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UPDATE ARTICLE

Animal models of neurodegenerative diseases

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The prevalence of neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), increases with age, and the number of affected patients is expected to increase worldwide in the next decades. Accurately understanding the etiopathogenic mechanisms of these diseases is a crucial step for developing disease-modifying drugs able to preclude their emergence or at least slow their progression. Animal models contribute to increase the knowledge on the pathophysiology of neurodegenerative diseases. These models reproduce different aspects of a given disease, as well as the histopathological lesions and its main symptoms. The purpose of this review is to present the main animal models for AD, PD, and Huntington's disease.

Keywords: Neurodegenerative diseases; Alzheimer's disease; Parkinson's disease; Huntington's disease; animal models

Introduction

The incidence of neurodegenerative diseases increases with age and, considering the aging process of the population worldwide, the prevalence of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) is expected to rise in the next years. This is particularly true for AD, the most common form of dementia, accounting for approximately 50-60% of all cases and representing a major public health concern with significant social and economic impact.[1]

There is still no curative treatment for AD or other neurodegenerative diseases, but ongoing trials are presently evaluating new therapeutic strategies.[2] The identification of effective disease-modifying drugs depends on the accurate understanding of the etiopathogenic mechanisms underlying the disease so that strategies that may eventually preclude its development or at least lessen its progression may be suggested.

To increase the knowledge on the etiopathogenic mechanisms of neurodegenerative diseases, a series of animal models is currently being used. These models aim to reproduce the causes, the pathological lesions, or the symptoms of a given disease.[3] Besides providing insights into the pathophysiology of the diseases, animal models are of paramount importance to assess the efficacy of potential treatments before conducting clinical trials in humans. In the present review, we present data on animal models for AD, PD, and Huntington's disease (HD).

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Animal models of Alzheimer's disease

AD affects mainly people over 60 years old and its initial presentation is usually memory impairment, but later symptoms include visuospatial, language, and executive dysfunctions. At present, there is no effective disease-modifying strategy in AD, and the available drugs are indicated to improve cognitive and behavioral symptoms.[4]

Although animal models have greatly advanced the understanding of AD pathogenesis, the lack of knowledge concerning its causes makes it difficult to develop a model exhibiting all AD features, which hinders the discovery and characterization of effective drugs. Currently, the most employed animal models were developed based on known genetic mutations associated with AD.[5] However, the vast majority of AD cases (over 90%) are sporadic, and the underlying causes are unknown. Therefore, these genetic-based AD animal models do not recapitulate all features of sporadic AD and do not cover all factors that may influence the etiopathogenesis of sporadic AD, such as apolipoprotein E. An additional complicating factor is that AD animal models do not exhibit the extensive neuronal cell loss observed in human patients.[6]

The histopathological hallmark of AD is the accumulation of neurofibrillary tangles and amyloid plaques. Extracellular amyloid plaques are formed from β-amyloid protein peptides (Aβ), which are fragments formed by cleavage of amyloid precursor protein (APP).[7] APP can be processed by α-and γ-secretases, generating a non-amyloidogenic product, or by β- and γ-secretases,

generating Aβ peptides, which are amyloidogenic and are prone to form plaques (Figure 1). However, there is no direct correlation between the number of cortical plaques and cognitive deficit in AD patients, and many individuals have amyloid plaques without cognitive impairment or dementia.[8] Moreover, the amount and the topography of the senile plaques are not correlated with the severity of dementia, and the amyloid deposition seems to remain stable during the progression of the disease.[9] The clinical progression of AD symptoms is not congruent with the progression of the amyloid deposition in the human brain, but it seems closely related to the progression of tau pathology.[10] This set of data indicates that factors other than amyloid deposits might have a role in the disease progression.[11] For instance, soluble oligomeric Aβ species formed by 1 to 30 Aβ amino acids correlate better than amyloid plaques with cognitive decline in both humans and AD transgenic mice. Synaptic loss that might be caused by the neurotoxic effect of soluble Aβ oligomers and/or tau pathology is also directly related to cognitive impairment.[11,12]

As Aβ is closely involved in AD pathogenesis, AD rodent models were generated by intracerebral infusion of Aβ peptides.[13,14] Importantly, direct intracerebral injection of Aβ peptides causes learning and memory deficits, as well as neuropathological changes that resemble human AD, including inflammation, microglial activation, and limited cell loss. The infusion model allows researchers to administer defined amounts of a specific Aβ species of known sequence and length, rather than waiting several months (i.e., aging process) for the development of pathological changes in transgenic animals. Aβ infusion models are very useful for pre-clinical drug testing as they can deliver experimental results, including plaque pathology, within a timeframe of few weeks.[13] However, the concentration of the Aβ administered is much higher than the Aβ levels found in the brain of AD patients, leading to brain alterations that surpass the effect of aging on AD progression.[14] Conversely, genetically modified mice overexpressing APP or $A\beta_{42}$ accumulate Aβ plaques and soluble Aβ oligomers in an age-dependent manner.[15] These APP mouse models display progressive Aβ deposition in both diffuse and neuritic plaques, cerebral amyloid angiopathy, astrocytosis, microgliosis, mild hippocampal atrophy, neurotransmission changes, and cognitive and behavioral deficits.[14]

Intracellular neurofibrillary tangles are formed due to hyperphosphorylation and oligomerization of tau, a

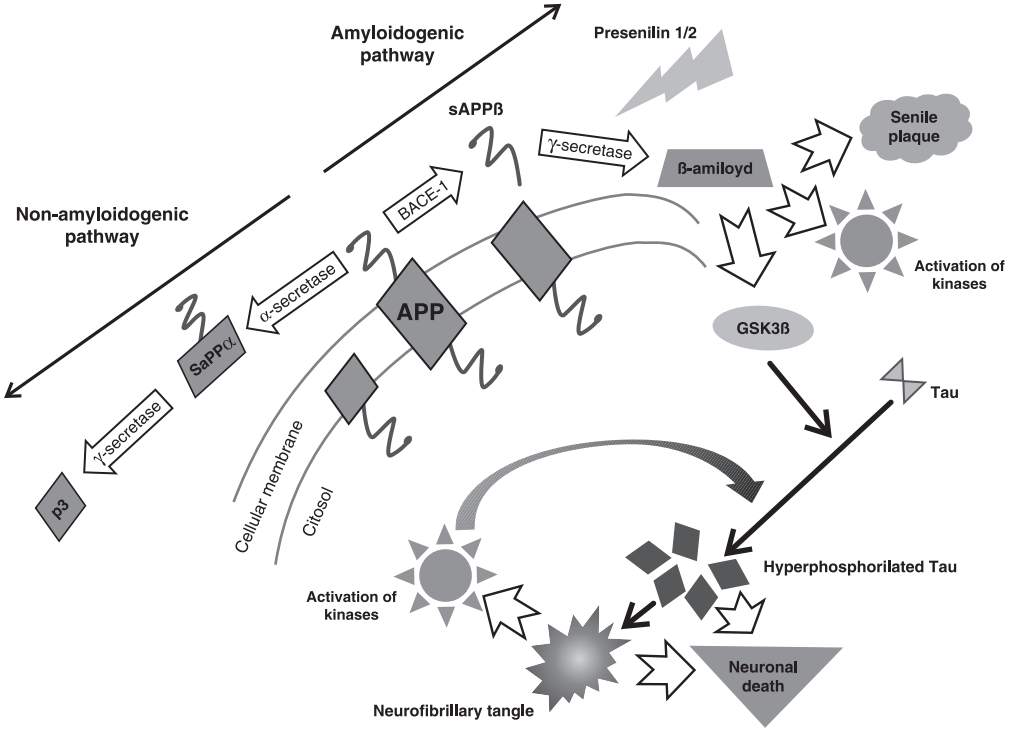

Figure 1 Basic pathophysiology of Alzheimer's disease. The amyloid precursor protein (APP) can be cleaved either by a "non-amyloidogenic pathway" or by the so-called "amyloidogenic pathway." In the non-amyloidogenic pathway, the APP is first cleaved by α-secretase, releasing a large fragment of APP (sAPPα), which is later digested by γ-secretase, producing non-toxic p3. In the amyloidogenic pathway, the APP is first processed by BACE-1 (a β-secretase), producing a fragment (sAPPβ) that will be subsequently cleaved by γ-secretase. The resulting protein of this "amyloidogenic pathway" is the toxic β-amyloid. In patients with presenilin mutations, the action of γ-secretase is disturbed and the production of β-amyloid is increased. The accumulation of insoluble β-amyloid leads to the formation of senile plaques and to the activation of kinases. β-amyloid can also activate GSK3β, an enzyme that modulates the phosphorylation of the tau protein. The accumulation of hyperphosphorylated forms of tau is toxic for the cell, leading to the formation of neurofibrillary tangles, which are associated with the activation of kinases and neuronal death.

microtubule-associated protein mainly present in axons.[16,17] APP mouse models do not develop neurofibrillary tangles and exhibit little neuronal loss, although hyperphosphorylated tau can be observed in different brain regions.[18] Mice overproducing Aβ do not exhibit neurofibrillary tangles as well. However, Aβ pathology can activate kinases, downregulate phosphatases, and impair tau degradation, leading to tau pathology.[6] These data supports the ''amyloid cascade theory,'' according to which the accumulation of Aβ is the initial pathophysiological event in AD, leading to tau aggregation, synaptic loss, and cell death.[9] It has been shown that removal of Aβ via immunotherapy also leads to the removal of hyperphosphorylated tau aggregate.[19] Aβ oligomers impair proteasome activity, contributing to the age-related pathological accumulation of Aβ and tau in humans and AD mouse models.[20,21] Mice expressing both mutated APP and tau exhibit greater neurofibrillary tangle pathology as compared to mutated tau mice, further suggesting that Aβ accumulation leads to tau pathology.[22] In addition, Aβ peptide injection into the brain of tau transgenic mice exacerbates tau pathology.[22,23] Crossing APP transgenic mice with tau knockout mice prevents all cognitive deficits associated with the presence of APP, indicating that tau pathology activation via Aβ is necessary for cognitive impairment.[24] Conversely, Aβ accumulation is not altered by the absence of tau. As mentioned before, APP transgenic mice do not develop extensive neurofibrillary tangles, and tau remains soluble.[18] Indeed soluble tau might be more important to the disease than aggregated tau.

During AD progression, the axonal protein tau accumulates within dendritic spines, impairing synaptic function.[25] Using tau knockout mice and truncated tau expressing mice, it has been shown that the tau protein present in the dendrites can target the protein kinase Fyn to the postsynaptic terminals, where it phosphorylates the NR2B subunit of the N-methyl-d-aspartate (NMDA) receptor. This receptor increases NMDA localization in postsynaptic membrane and, hence, the influx of calcium into the neuron, facilitating excitotoxicity.[26] Using an APP mouse model of AD, it has been demonstrated that Aβ oligomers can also regulate NMDA receptor cellular trafficking.[27] Therefore, tau knockout mice and APP overexpressing mice have been useful for elucidating essential mechanisms related to AD pathophysiology.

Knockout mice for genes involved in APP processing and secretion have also been generated. Presenilin is an important component of the γ-secretase complex and the knockout of presenilin 1 is lethal due to developmental defects in both the central nervous and skeletal systems.[28] These data indicate that presenilin 1 may be involved in physiological functions other than Aβ production and that presenilin 1 blockage might not be a good pharmacological strategy to treat AD. Presenilin 2 knockout mice exhibit no change in APP processing, although lack of presenilin 2 can exacerbate the lethal phenotype of presenilin 1.[29] The knockout of BACE1, which is the β-secretase enzyme, does not lead to any obvious alteration other than the absence of Aβ production.[30] Thus, BACE1 appears to be a potential target for AD treatment. Supporting this hypothesis, crossing the APP transgenic mice, Tg2576 mice, with the BACE1 knockout mice, resulted in a mouse that did not exhibit cognitive decline, cholinergic dysfunction, and high levels of Aβ, which were observed in the Tg2576 mice.[31]

Although AD mouse models have greatly contributed to elucidate different aspects of disease pathogenesis, so far no drug has been developed to treat AD using such models. The extensive neuronal cell loss that takes place in AD patients is not observed in AD models. Moreover, tau pathology is absent in most APP models. An animal model exhibiting most of the typical pathological aspects of AD, including increased neuronal death, seem to be necessary to select drugs that could have a greater potential in AD. Transgenic mice expressing mutated presenilin 1 and 2 do not exhibit any major phenotype.[32-34] However, when these presenilin mice were crossed with APP overexpressing mice, the resulting double mutant mice displayed increased Aβ42/Aβ40 ratio, accelerated Aβ pathology, neuronal loss, and cognitive decline.[35] However, neurofibrillary tangles were very rare in this double transgenic model. To overcome this problem, a triple transgenic mouse expressing mutated tau was developed, and this AD mouse model exhibit most of the AD-related features, including tau pathology.[36] To generate this triple mutant, transgenic constructs (mutant APP and tau) were microinjected into single-cell embryos from homozygous mutant presenilin 1 mice, thereby preventing segregation of APP and tau genes in subsequent generations. In accordance with the amyloid cascade theory, these triple transgenic mice develop Aβ plaques prior to neurofibrillary tangles, with a temporal and spatial profile equivalent to AD, in addition to inflammation, synaptic dysfunction, and cognitive decline.[36] Due to the growing number of AD rodent models, this review only mentioned a few representative mouse models of AD. For an updated overview of available genetically modified AD models, we refer the readers to specialized websites, such as http://www.alzforum.org.

Besides mammal models, zebra fish have been increasingly recognized as a model organism for studying AD. Zebra fish present some characteristics that make them an interesting model for central nervous system (CNS) diseases, such as short time to reach sexual maturity and a high reproductive rate.[37] Moreover, their embryos have external development and are transparent, thus allowing direct observation of embryogenesis and CNS formation. Zebra fish may present complex behaviors in memory and conditioned responses tasks. Transgenic zebra fish models may be of particular interest for investigating the neurodegeneration associated with taupathy.[37]

In addition to vertebrate models of AD, invertebrate animals, such as *Caenorhabditis elegans* and *Drosophila*, may be suitable to study AD, as they have short reproduction time, short life span, known genomics, a variety of phenotypes, and are able to express human genes of interest. These invertebrate animals allow rapid construction of different transgenic models, boosting

genetic and drug screens to identify mechanisms related to age-dependent neurodegeneration.

Drosophila expressing genetically modified tau exhibits adult onset, progressive neurodegeneration, early death, enhanced toxicity of mutant tau, and accumulation of abnormal tau, but no neurofibrillary tangles.[38] Intracellular inclusion resembling neurofibrillary tangles can be provoked in wild-type tau expressing flies when glycogen synthase kinase 3β (GSK-3β) activity is increased, as GSK-3β can promote hyperphosphorylation of tau and subsequent aggregation.[39] A number of APP *Drosophila* models has also been developed, and it has been demonstrated that *Drosophila* can produce Aβ peptide and develop neurodegeneration and memory decline.[40,41] Moreover, *Drosophila* overexpressing APP and BACE have been used for drug testing. Administration of either BACE inhibitor or γ-secretase inhibitor increased survival rates of this *Drosophila* model.[42]

C. elegans have only about 302 neurons, greatly facilitating the study of neuronal morphology and physiology. Moreover, about 65% of the human disease genes have a counterpart in the nematode's genes.[43] Although *C. elegans* are not able to process APP to form Aβ peptide, *C. elegans* expressing $A\beta_{42}$ peptide intracellularly in muscle cells exhibit aggregation and, hence, muscle dysfunction (paralysis phenotype).[44] This model provides important insights into Aβ toxicity, but does not allow screening of genetic or chemical modifiers of APP processing. Transgenic nematodes expressing $A\beta_{42}$ in neurons develop amyloid deposits, but display only a very mild phenotype.[45] To create nematode tau pathology models, either wild-type or mutated human tau proteins were expressed in *C. elegans* neurons, inducing age-dependent motor neuron dysfunction, neurodegeneration, and locomotor deficits due to impaired neurotransmission.[46,47] In conclusion, although invertebrates lack the neuronal cognitive complexity of mammals, they represent a feasible model to study AD mechanisms and to perform drug screening.

Even though these animal models provided valuable and important data concerning the pathophysiology of AD, the recent failure of anti-amyloid immunotherapy in AD points the limits of the pathophysiological paradigms established from these animal models. Indeed, new animal models for sporadic AD taking into account the genetic variability and the immunological factors that may influence the pathophysiology of the disease are required for the development of effective disease-modifying drugs for AD.

Animal models of Parkinson's disease

PD is the second most common age-related human neurodegenerative disorder. Prevalence rate varies from 1 to 4% in people over 60 years old.[48,49] However, prevalence rates up to 10% have been reported in elderly people depending on the epidemiological approach, diagnostic criteria, and population survival rate.

The main histopathological hallmark of PD is the loss of dopaminergic neurons in the substantia nigra pars compacta. The progressive striatal dorsoventral dopamine depletion leads to the cardinal motor signs of PD, bradykinesia, resting tremor, rigidity, and postural instability.[50] Therapeutic strategy is based on dopamine analogs, dopamine-degrading enzyme inhibitors, and deep brain stimulation, but none is able to halt the progressive neuronal death.[51]

Olfactory deficits are frequently evident in the very early stage of PD. Sleep abnormalities and autonomic failure accompanies motor symptoms. Dementia is often observed in the later stages of PD. In consonance with this broad spectrum of non-motor symptoms, histopathological abnormalities have been also described in other encephalic areas, comprising the dorsal motor nucleus of the vagus, *nucleus basalis* of Meynert, *locus coeruleus*, raphe nuclei, amygdala, olfactory bulb, neocortex, and hypothalamus.[52] Interestingly, many clinical studies have shown that non-motor symptoms may antedate the onset of typical motor signs in PD, stressing the need for understanding the molecular pathways that might trigger the neurodegenerative process.[53]

The cellular pathological hallmark for PD is the presence of small eosinophilic inclusions known as Lewy bodies in all the affected brain areas. Lewy bodies are composed of unbranched α-synuclein filaments and ubiquitin, and most likely result from ineffective protein degradation. Post-mortem analysis of brain from PD patients has shown that α-synuclein inclusions emerge in a predictable order in different parts of the brain and may be linked to the progressive stages of this disease.[52]

Although the etiopathogenesis of PD is not yet clarified, animal models have provided a better understanding of the cellular and molecular mechanisms underlying the progressive neurodegenerative process. In the fifties, pharmacological models based on the administration of monoamine-depleting drugs had an important role in demonstrating the relationship between dopamine depletion and Parkinson-like motor symptoms as well as the efficacy of L-dopa therapy. Nevertheless, reserpine and haloperidol models had serious limitations in mimicking PD pathogenesis since drug-treated animals exhibited transient striatal dopamine depletion not associated with the typical neurodegeneration in substantia nigra.[54] However, the pivotal role played by these models in assessing the therapeutic efficacy of drugs still in current clinical use cannot be undermined.

The so-called neurotoxin-based models of PD are the most effective in reproducing irreversible dopaminergic neuron death and striatal dopamine deficit in nonhuman primates and rodents. MPTP (1-methyl-4-phenyl-1,2,3,6-terahydropyridine), 6-OHDA (6-hydroxy-dopamine), and rotenone are so far the most widely used compounds. They are particularly attractive for inducing cytotoxicity by oxidative stress mechanisms, as brain from PD patients show decreased levels of reduced glutathione and oxidative modifications to DNA, lipids, and proteins.[55,56]

Interestingly, MPTP was accidently discovered during the investigations of the potential factors that led young addicts to develop PD-like symptoms. MPTP was found to be the heroin contaminant responsible for parkinsonism in

these subjects.[57] MPTP can be administered systemically since it is highly lipophilic and freely crosses the blood brain barrier. Astrocytes and endothelia convert MPTP into the active neurotoxic MPP+ (1-methyl-4-phenylpyridinium), which is taken up by dopaminergic neurons through the dopamine transporter. MPP+ interacts with the mitochondrial complexes I-III-IV, inhibiting the electron transport chain and inducing ATP depletion and oxidative stress.[58] MPP+ is also linked to impairment of glutamate uptake by astrocytes and neuronal apoptosis.[59,60]

MPTP administration to nonhuman primates is the experimental model that more closely resembles the pathological features of PD, including nigrostriatal dopamine depletion and extrastriatal dopamine, noradrenaline, and serotonin changes observed in PD patients.[61] In this model, the motor symptoms are closely similar to those observed in man (akinesia, bradykinesia, rigidity, and postural abnormalities) except for rest tremor. The symptoms are also reversible by all dopaminergic drugs known to be effective in PD. This model has been extensively used to investigate new pharmacological treatments for PD, as well as strategies to avoid treatment-related dyskinesia.[62] No typical Lewy bodies are observed in a MPTP primate model, but α-synuclein immunoreactivity is enhanced in the nigrostriatal system and in many brain areas.[63] The relevant role for neuroinflammation in PD pathology, specifically IFN-γ and TNF-α inducing early microglial activation that precedes neuronal death, has been recently highlighted in this model.[64] In mice, MPTP also induces nigrostriatal dopaminergic degeneration, making it a widely used model. More recently, Prediger et al. showed that intranasal infusion of MPTP in rodents causes motor impairments and olfactory and cognitive deficits that resemble the different stages of PD.[65,66]

Rotenone, a pesticide used in farming, is also highly lipophilic and easily crosses the blood brain barrier. Rotenone is a high-affinity inhibitor of mitochondrial complex I, but unlike MPTP, its entrance into cells is not dependent on a specific transporter. Rotenone cytotoxicity is based on oxidative stress and reactive oxygen species production.[67] High doses of rotenone can induce generalized neurodegeneration, so studies have been directed to chronic low-dose regimen in systemic administration of this compound in rodents. In this condition, α-synuclein positive Lewy bodies are observed in the nigrostriatal system.[54]

Unlike MPTP and rotenone, 6-OHDA does not cross the blood-brain barrier and it must be injected into the brain through a stereotaxic-guided surgical procedure. 6-OHDA is taken up into the dopaminergic neurons due to its high affinity to dopamine transporter. Once inside neurons, 6-OHDA is readily oxidized in reactive oxygen species leading to electron transport chain inhibition and oxidative stress.[68] 6-OHDA is usually injected unilaterally in the substantia nigra or in the striatum (retrograde degeneration). The unilateral injection allows the evaluation of neuron cell death and molecular parameters in the lesion hemisphere compared with the intact contralateral one. Dopamine depletion, percentage of neuronal cell death necessary to cause motor symptoms, and behavioral deficits have been assessed in this model. Neither Lewy bodies nor olfactory deficits were observed in 6-OHDA-treated animals.[69] This model has been proven to be useful to study glia involvement in the neurodegenerative process. For instance, Saura et al. showed that glia activation by interleukin-1β before 6-OHDA injection protects rather than stimulates neuron cell degeneration.[70] Conversely, microglia activated by overexpression or aberrant expression of α-synuclein secretes inflammatory cytokines and reactivates oxygen species that contribute to neurodegeneration.[71]

Although most PD cases are sporadic, approximately 5 to 10% are inherited. At least 16 gene loci (PARK1-16) have been implicated in PD, but the heritability is not fully understood. The most common cause of familial PD is the dominant mutation in leucine-rich repeat kinase 2 (LRRK2), an enzyme involved in the cytoskeleton dynamics and synaptic vesicle function.[72] Dominant mutation has also been linked to many important molecular pathways such as α-synuclein folding and ubiquitin-dependent proteolysis. Recessive mutation has also been involved in important mitochondrial pathways related to oxidative stress response. Although genetically modified rodents have been used for elucidating molecular pathways involved in neuron death and for developing new therapeutic strategies, none of them displays the significant neurodegeneration typical of PD.[73]

Neuroinflammation is also considered to play an important role in PD pathogenesis since enhanced levels of cytokines are detected in post-mortem analysis of the nigrostriatal system, in the cerebrospinal fluid and in plasma from PD patients.[74,75] LPS infusion into the substantia nigra induces microglia activation that precedes the degeneration of dopaminergic neurons. Although it has been shown that activated microglia releases TNF-α, IL-1β, nitric oxide, and reactivates oxygen species after LPS injection, a direct cause-effect association between these mediators and neuronal cell death has not been established yet in this model.[76]

It is worth mentioning the contribution of invertebrate models, particularly the *Drosophila* model, to assess the genetic pathways related to PD-genes. This fly model has pointed out the importance of parkin and PINK1 for mitochondrial integrity, fission-fusion events, and turn-over through autophagy, most likely acting in a common genetic pathway.[77,78] The α-synuclein gene is the only known gene related to familial PD that does not have a homolog in *Drosophila*.[79] LRRK2 mutation also induces mitochondrial and dopaminergic dysfunction in *Drosophila*.[80] In this particular model, activation of adenosine monophosphate-activated protein kinase (AMPK), a cellular energy sensor, exerts potent protection against dopaminergic and mitochondrial dysfunction in both LRRK2 and parkin mutant flies.

Animal models of Huntington's disease

HD is an autosomal dominant inherited neurodegenerative disorder characterized by progressive motor, cognitive, and psychiatric symptoms, leading inevitably to

death.[81,82] Choreoatetosis, dementia, and an autosomal dominant inheritance is classically regarded as 'the Huntington's triad.' A polyglutamine expansion in the amino-terminal region of the huntingtin (HTT) protein is the cause of HD, and the length of the polyglutamine repeat is inversely correlated with the age of disease onset and directly correlated with the severity of symptoms.[83] Although it is well established that the mutated HTT is responsible for triggering HD, the mechanisms underlying mutant HTT pathogenicity are still largely unknown. There is no data explaining why the mutant protein, which is expressed throughout the body results in the selective death of striatal medium sized spiny neurons. Cleavage of polyglutamine expanded HTT leads to the release of amino-terminal fragments containing the polyglutamine repeats, which can aggregate in neurites, cytoplasm, and nuclei. However, it is still controversial whether mutated HTT aggregates are cytotoxic or may reflect successful sequestration of toxic soluble HTT oligomers.[84,85] Importantly, loss of striatal and cortical neurons strongly correlate with HD symptom severity.[86]

Unlike the majority of AD and PD cases, which are sporadic, HD is an inherited neurologic disease caused by a single gene mutation, which made it feasible to develop animal models using genetic manipulations that closely recapitulate HD pathology. These models include transgenic mice, such as R6/2 and N171-82Q, expressing the amino-terminal region of human mutant HTT[87-89]; transgenic mice, such as yeast artificial chromosome mice (YAC128) and bacterial artificial chromosome mice (BACHD), expressing full-length human mutant HTT[90,91]; and knock-in mice, such as $Hdh^{Q97/Q97}$, $Hdh^{Q111/Q111}$ and $Hdh^{Q150/Q150}$, generated by replacing the first exon of the murine HTT gene by the first exon of the human HTT gene containing expanded CAG repeats.[92-94]

R6/2 mice display a robust phenotype, including motor deficits, such as lack of motor coordination, abnormal gait and hypoactivity, and learning impairment, with age of onset of about four weeks.[89,95,96] Aggregate formation is very pronounced in R6/2 mice, with intranuclear inclusions similar to those observed in biopsy material from HD patients and occurring prior to the development of symptoms.[87,97] These transgenic mice exhibit severe neurological symptoms and early death at 3-6 months of age.[89] The rapid onset and pronounced phenotype has made this a useful model for drug testing.[98,99] However, despite of having a robust phenotype, R6/2 mice do not represent an accurate model of HD, as this model only expresses the amino-terminal region of the HTT protein, which is mainly composed of polyglutamines. Thus, R6/2 may be considered a model of polyglutamine diseases, such as autosomal-dominant spinocerebellar ataxias (e.g., SCA3 or Machado-Joseph disease) and X-linked spinobulbar muscular atrophy (Kennedy disease), rather than a specific HD mouse model. In that sense, the R6/2 mice can be useful to model common features of polyglutamine diseases including abnormal protein conformation promoted by polyglutamine expansion, which appears to be central to the pathogenesis. Although the clinical features and pattern of neuronal degeneration differ, all polyglutamine expansion diseases are ultimately fatal disorders that typically begin in adulthood and progress over 10 to 30 years.

YAC128 and BACHD transgenic mice, which exhibit 128 and 97 polyglutamine, respectively, in the amino-terminal region of the full-length mutant human HTT, present milder deficits than R6/2.[100] It has been shown that BACHD displays a stronger phenotype than that of YAC128 when both mice were tested under the same behavioral protocol.[101] Moreover, the same study also demonstrates that $Hdh^{Q111/Q111}$ displays a very mild phenotype, exhibiting less behavioral abnormalities than R6/2, BACHD, and YAC128 mice.[101] The knock-in mouse model of HD displays milder phenotype than R6/2 even when expressing 150 polyglutamines, as in the case of $Hdh^{Q150/Q150}$. $Hdh^{Q150/Q150}$ exhibits late-onset behavioral changes, including motor task deficit and gait abnormalities.[93,102] Thus, as observed in HD patients, HD mouse models with more repeats ($Hdh^{Q111/Q111}$ versus $Hdh^{Q150/Q150}$) show stronger phenotype. That is also the case for transgenic mice, as YAC46 and YAC72 mice show no clear behavioral abnormalities, while YAC128 mice display marked phenotype.[103]

In general, HD mouse models displaying more severe phenotypes show earlier accumulation of HTT aggregates and premature neuronal death.[104] YAC128, BACHD, and Knock-in HD mice with expanded polyglutamine repeats from 97 to 150 polyglutamines display obvious HTT aggregates only at older ages and have a lifespan similar to wild-type mice.[90,91,93] BACHD mice exhibit pronounced striatal and cortical atrophy, and neurodegeneration at the age of 12 months.[91] However, very few HTT aggregates could be observed in BACHD brain. YAC128 mice exhibit striatal atrophy at the age of 12 months, as well as cortical atrophy at the age of 18 months.[90] Moreover, intranuclear inclusions and HTT aggregates could be observed in 12- and 18-month-old YAC128 mice, respectively. $Hdh^{Q150/Q150}$ and $Hdh^{Q111/Q111}$ mice exhibit neuronal intranuclear inclusions predominantly in the striatum, but only at older ages, such as from 15 to 22 months.[93,102,104] Thus, although knock-in HD mouse models accurately replicate the underlying genetic defect of HD, they do not display the robust motor deficit and neuronal cell loss observed in HD patients. In that sense, BACHD and YAC128 could be regarded as better models for drug testing.

Even though HD rodent models replicate the genetic event causing HD, most of the mouse models do not exhibit the robust neuronal cell loss that takes place in HD patients. This is the main drawback feature of not only HD mouse models, but also of AD and PD models. Future manipulations or implementations of other disease model organisms will be necessary to overcome this problem, as neurodegeneration is the major pathological event in HD, AD, and PD patients.[105,106] Mutant HTT appears to be more toxic to larger animals, such as pigs and monkeys, than to mouse HD models.[107] However, despite this advantage, the high cost and more elaborated infrastructure necessary to keep these bigger animals that

have a much longer life-span pose difficulties in using these types of HD models.

Small animals, including *Drosophila* and *C. elegans*, are also used as HD animal models. As stated before, the short life-span and reproduction time make these animals ideal for modeling neurodegenerative diseases and performing a number of assays, including genetic and drug screens. The identification of a *Drosophila* orthologue of human HTT suggests that many of the pathways in which HTT normally functions might be present in fruit flies, further supporting *Drosophila* as a good model to study HD.[108] Moreover, another interesting feature of *Drosophila* as an HD model is that neurodegeneration can be easily scored in the eye. Overexpressing mutant HTT in *Drosophila* leads to aggregate formation, neuronal death, and reduced longevity.[109,110] In addition, *Drosophila* HD models recapitulate many features of HD in patients, including motor deficit and learning and memory deterioration.[111,112] All these features make *Drosophila* a suitable model for drug testing.

C. elegans expressing polyglutamine-expanded green fluorescent protein (GFP) in muscle cells were developed, and this mutant nematode exhibited aggregate formation, cellular toxicity, and paralysis in an age- and repeat length-dependent manner.[113,114] *C. elegans* expressing an amino-terminal fragment of human HTT containing expanded polyglutamine in sensory and touch mechanosensory neurons have also been developed.[115,116] Degeneration displayed by these *C. elegans* HD models are dependent on both age and polyglutamine tract length.[115] These *C. elegans* models have been used to investigate proteins involved in aging and aggregation, as well as drug testing.[117-120] However, neuronal cell death is not robust in these HD *C. elegans* models.[115,116]

Concluding remarks

Animal models have provided significant contribution to the understanding of the pathophysiology of neurodegenerative diseases. Conversely, as neurodegenerative human diseases are heterogeneous in both pathological and clinical (or behavioral) domains, animal models only recapitulate part of this complex scenario. Moreover, much attention has been paid to genetic or transgenic animal models, while most human cases of AD and PD are sporadic, rather than familial. Together these aspects may explain the limited contribution of animal models to the development of effective disease-modifying therapeutic strategies. Therefore, there is a great challenge ahead to develop the next generation of animal models to effectively help treat and prevent neurodegenerative diseases.

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Disclosure

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References

1 Wimo A, Winblad B, Jonsson L. The worldwide societal costs of dementia: Estimates for 2009. Alzheimers Dement. 2010;6:98-103.
2 Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. Lancet. 2011;377:1019-31.
3 Duyckaerts C, Potier MC, Delatour B. Alzheimer disease models and human neuropathology: similarities and differences. Acta Neuropathol. 2008;115:5-38.
4 Querfurth HW, LaFerla FM. Alzheimer's disease. N Engl J Med. 2010;362:329-44.
5 LaFerla FM, Green KN. Animal models of Alzheimer disease. Cold Spring Harb Perspect Med. 2012;2. pii:a006320.
6 Blurton-Jones M, Laferla FM. Pathways by which Abeta facilitates tau pathology. Cur Alzheimer Res. 2006;3:437-48.
7 Esch FS, Keim PS, Beattie EC, Blacher RW, Culwell AR, Oltersdorf T, et al. Cleavage of amyloid beta peptide during constitutive processing of its precursor. Science. 1990;248:1122-4.
8 Duyckaerts C, Delatour B, Potier MC. Classification and basic pathology of Alzheimer disease. Acta Neuropathol. 2009;118:5-36.
9 Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010;9:119-28.
10 Hyman BT. Amyloid-dependent and amyloid-independent stages of Alzheimer disease. Arch Neurol. 2011;68:1062-4.
11 Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol. 1991;30:572-80.
12 Selkoe DJ. Alzheimer's disease is a synaptic failure. Science. 2002;298:789-91.
13 Frautschy SA, Yang F, Calderon L, Cole GM. Rodent models of Alzheimer's disease: rat A beta infusion approaches to amyloid deposits. Neurobiol Aging. 1996;17:311-21.
14 Van Dam D, De Deyn PP. Animal models in the drug discovery pipeline for Alzheimer's disease. Br J Pharmacol. 2011;164:1285-300.
15 Savonenko AV, Xu GM, Price DL, Borchelt DR, Markowska AL. Normal cognitive behavior in two distinct congenic lines of transgenic mice hyperexpressing mutant APP SWE. Neurobiol Dis. 2003;12:194-211.
16 Kosik KS, Joachim CL, Selkoe DJ. Microtubule-associated protein tau (tau) is a major antigenic component of paired helical filaments in Alzheimer disease. Proc Natl Acad Sci U S A. 1986;83:4044-8.
17 Wood JG, Mirra SS, Pollock NJ, Binder LI. Neurofibrillary tangles of Alzheimer disease share antigenic determinants with the axonal microtubule-associated protein tau (tau). Proc Natl Acad Sci U S A. 1986;83:4040-3.
18 Gotz J, Deters N, Doldissen A, Bokhari L, Ke Y, Wiesner A, et al. A decade of tau transgenic animal models and beyond. Brain Pathol. 2007;17:91-103.
19 Oddo S, Billings L, Kesslak JP, Cribbs DH, LaFerla FM. Abeta immunotherapy leads to clearance of early, but not late, hyperphosphorylated tau aggregates via the proteasome. Neuron. 2004;43:321-32.
20 Tseng BP, Green KN, Chan JL, Blurton-Jones M, LaFerla FM. Abeta inhibits the proteasome and enhances amyloid and tau accumulation. Neurobiol Aging. 2008;29:1607-18.

21 Keller JN, Hanni KB, Markesbery WR. Impaired proteasome function in Alzheimer's disease. J Neurochem. 2000;75:436-9.
22 Lewis J, Dickson DW, Lin WL, Chisholm L, Corral A, Jones G, et al. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. Science. 2001;293:1487-91.
23 Gotz J, Chen F, van Dorpe J, Nitsch RM. Formation of neurofibrillary tangles in P301I tau transgenic mice induced by Abeta 42 fibrils. Science. 2001;293:1491-5.
24 Roberson ED, Scearce-Levie K, Palop JJ, Yan F, Cheng IH, Wu T, et al. Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model. Science. 2007;316:750-4.
25 Hoover BR, Reed MN, Su J, Penrod RD, Kotilinek LA, Grant MK, et al. Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration. Neuron. 2010;68:1067-81.
26 Ittner LM, Ke YD, Delerue F, Bi M, Gladbach A, van Eersel J, et al. Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. Cell. 2010;142:387-97.
27 Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, et al. Regulation of NMDA receptor trafficking by amyloid-beta. Nat Neurosci. 2005;8:1051-8.
28 Shen J, Bronson RT, Chen DF, Xia W, Selkoe DJ, Tonegawa S. Skeletal and CNS defects in Presenilin-1-deficient mice. Cell. 1997;89:629-39.
29 Herreman A, Hartmann D, Annaert W, Saftig P, Craessaerts K, Serneels L, et al. Presenilin 2 deficiency causes a mild pulmonary phenotype and no changes in amyloid precursor protein processing but enhances the embryonic lethal phenotype of presenilin 1 deficiency. Proc Natl Acad Sci U S A. 1999;96:11872-7.
30 Luo Y, Bolon B, Kahn S, Bennett BD, Babu-Khan S, Denis P, et al. Mice deficient in BACE1, the Alzheimer's beta-secretase, have normal phenotype and abolished beta-amyloid generation. Nat Neurosci. 2001;4:231-2.
31 Ohno M, Sametsky EA, Younkin LH, Oakley H, Younkin SG, Citron M, et al. BACE1 deficiency rescues memory deficits and cholinergic dysfunction in a mouse model of Alzheimer's disease. Neuron. 2004;41:27-33.
32 Wen PH, Shao X, Shao Z, Hof PR, Wisniewski T, Kelley K, et al. Overexpression of wild type but not an FAD mutant presenilin-1 promotes neurogenesis in the hippocampus of adult mice. Neurobiol Dis. 2002;10:8-19.
33 Duff K, Eckman C, Zehr C, Yu X, Prada CM, Perez-tur J, et al. Increased amyloid-beta42(43) in brains of mice expressing mutant presenilin 1. Nature. 1996;383:710-3.
34 Oyama F, Sawamura N, Kobayashi K, Morishima-Kawashima M, Kuramochi T, Ito M, et al. Mutant presenilin 2 transgenic mouse: effect on an age-dependent increase of amyloid beta-protein 42 in the brain. J Neurochem. 1998;71:313-22.
35 Jankowsky JL, Slunt HH, Gonzales V, Jenkins NA, Copeland NG, Borchelt DR. APP processing and amyloid deposition in mice haploinsufficient for presenilin 1. Neurobiol Aging. 2004;25:885-92.
36 Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, et al. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. Neuron. 2003;39:409-21.
37 Santana S, Rico EP, Burgos JS. Can zebrafish be used as animal model to study Alzheimer's disease? Am J Neurodegener Dis. 2012;1:32-48.
38 Wittmann CW, Wszolek MF, Shulman JM, Salvaterra PM, Lewis J, Hutton M, et al. Tauopathy in Drosophila: neurodegeneration without neurofibrillary tangles. Science. 2001;293:711-4.
39 Jackson GR, Wiedau-Pazos M, Sang TK, Wagle N, Brown CA, Massachi S, et al. Human wild-type tau interacts with wingless pathway components and produces neurofibrillary pathology in Drosophila. Neuron. 2002;34:509-19.
40 Fossgreen A, Bruckner B, Czech C, Masters CL, Beyreuther K, Paro R. Transgenic Drosophila expressing human amyloid precursor protein show gamma-secretase activity and a blistered-wing phenotype. Proc Natl Acad Sci U S A. 1998;95:13703-8.
41 Iijima K, Liu HP, Chiang AS, Hearn SA, Konsolaki M, Zhong Y. Dissecting the pathological effects of human Abeta40 and Abeta42 in Drosophila: a potential model for Alzheimer's disease. Proc Natl Acad Sci U S A. 2004;101:6623-8.
42 Greeve I, Kretzschmar D, Tschape JA, Beyn A, Brellinger C, Schweizer M, et al. Age-dependent neurodegeneration and Alzheimer-amyloid plaque formation in transgenic Drosophila. J Neurosci. 2004;24:3899-906.
43 Sonnhammer EL, Durbin R. Analysis of protein domain families in Caenorhabditis elegans. Genomics. 1997;46:200-16.
44 Link CD. Expression of human beta-amyloid peptide in transgenic Caenorhabditis elegans. Proc Natl Acad Sci U S A. 1995;92:9368-72.
45 Link CD. C. elegans models of age-associated neurodegenerative diseases: lessons from transgenic worm models of Alzheimer's disease. Exp Gerontol. 2006;41:1007-13.
46 Kraemer BC, Zhang B, Leverenz JB, Thomas JH, Trojanowski JQ, Schellenberg GD. Neurodegeneration and defective neurotransmission in a Caenorhabditis elegans model of tauopathy. Proc Natl Acad Sci U S A. 2003;100:9980-5.
47 Miyasaka T, Ding Z, Gengyo-Ando K, Oue M, Yamaguchi H, Mitani S, et al. Progressive neurodegeneration in C. elegans model of tauopathy. Neurobiol Dis. 2005;20:372-83.
48 Willis AL, Evanoff BA, Lian M, Criswell SR, Racette BA. Geographic and ethnic variation in Parkinson disease: a population-based study of US medicare beneficiaries. Neuroepidemiology. 2010;34:143-51.
49 de Rijk MC, Tzourio C, Breteler MM, Dartigues JF, Amaducci L, Lopez-Pousa S, et al. Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON collaborative study. European Community Concerted Action on the Epidemiology of Parkinson's disease. J Neurol Neurosurg Psychiatry. 1997;62:10-5.
50 Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008;79:368-76.
51 Lees AJ, Hardy J, Revesz T. Parkinson's disease. Lancet. 2009;373:2055-66.
52 Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res. 2004;318:121-34.
53 Obeso JA, Rodriguez-Oroz MC, Goetz CG, Marin C, Kordowr JH, Rodriguez M, et al. Missing pieces in the Parkinson's disease puzzle. Nat Med. 2010;16:653-61.
54 Tieu K. A guide to neurotoxic animal models of Parkinson's disease. Cold Spring Harb Perspect Med. 2011;1:a009316.
55 Pearce RK, Owen A, Daniel S, Jenner P, Marsden CD. Alterations in the distribution of glutathione in the substantia nigra in Parkinson's disease. J Neural Transm. 1997;104:661-77.
56 Floor E, Wetzel MG. Increased protein oxidation in human substantia nigra pars compacta in comparison with basal ganglia and prefrontal cortex measured with an improved dinitrophenylhydrazine assay. J Neurochem. 1998;70:268-75.
57 Bezard E, Przedborski S. A tale on animal models of Parkinson's disease. Mov Disord. 2011;26:993-1002.
58 Bezard E, Gross CE, Fournier MC, Dovero S, Bloch B, Jaber M. Absence of MPTP-induced neuronal death in mice lacking the dopamine transporter. Exp Neurol. 1999;155:268-73.
59 Hazell AS, Norenberg MD. Manganese decreases glutamate uptake in cultured astrocytes. Neurochem Res. 1997;22:1443-7.
60 Przedborski S, Tieu K, Perier C, Vila M. MPTP as a mitochondrial neurotoxic model of Parkinson's disease. J Bioenerg Biomembr. 2004;36:375-9.
61 Porras G, Li Q, Bezard E. Modeling Parkinson's disease in primates: the MPTP model. Cold Spring Harb Perspect Med. 2012;2:a009308.
62 Jenner P. From the MPTP-treated primate to the treatment of motor complications in Parkinson's disease. Parkinsonism Relat Disord. 2009;15:S18-23.
63 Purisai MG, McCormack AL, Langston WJ, Johnston LC, Di Monte DA. Alpha-synuclein expression in the substantia nigra of MPTP-lesioned non-human primates. Neurobiol Dis. 2005;20:898-906.
64 Barcia C, Ros CM, Annese V, Gómez A, Ros-Bernal F, Aguado-Year D, et al. IFN-γ signaling, with the synergistic contribution of TNF-α, mediates cell specific microglial and astroglial activation in experimental models of Parkinson's disease. Cell Death Dis. 2011;2:e142.
65 Prediger RD, Aguiar AS Jr, Moreira EL, Matheus FC, Castro AA, Walz R, et al. The Intranasal Administration of 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP): A New Rodent Model to Test

Palliative and Neuroprotective Agents for Parkinson's disease. Curr Pharm Des. 2001;17:489-507.
66 Prediger RD, Aguiar AS Jr, Matheus FC, Walz R, Antoury L, Raisman-Vozari R, et al. Intranasal administration of neurotoxicants in animals: support for the olfactory vector hypothesis of Parkinson's disease. Neurotox Res. 2012;21:90-116.
67 Sherer TB, Betarbet R, Testa CM, Seo BB, Richardson JR, Kim JH, et al. Mechanism of toxicity in rotenone models of Parkinson's disease. J Neurosci. 2003;23:10756-64.
68 Mazzio EA, Reams RR, Soliman KF. The role of oxidative stress, impaired glycolysis and mitochondrial respiratory redox failure in the cytotoxic effects of 6-hydroxydopamine in vitro. Brain Res. 2004;1004:29-44.
69 Duty S, Jenner P. Animal models of Parkinson's disease: a source of novel treatments and clues to the cause of the disease. Br J Pharmacol. 2011;164:1357-91.
70 Saura J, Parés M, Bové J, Pezzi S, Alberch J, Marin C, et al. Intranigral infusion of interleukin-1beta activates astrocytes and protects from subsequent 6-hydroxydopamine neurotoxicity. J Neurochem. 2003;85:651-61.
71 Mosley RL, Hutter-Saunders JA, Stone DK, Gendelman HE. Inflammation and adaptative immunity in Parkinson's disease. Cold Spring Harb Perspect Med. 2012;2:a009381.
72 Scholz SW, Mhyre T, Ressom H, Shah S, Federoff HJ. Genomics and Bioinformatics of Parkinson's Disease. Cold Spring Harb Perspect Med. 2012;2:a009449.
73 Yue Z, Lachenmayer ML. Genetic LRRK2 models of Parkinson's disease: Dissecting the pathogenic pathway and exploring clinical applications. Mov Disord. 2011;26:1386-97.
74 Mogi M, Harada M, Riederer P, Narabayashi H, Fujita K, Nagatsu T. Tumor necrosis factor-alpha (TNF-alpha) increases both in the brain and in the cerebrospinal fluid from parkinsonian patients. Neurosci Lett. 1994;165:208-10.
75 Scalzo P, Kümmer A, Cardoso F, Teixeira AL. Increased serum levels of soluble tumor necrosis factor-alpha receptor-1 in patients with Parkinson's disease. J Neuroimmunol. 2009;216:122-5.
76 Dutta G, Zhang P, Liu B. The Lipopolysaccharide Parkinson's disease animal model: mechanistic studies and drug discovery. Fundam Clin Pharmacol. 2008;22:453-64.
77 Clark IE, Dodson MW, Jiang C, Cao JH, Huth JR, Seol JH, et al. Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin. Nature. 2006;441:1162-6.
78 Sha D, Chin LS, Li L. Phosphorylation of Parkin by Parkinson disease-linked kinase PINK1 activates Parkin E3 ligase function and NF-kB signaling. Hum Mol Genet. 2010;19:352-63.
79 Guo M. Drosophila as a model to study mitochondrial dysfunction in Parkinson's disease. Cold Spring Harb Perspect Med. 2012;2:a009944.
80 Ng CH, Guan MS, Koh C, Ouyang X, Yu F, Tan EK, et al. AMP kinase activation mitigates dopaminergic dysfunction and mitochondrial abnormalities in Drosophila models of Parkinson's disease. J Neurosci. 2012;32:14311-7.
81 Li SH, Li XJ. Huntingtin-protein interactions and the pathogenesis of Huntington's disease. Trends Genet. 2004;20:146-54.
82 Young AB. Huntingtin in health and disease. J Clin Invest. 2003;111:299-302.
83 A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell. 1993;72:971-83.
84 Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. Nature. 2004;431:805-10.
85 Sanchez I, Mahlke C, Yuan J. Pivotal role of oligomerization in expanded polyglutamine neurodegenerative disorders. Nature. 2003;421:373-9.
86 Myers RH, Vonsattel JP, Stevens TJ, Cupples LA, Richardson EP, Martin JB, et al. Clinical and neuropathologic assessment of severity in Huntington's disease. Neurology. 1988;38:341-7.
87 Davies SW, Turmaine M, Cozens BA, DiFiglia M, Sharp AH, Ross CA, et al. Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. Cell. 1997;90:537-48.
88 Schilling G, Becher MW, Sharp AH, Jinnah HA, Duan K, Kotzuk JA, et al. Intranuclear inclusions and neuritic aggregates in transgenic mice expressing a mutant N-terminal fragment of huntingtin. Hum Mol Genet. 1999;8:397-407.
89 Mangiarini L, Sathasivam K, Seller M, Cozens B, Harper A, Hetherington C, et al. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. Cell. 1996;87:493-506.
90 Slow EJ, van Raamsdonk J, Rogers D, Coleman SH, Graham RK, Deng Y, et al. Selective striatal neuronal loss in a YAC128 mouse model of Huntington disease. Hum Mol Genet. 2003;12: 1555-67.
91 Gray M, Shirasaki DI, Cepeda C, Andre VM, Wilburn B, Lu XH, et al. Full-length human mutant huntingtin with a stable polyglutamine repeat can elicit progressive and selective neuropathogenesis in BACHD mice. J Neurosci. 2008;28:6182-95.
92 Wheeler VC, White JK, Gutekunst CA, Vrbanac V, Weaver M, Li XJ, et al. Long glutamine tracts cause nuclear localization of a novel form of huntingtin in medium spiny striatal neurons in HdhQ92 and HdhQ111 knock-in mice. Hum Mol Genet. 2000;9:503-13.
93 Lin CH, Tallaksen-Greene S, Chien WM, Cearley JA, Jackson WS, Crouse AB, et al. Neurological abnormalities in a knock-in mouse model of Huntington's disease. Hum Mol Genet. 2001;10: 137-44.
94 Menalled LB, Sison JD, Wu Y, Olivieri M, Li XJ, Li H, et al. Early motor dysfunction and striosomal distribution of huntingtin micro-aggregates in Huntington's disease knock-in mice. J Neurosci. 2002;22:8266-76.
95 Carter RJ, Lione LA, Humby T, Mangiarini L, Mahal A, Bates GP, et al. Characterization of progressive motor deficits in mice transgenic for the human Huntington's disease mutation. J Neurosci. 1999;19:3248-57.
96 Lione LA, Carter RJ, Hunt MJ, Bates GP, Morton AJ, Dunnett SB. Selective discrimination learning impairments in mice expressing the human Huntington's disease mutation. J Neurosci. 1999;19:10428-37.
97 Li H, Li SH, Cheng AL, Mangiarini L, Bates GP, Li XJ. Ultrastructural localization and progressive formation of neuropil aggregates in Huntington's disease transgenic mice. Hum Mol Genet. 1999;8:1227-36.
98 Ferrante RJ, Andreassen OA, Jenkins BG, Dedeoglu A, Kuemmerle S, Kubilus JK, et al. Neuroprotective effects of creatine in a transgenic mouse model of Huntington's disease. J Neurosci. 2000;20:4389-97.
99 Ona VO, Li M, Vonsattel JP, Andrews LJ, Khan SQ, Chung WM, et al. Inhibition of caspase-1 slows disease progression in a mouse model of Huntington's disease. Nature. 1999;399:263-7.
100 Menalled LB, Chesselet MF. Mouse models of Huntington's disease. Trends Pharmacol Sci. 2002;23:32-9.
101 Menalled L, El-Khodor BF, Patry M, Suarez-Farinas M, Orenstein SJ, Zahasky B, et al. Systematic behavioral evaluation of Huntington's disease transgenic and knock-in mouse models. Neurobiol Dis. 2009;35:319-36.
102 Woodman B, Butler R, Landles C, Lupton MK, Tse J, Hockly E, et al. The Hdh(Q150/Q150) knock-in mouse model of HD and the R6/2 exon 1 model develop comparable and widespread molecular phenotypes. Brain Res Bull. 2007;72:83-97.
103 Slow EJ, Graham RK, Osmand AP, Devon RS, Lu G, Deng Y, et al. Absence of behavioral abnormalities and neurodegeneration in vivo despite widespread neuronal huntingtin inclusions. Proc Natl Acad Sci U S A. 2005;102:11402-7.
104 Wang CE, Tydlacka S, Orr AL, Yang SH, Graham RK, Hayden MR, et al. Accumulation of N-terminal mutant huntingtin in mouse and monkey models implicated as a pathogenic mechanism in Huntington's disease. Hum Mol Genet. 2008;17:2738-51.
105 Yuan J, Yankner BA. Apoptosis in the nervous system. Nature. 2000;407:802-9.
106 Mattson MP. Apoptosis in neurodegenerative disorders. Nat Rev Mol Cell Biol. 2000;1:120-9.
107 Li XJ, Li S. Influence of species differences on the neuropathology of transgenic Huntington's disease animal models. J Genet Genomics. 2012;39:239-45.
108 Li Z, Karlovich CA, Fish MP, Scott MP, Myers RM. A putative Drosophila homolog of the Huntington's disease gene. Hum Mol Genet. 1999;8:1807-15.

109 Jackson GR, Salecker I, Dong X, Yao X, Arnheim N, Faber PW, et al. Polyglutamine-expanded human huntingtin transgenes induce degeneration of Drosophila photoreceptor neurons. Neuron. 1998;21:633-42.
110 Marsh JL, Walker H, Theisen H, Zhu YZ, Fielder T, Purcell J, et al. Expanded polyglutamine peptides alone are intrinsically cytotoxic and cause neurodegeneration in Drosophila. Hum Mol Genet. 2000;9:13-25.
111 Kahsai L, Zars T. Learning and memory in Drosophila: behavior, genetics, and neural systems. Int Rev Neurobiol. 2011;99:139-67.
112 Agrawal N, Pallos J, Slepko N, Apostol BL, Bodai L, Chang LW, et al. Identification of combinatorial drug regimens for treatment of Huntington's disease using Drosophila. Proc Natl Acad Sci U S A. 2005;102:3777-81.
113 Satyal SH, Schmidt E, Kitagawa K, Sondheimer N, Lindquist S, Kramer JM, et al. Polyglutamine aggregates alter protein folding homeostasis in Caenorhabditis elegans. Proc Natl Acad Sci U S A. 2000;97:5750-5.
114 Morley JF, Brignull HR, Weyers JJ, Morimoto RI. The threshold for polyglutamine-expansion protein aggregation and cellular toxicity is dynamic and influenced by aging in Caenorhabditis elegans. Proc Natl Acad Sci U S A. 2002;99:10417-22.
115 Faber PW, Alter JR, MacDonald ME, Hart AC. Polyglutamine-mediated dysfunction and apoptotic death of a Caenorhabditis elegans sensory neuron. Proc Natl Acad Sci U S A. 1999;96:179-84.
116 Parker JA, Connolly JB, Wellington C, Hayden M, Dausset J, Neri C. Expanded polyglutamines in Caenorhabditis elegans cause axonal abnormalities and severe dysfunction of PLM mechanosensory neurons without cell death. Proc Natl Acad Sci U S A. 2001;98:13318-23.
117 Hsu AL, Murphy CT, Kenyon C. Regulation of aging and age-related disease by DAF-16 and heat-shock factor. Science. 2003;300:1142-5.
118 Faber PW, Voisine C, King DC, Bates EA, Hart AC. Glutamine/proline-rich PQE-1 proteins protect Caenorhabditis elegans neurons from huntingtin polyglutamine neurotoxicity. Proc Natl Acad Sci U S A. 2002;99:17131-6.
119 Haldimann P, Muriset M, Vigh L, Goloubinoff P. The novel hydroxylamine derivative NG-094 suppresses polyglutamine protein toxicity in Caenorhabditis elegans. J Biol Chem. 2011;286:18784-94.
120 Voisine C, Varma H, Walker N, Bates EA, Stockwell BR, Hart AC. Identification of potential therapeutic drugs for huntington's disease using Caenorhabditis elegans. PloS One. 2007;2:e504.