DOPAC) and hydrogen peroxide (H_2O_2) [105]. Though not lethal, H_2O_2 can react with transition metals such as iron to generate highly toxic hydroxyl radicals *via* 'Fenton-type' chemistry [45]. A number of investigators have assessed DA levels in the HD brain. Major loss of the D_2 receptor was observed in the HD brain. D_1 receptors are moderately decreased in the substantia nigra as well as in the GPe in early stages of HD. As the disease progresses, vulnerability of both D_1 and D_2 receptors increase in the HD brain. These receptors (especially D_2) are markedly reduced in asymptomatic HD mutation carriers, suggesting that the loss of DA innervations contributes to HD pathophysiology [17, 92].

Acetylcholine

Loss of acetylcholine and its synthesizing enzyme choline acetyltransferase (ChAT) has been observed in HD patients. Further imbalance in DA and acetylcholine levels may contribute to HD symptoms [43]. Reports indicate that the acetylcholine synthetic enzyme ChAT decreases in the nucleus accumbens, septal nuclei, and hippocampus. Muscarinic M_2 acetylcholine receptors also decrease in the striatum and GPe but are unchanged in the substantia nigra pars reticulate and cortex [75]. Decreased choline levels have been observed in cerebrospinal fluid samples of HD patients.

Adenosine receptors

Adenosine is a purinergic messenger that can be released to the extracellular medium by membrane transporters, can result from the cytoplasmic leakage of dying cells and represents the final product of extracellular nucleotide hydrolysis by enzymes known as ectonucleotidases [55]. This is known to reduce neuronal activity through the activation of high-affinity receptors. Adenosine activities are mediated by binding to four distinct G-protein-coupled receptors (A_1, A_{2A}, A_{2B}, and A_3 adenosine receptor subtypes) [39]. Adenosine receptors have a unique cellular and regional distribution in the basal ganglia and are particularly concentrated in caudate putamen and the GP areas, which are richly innervated by DA [78]. Changes in A_{2A} receptor expression and signaling have been observed in various experimental HD models. In 2001, Varani et al. reported an aberrant amplification of A_{2A} adenosine receptor-stimulated adenylyl cyclase in striatal-derived cells engineered to express mutant htt [107], opened the possibility that an aberrant A_{2A} receptor phenotype may represent a novel potential biomarker of HD. This is useful for monitor-

ing disease progression and assessing the efficacy of novel neuroprotective strategies [72]. An increase in A_{2A} receptor density has been found in a 3-nitropropionic acid (3-NP) model of HD [9]. Recently, it was investigated the presence of an altered A_{2A} receptor phenotype in R6/2 mice models of HD [74].

The highest expression of adenosine A_{2A} receptors is found in the basal ganglia, particularly in the corpus striatum, which is involved in controlling complex motor activities by specific motivational stimuli as well as in habit formation [111]. A_{2A} receptors are found both pre- and postsynaptically; they are found post-synaptically on the GABAergic striatopallidal neurons projecting to the GP, which contain the peptide enkephalin and are enriched with DA D_2 receptors [51, 100].

It has been reported that A_{2A} antagonists have protective effects in HD animal models [40]. The neuroprotective effects of A_{2A} receptor antagonists seem to be mainly linked to the counteraction of the facilitatory effects of pre-synaptic receptors on glutamate release. The mechanistic basis of the beneficial effects induced by A_{2A} agonists remains to be fully elucidated. Nevertheless, these beneficial effects are thought to include non-neuronal effects in HD metabolic abnormalities [24] or on brain oxygenation through A_{2A} receptor-mediated vasodilatation.

Cannabinoid receptors in HD

Marijuana has been used by numerous cultures throughout recorded history. Marijuana has a number of effects on the central nervous system. It has been reported that marijuana could ameliorate some major neurological symptoms and disorders, including chorea [81]. In 1964, tetrahydrocannabinol, the major active constituent of marijuana, was identified. Since that time, approximately 60 other cannabinoids and 260 other non-cannabinoid compounds have been identified in marijuana. Cannabinoids mainly act through two types of receptors, CB_1 (present in CNS and to a lesser extent in the peripheral nervous system) and CB_2 (present outside the CNS, preferentially in the immune system). Activation of the CB_1 receptor may influence neurotransmitter release and influence a variety of processes, such as regulation of motor behavior, learning and memory and antinociception [60]. Several studies have clearly demonstrated that there is an almost complete disappearance of CB_1 receptor binding in the substantia nigra, in the lateral part of GP and, to a lesser extent, in the putamen in HD. An autoradiography study regarding the human brain showed a complete loss of the CB_1 receptor in HD patients.

Neuropeptides

While most striatal neurons are medium spiny GABAergic neurons, their synaptic targets can be separated into two separate anatomical pathways, which can be classified as 'direct' and 'indirect' pathways [44]. These two classes of pathways differ in the peptidergic co-neurotransmitter they use in addition to GABA, with striatolateral pallidal neurons containing enkephalin and the striatomedial pallidal and striatonigral neurons containing substance P and dynorphin [14].

Reflecting the preferential impact of striatal medium spiny neurons in HD, decreased concentrations of co-neurotransmitter peptides have been reported in synaptic target areas. Substance P is decreased in the substantia nigra and GPi, with lesser reductions being reported in the striatum, substantia nigra pars compacta, and GPe. Reduction of substance P has also been reported in the HD spinal cord. Enkephalin, contained in GABAergic medium spiny neurons that project to the GPe, has decreased levels in HD patients [91]. Decreases in mRNAs of substance P and enkephalin have been detected in early-grade HD, indicating that medium spiny neuron dysfunction is an early event in HD pathogenesis. The loss of indirect pathway striato-external pallidal neurons are predicted to result in a relative excess of involuntary movements, whereas the loss of direct pathway striatonigral and striato-internal pallidal neurons tend to produce bradykinesia [106].

Mitochondrial function and energy metabolism in HD

Substantial evidence suggests that defects in cerebral energy metabolism are early phase events in HD [1]. Metabolic pathways and mitochondrial functions are

intrinsically linked to a number of cellular systems and processes that are ultimately disrupted during HD progression, including generation and free radical scavenging. It appears that oxidative damage is linked to bioenergetic dysfunction in HD. Impairments in energy metabolism may affect brain regions of HD patients. In brief, classic signs of HD include profound weight loss and skeletal muscle wasting, which are associated with defects in ATP generation [13, 41]. Glucose metabolism is reduced in brain regions targeted by the disease by the time patients are symptomatic and for some period before symptom onset, indicating neuronal dysfunction and/or loss principally in the basal ganglia and cerebral cortex. Biochemical studies in HD postmortem tissue have revealed selective dysfunction of components of the mitochondrial tricarboxylic acid (TCA) cycle and electron transport chain in affected brain regions, particularly complex II, complex IV, and aconitase. The 3-NP-induced mitochondrial complex II inhibition significantly reduced O_2 consumption and ATP production rates relative to wild-type cells, which is attributed to increased Ca^{2+} influx through NMDA receptors [70, 73]. Excitotoxic damage may also occur in circumstances in which extracellular glutamate levels are normal but energy metabolism is impaired, so-called "secondary excitotoxicity."In conditions of impaired energy metabolism, reduced ATP production may disrupt the maintenance of Na^+/K^+ ATPase pumps that regulate ionic and voltage gradients across cell membranes, leading to prolonged or inappropriate opening of voltage-dependent ion channels and partial membrane depolarization. If this effect is sufficiently severe, then normally inert extracellular glutamate levels can trigger NMDA receptor activation, resulting in Ca^{2+} influx, nitric oxide synthase (NOS) activation, and free radical production *via* increased peroxynitrite ($ONOO^-$) formation. The compound $ONOO^-$, produced by the reaction of NO with superoxide radical ($O_2^{\bullet-}$), may then react with CuZn-SOD to form nitronium ion, which nitrates tyrosine residues in proteins [98]. Elevated induced Ca^{2+} influx may also result in sequestering of Ca^{2+} in mitochondria, which in turn increases free radical generation by mitochondria. Free radicals, including $O_2^{\bullet-}$ and hydroxyl radicals ($OH^{\bullet-}$), are constantly produced as byproducts of aerobic metabolism, but production increases under circumstances of electron transport chain inhibition or molecular defects. Ca^{2+} concentrations similar to those induced by neuronal exposure to excitotoxins increase mitochondrial generation of $OH^{\bullet-}$ and carbon-centered radicals. Increased free radical generation that outstrips the antioxidant and repair capabilities of mitochondria can lead to a negative cycle of progressively increasing oxidative damage to the mitochondria, ultimately exacerbating cellular injury. This phenomenon may explain the slow, progressive nature of neuronal injury in chronic neurodegenerative disorders such as HD. Therefore, this may reflect the cycling of free radicals and mitochondrial dysfunction, leading to the gradual buildup of damaged and dysfunctional cell components, until a threshold level is reached [108].

Animal models of HD

Genetic HD models

Genetic mouse models of HD may aid in the understanding of dysfunctions underlying behavioral phenotypes, neuronal abnormalities and neurodegeneration. A great advantage of these classic models of HD is that they can be used to understand the evolution of the disease and the cause-effect relationships involved [12, 52, 68, 76]. At present, a number of transgenic, knock-in and conditional mouse models have been developed, including R6/1 and R6/2 [74], YAC72 and 128 [53] and Tg100 [66], as well as several knock-in models, such as CAG71 and CAG94. Electrophysiological and morphological cellular alterations of these models have been examined extensively [74]. The generation of genetic mouse models of HD expressing mouse htt has provided an exceptional opportunity to study the evolution of pathogenic processes in the context of a chronically progressing disease phenotype.

The nature of the disease phenotype expressed depends on the context in which the mutant gene is expressed. In general terms, mice expressing N-terminal fragments of HD exon 1 develop a rapidly progressing disease phenotype that recapitulates aspects of motor defects and weight loss seen in HD, whereas mice expressing full-length human mhtt or have mutations knocked into the full-length endogenous murine Hdh gene have a more protracted disease course with fewer prominent motor defects but develop selective neuronal degeneration. The majority

of reports of oxidative damage in HD mice are from "fragment" mouse models of HD that express an N-terminal fragment of human mhtt, particularly the R6/2 mouse line. These are most thoroughly characterized and commonly used models available to date. It remains to be determined whether oxidative damage occurs before overt neuronal dysfunction in genetic models of HD, which suggests a causative role in the pathogenetic mechanism.

Toxin models of HD

The activity of complex II (succinate ubiquinol oxidoreductase) of the respiratory chain is severely reduced in affected brain regions (caudate and putamen) of symptomatic HD patients. Consequently, pharmacologic inhibitors of mitochondrial complex II have been found to induce striatal damage and motor phenotypes in animals, which closely resemble the symptoms seen in HD patients. Here, we discuss observations from studies using mitochondrial complex II toxins (3-NP and malonate) and excitotoxins (quinolinic acid), suggesting that oxidative damage associated with HD-like lesions is linked with mitochondrial energetic dysfunction and excitotoxicity.

Excitotoxin HD models: quinolinic acid

Behavioral and neuropathological features of HD could be replicated by intrastriatal injections of the endogenous NMDA-receptor agonist quinolinic acid, which induces preferential loss of medium spiny neurons but spares NADPH-d and parvalbumin-positive neurons, whereas injection of non-NMDA-receptor agonists (kainate or quisqualate) results in a loss of both spiny and NADPH-d-positive aspiny neurons [5, 46, 98, 103]. NMDA receptor-mediated lesions in primates are associated with an apomorphine-inducible movement disorder that resembles the choreic movements seen in HD [99]. Some but not all genetic models of HD also show age-dependent declines in glutamate-receptor densities in the striatum and cerebral cortex, altered striatal neuron responses to glutamate agonists, increased vulnerability to NMDA and quinolinic acid-induced excitotoxic damage [46]. Toxicity induced by the kynurenine pathway metabolite quinolinic acid involves an increase in ROS, DNA damage, reduced glutathione levels and peroxidative damage that can be rescued by Fe-porphyrin compounds. The energy substrate pyruvate is also protective against quinolinic acid toxicity. Interestingly, intrastriatal administration of quinolinic acid in rodents has been shown to increase htt immunoreactivity, leading to the suggestion that htt may be induced as a cytoprotective agent after activation of the kynurenine pathway, again emphasizing the close links between this pathway and HD pathogenesis [103].

3-NP

The mitochondrial toxin 3-NP irreversibly inhibits the activity of the mitochondrial metabolic enzyme succinate dehydrogenase, which participates in both the TCA cycle and complex II–III of the electron transport chain [3]. Systemic administration of 3-NP to humans, nonhuman primates, and rodents results in CNS lesions that selectively target medium spiny neurons within the striatum, recapitulating the regional and neuronal specificity of pathologic events in HD [4, 38]. In humans, ingestion of 3-NP induces cognitive impairment and motor abnormalities, including dystonia, involuntary jerky movements, torsion spasms, and facial grimaces. Systemic administration of 3-NP to both rats and primates produces striatal lesions that are strikingly similar to those seen in the HD brain; thus, 3-NP has become a widely used experimental tool to study neuronal susceptibility and motor phenotypes that are characteristic of HD. In rats, 3-NP-induced lesions in the basal ganglia that are associated with elevated lactate levels resulted in increased NMDA-receptor binding [46]. This effect can be ameliorated by reducing glutamatergic innervation of the striatum, through either application of NMDA-receptor antagonists or decortication. These observations are consistent with the 3-NP toxicity arising from secondary excitotoxic mechanisms, whereby energy depletion within vulnerable neurons facilitates abnormal activation of NMDA receptors and subsequent Ca^{2+} influx. Stimulating energy generation by administering creatine markedly attenuates 3-NP toxicity and ameliorates lesion volume, lactate production and ATP depletion in the striata of 3-NP-treated rats [85]. Numerous reports assert that 3-NP toxicity is associated with increased oxidative damage within the CNS. Administration of 3-NP to rodents results in elevations of striatal hydroxyl (OH^-) and superoxide ($O_2^{\bullet -}$) free radical generation and a number of oxidative damage markers. Susceptibility to 3-NP-induced oxidative stress also worsens with age, demonstrated by increased DNA fragmentation and reduced expres-

sions of the DNA repair enzyme apurinic/apyrimidinic endonuclease in older mice [88, 91]. The involvement of impairments in intrinsic antioxidant protection pathways after 3-NP administration is further supported by observations of reduced striatal glutathione (GSH) levels.

Malonate

Malonate is another selective inhibitor of succinate dehydrogenase that causes motor impairments and neuronal pathology resembling HD after intrastriatal administration in rodents (malonate does not cross the blood-brain barrier). Similar to 3-NP, malonate produces age-dependent striatal lesions that can be significantly attenuated by NMDA-receptor antagonists. Further indirect evidence contributes to malonate-induced neurodegeneration [96, 99].

Creatine and cyclocreatine are neuroprotective against malonate-induced toxicity in mice, *via* alteration of hydroxyl radical generation [91]. Malonate-induced lesion volume can be further reduced by combining creatine treatment with administration of the antioxidant nicotinamide.

Malonate induced an increase in the conversion of salicylate to 2,3- and 2,5-dihydroxybenzoic acid, an index of hydroxyl radical generation, which is exacerbated in mice lacking the free radical scavenger glutathione peroxidase. A mouse lacking a neuronal isoform of the NOS gene, with impaired nitric oxide generation, shows reductions in the sizes of malonate-induced striatal lesions. Further, 3-NT concentrations are elevated after intrastriatal malonate injection, whereas lesion size is attenuated by free radical spin traps and NOS inhibitors. Substantial evidence suggests that NO-mediated oxidative damage is involved in cell death processes after energetic disruption induced by both 3-NP and malonate. These mitochondrial toxins induce a pattern of cell damage mimicking that seen in HD by a mechanism that involves interference with the activity of an oxidative phosphorylation enzyme complex known to be impaired in the HD brain [85]. It is therefore tempting to extrapolate a key role for oxidative damage as an execution step in the cell-death pathway initiated by mhtt in HD patients.

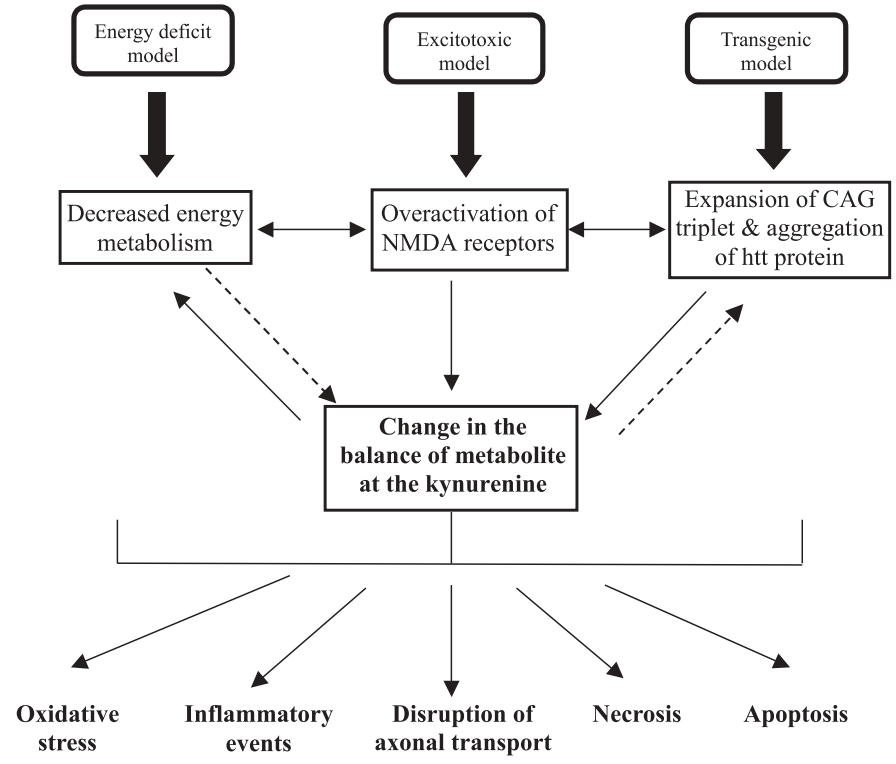

Fig. 4. Suggested interactions between the different hypotheses proposed to explain neurotoxicity and cell death in Huntington's disease

Conclusions

The exact mechanisms underlying neuronal death in HD remain to be explained. In the past decade, leading models of neurodegeneration, including mitochondrial dysfunction and subsequent excitotoxic injury, oxidative stress, and apoptosis, have been suggested, as shown in Figure 4.

Recent studies have lent support to these models, but additional theories involving protein metabolism abnormalities and transcriptional dysregulation have emerged as well. Since the identification of the HD gene in 1993, great advancements in the understanding of the molecular biology and pathophysiology of the disorder have occurred. These advances have suggested a new therapeutic strategy aimed at slowing disease progression or forestalling the onset of this devastating neurodegenerative disease. In preparation for future clinical trials, clinical studies have begun to provide more quantitative measures of disease onset and progression. Recent progress in the basic science and clinical realms raises hopes for the development of effective therapies in the near future.

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