Ageing and neuronal vulnerability

Mark P. Mattson[*‡] *and Tim Magnus*[*]

Abstract | Everyone ages, but only some will develop a neurodegenerative disorder in the process. Disease might occur when cells fail to respond adaptively to age-related increases in oxidative, metabolic and ionic stress, thereby resulting in the accumulation of damaged proteins, DNA and membranes. Determinants of neuronal vulnerability might include cell size and location, metabolism of disease-specific proteins and a repertoire of signal transduction pathways and stress resistance mechanisms. Emerging evidence on protein interaction networks that monitor and respond to the normal ageing process suggests that successful neural ageing is possible for most people, but also cautions that cures for neurodegenerative disorders are unlikely in the near future.

Selective neuronal vulnerability
(SNV). The susceptibility of specific populations of neurons that is limited to a region or regions of the nervous system.

Proteasome
A protein complex responsible for degrading intracellular proteins that have been tagged for destruction by the addition of ubiquitin.

*Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, Baltimore, Maryland 21224-6825, USA.
‡Department of Neuroscience and Johns Hopkins University School of Medicine, Baltimore, Maryland 21205-2196, USA.
Correspondence to M.P.M.
e-mail:
mattsonm@grc.nia.nih.gov
doi:10.1038/nrn1886

Are occasional problems with short-term memory, shakiness and muscle weakness just unavoidable changes that occur during normal ageing? Or are they prodromal to a fatal neurodegenerative disorder? Cells in all regions of the nervous system are affected by ageing, as indicated by the decline of sensory, motor and cognitive functions with time[1]. However, there is considerable variability among individuals in the apparent rate of ageing, the neural systems most affected, and whether and how age-related deficits are compensated. There is a dramatic increase in the probability of developing a neurodegenerative disorder during the sixth, seventh and eighth decades of life. There is a high probability that a person who lives to the age of 85 years will suffer from Alzheimer's disease (AD); Parkinson's disease (PD) is most common in those above the age of 70 years and the probability of developing amyotrophic lateral sclerosis (ALS) rises sharply above the age of 40 years[2–6]. There is growing evidence that ageing has an important role in the occurrence of such diseases, and this article focuses on the relationship between ageing and neurodegenerative disorders. It is conceivable that the initiation of nerve cell death is programmed to occur after a given period of time independently of the cell modifications caused by ageing. However, a purely genetically programmed neuronal fate seems unlikely given that late-onset neurodegenerative disorders are sporadic within families and that some individuals live for a century or more with little or no evidence of neuronal degeneration.

Why is the hippocampus primarily affected in AD, the substantia nigra in PD, the striatum in Huntington's disease (HD) and the spinal cord and primary motor cortex in ALS (FIG. 1)? Why is it that, although certain neuronal populations are affected earlier and more severely than others, neuronal death also occurs in other brain regions as the disease progresses? Despite recent advances in our understanding of the molecular genetics and pathophysiology of neurodegenerative disorders, the problem of selective neuronal vulnerability (SNV) has proved difficult to solve. However, recent progress has begun to show how cellular and molecular changes that occur during normal ageing render neurons vulnerable to degeneration, and how disease-specific genetic and environmental factors determine which neurons succumb. Rare cases of AD, PD and ALS are caused by mutations in specific genes and, in such cases, disease onset occurs at an early age (30s, 40s or 50s), which is up to 40 years earlier than the more common sporadic forms of these diseases[1–6]. The clinical presentation and histopathological findings are essentially indistinguishable in familial and sporadic forms of the diseases, which suggests that the genetic mutations accelerate the same molecular and cellular cascades that occur in late-onset disease. For example, mutations in presenilin 1 and the amyloid precursor protein (APP) that cause early-onset AD enhance production of neurotoxic forms of the amyloid β-peptide (Aβ)[2]. Mutations in α-synuclein, parkin (a ubiquitin E3 ligase) and DJ1 that cause PD are thought to result in impaired proteasome-mediated proteolysis[4], and mutations in copper/zinc-superoxide dismutase (Cu/Zn-SOD) that cause early-onset ALS exacerbate oxidative stress in motor neurons[6].

Here, we describe cellular and molecular changes that occur during normal ageing, and discuss how these changes might interact with genes and the environment to determine whether neurons age successfully or degenerate.

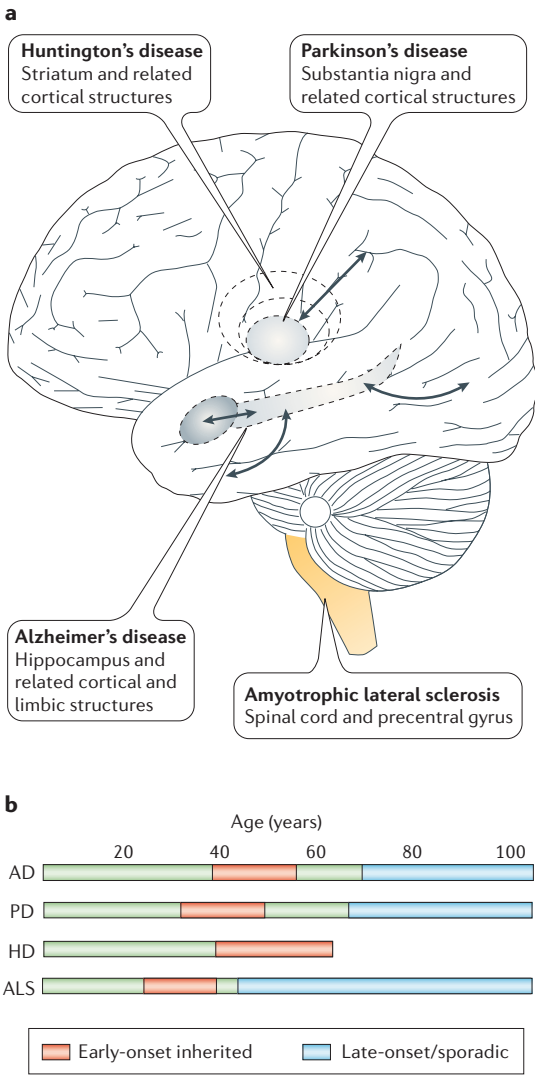


Figure 1 | **The who, where and when of neuronal death in age-related neurodegenerative disorders.** **a** | Different neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Huntington's disease and Alzheimer's disease (AD), affect different areas of the adult brain. Each starts in specific regions and later affects other regions. Even within these early affected regions, a selective injury of neuronal subclasses can be observed; for example, the dopaminergic neurons in PD, the motor neurons in ALS, or the cholinergic and glutmatergic neurons in AD. **b** | Ages of disease onset of early-onset inherited forms and late-onset sporadic forms of neurodegenerative disorders (see Further information for relevant URLs).

Ageing: setting the stage for a neurocatastrophe

Cells in the nervous system are affected by, and respond to, ageing much as cells in other organ systems do, and so cells in the brain experience increased amounts of oxidative stress[7,8], perturbed energy homeostasis[9], accumulation of damaged proteins[10,11] and lesions in their nucleic acids[12,13]. These changes during normal ageing are exacerbated in vulnerable populations of neurons in neurodegenerative disorders. So, whether an individual develops a neurodegenerative disorder during ageing is determined by genetic and environmental factors that counteract or facilitate fundamental molecular and cellular mechanisms of ageing (FIG. 2). Molecular genetic studies support the existence of evolutionarily conserved genes associated with successful neural ageing[14], as well as genes that cause or increase the risk of a neurodegenerative disorder[2–6]. Among the genes that are believed to have important roles in ageing are those that encode proteins involved in insulin signalling[15], DNA and protein methylation and acetylation[16], DNA repair[12] and lipid metabolism[17].

Molecular alterations that are qualitatively similar to those that occur in the nervous system during normal ageing are amplified in vulnerable neuronal populations by disease-related processes, which results in their dysfunction and death: several of these processes are illustrated in BOX 1. For example, during normal ageing there are progressive increases in the amounts of oxidatively modified DNA bases, proteins and lipids in the brain. Specific age-related modifications of proteins include carbonylation, nitration and covalent binding of the lipid peroxidation product 4-hydroxynonenal[18]. Such protein modifications are dramatically increased in vulnerable neurons in AD, PD, HD and ALS[2,5,19,20]. Similarly, the accumulation of Aβ in AD, α-synuclein in dopaminergic neurons in PD and Cu/Zn-SOD in motor neurons in ALS occur to a lesser extent during normal ageing[11,21]. Such protein aggregates might arise, in part, as a consequence of impaired proteasomal and/or autophagic removal of the (oxidatively) damaged proteins[10,22]. Alterations in numerous neurotransmitter and neurotrophic factor signalling pathways occur during normal ageing, and many such changes are amplified in neurodegenerative disease. Examples include depletion of dopamine in substantia nigra neurons in normal ageing and PD[23], and lower levels of brain-derived neurotrophic factor (BDNF) in ageing, AD and HD[2,24].

If the processes of ageing are central to all neurodegenerative disorders (FIG. 3), then it would be expected that an intervention that slows this process would also guard against neurodegenerative disorders. Studies of the effects of dietary restriction a manipulation that can retard ageing processes in rodents, monkeys and humans, indicate that this might be the case[25–28]. Low calorie diets and intermittent fasting retard the physiological manifestations of ageing and extend the average and maximum lifespan of rodents by up to 40%[25], and might also increase the lifespan of primates, including humans[27,28]. Age-related deficits in cognitive and motor function, and increases in oxidative stress and DNA damage, are lessened in animals maintained on dietary restriction compared with *ad libitum* diets[29]. As well as protecting neurons against dysfunction and degeneration in animal models relevant to AD[30], PD[31], HD[32] and stroke[33], dietary restriction enhances BDNF production and neurogenesis, which are processes that might, in part, counteract age-related dysfunction and degeneration of neuronal circuits[34].

Lipid peroxidation
An autocatalytic process in which free radicals attack double bonds in membrane lipids, resulting in structural damage to membranes and the liberation of toxic aldehydes such as 4-hydroxynonenal.

Autophagy
A process in which damaged organelles are degraded within membrane-bound organelles.

Dietary restriction
A decrease in the amount of food consumed over time (caloric restriction) and/or the frequency of meals (intermittent fasting).

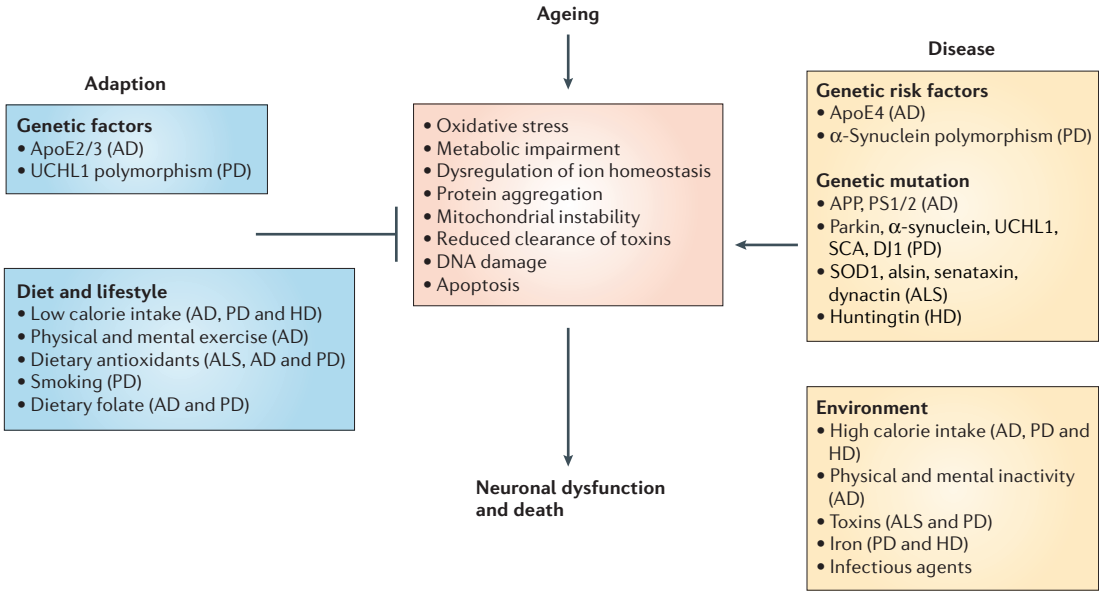


Figure 2 | **The nervous system can respond adaptively, or can succumb, to ageing.** In ageing and neurodegenerative diseases, neuronal death can be triggered by specific genetic mutations (for example, mutations in huntingtin, presenilins, α-synuclein and Cu/Zn-superoxide dismutase (SOD)) and/or environmental factors such as toxins or dietary components. Initiating factors promote cellular alterations, including increased oxyradical production, perturbed energy and calcium homeostasis, and activation of apoptotic cascades. However, each factor cooperates with age-related increases in oxidative stress, metabolic compromise, DNA instability and ion homeostasis dysregulation to disrupt neuronal integrity, thereby resulting in synaptic dysfunction and cell death. In addition, changes in glial cell homeostasis occur and contribute to inflammatory processes and white matter damage in neurodegenerative disorders. AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ApoE2/3, apolipoprotein E isoforms 2 and 3; APP, amyloid precursor protein; HD, Huntington's disease; PD, Parkinson's disease; PS1/2, presenilins 1 and 2; SCA, spinocerebellar ataxia; UCHL1, ubiquitin carboxy-terminal hydrolase 1.

Reactive oxygen species
(ROS). Highly reactive oxygen-based molecules with an unpaired electron in their outer orbital that are capable of damaging proteins, lipids and nucleic acids. Examples include hydrogen peroxide and hydroxyl radicals.

Hormesis
A process in which exposure of a cell or organism to a sublethal level of stress increases the resistance of that cell or organism to a subsequent higher and otherwise lethal level of the same or different stress.

Sirtuins
A family of histone deacetylases that have important roles in cellular stress responses and energy metabolism.

Mitochondrial uncoupling proteins
A family of proteins that reside in the mitochondrial inner membrane and promote a proton leak across the membrane, thereby decreasing oxidative phosphorylation and reactive oxygen species production.

One mechanism responsible for the anti-ageing effects of dietary restriction on the nervous system might be decreased production of reactive oxygen species (ROS) in mitochondria. Highly reactive superoxide anion radicals are produced during the metabolism of glucose. So, a reduction in glucose metabolism[35] leads to a decrease in superoxide anion radical concentrations, which, in turn, results in lower levels of hydrogen peroxide, hydroxyl radicals (formed by the reaction of hydrogen peroxide with Fe^{2+} or Cu^{+}) and peroxynitrite (formed by the reaction of superoxide with nitric oxide). Accordingly, there is a decrease in the cumulative damage to proteins, lipids and DNA[35]. Because ROS are involved in the dysfunction and death of neurons in neurodegenerative disorders, suppression of ROS production by dietary restriction might protect brain cells against age-related diseases. A second major mechanism by which dietary restriction might promote neural cell plasticity and survival is hormesis. Like vigorous exercise or cognitive stimulation, dietary restriction seems to impose a mild beneficial stress on neurons that 'conditions' them such that they are more resistant to ageing and disease[34,36,37]. At the molecular level, the cellular stress response involves upregulation of the expression of neurotrophic factors, heat-shock proteins, sirtuins and mitochondrial uncoupling proteins[34,38,39].

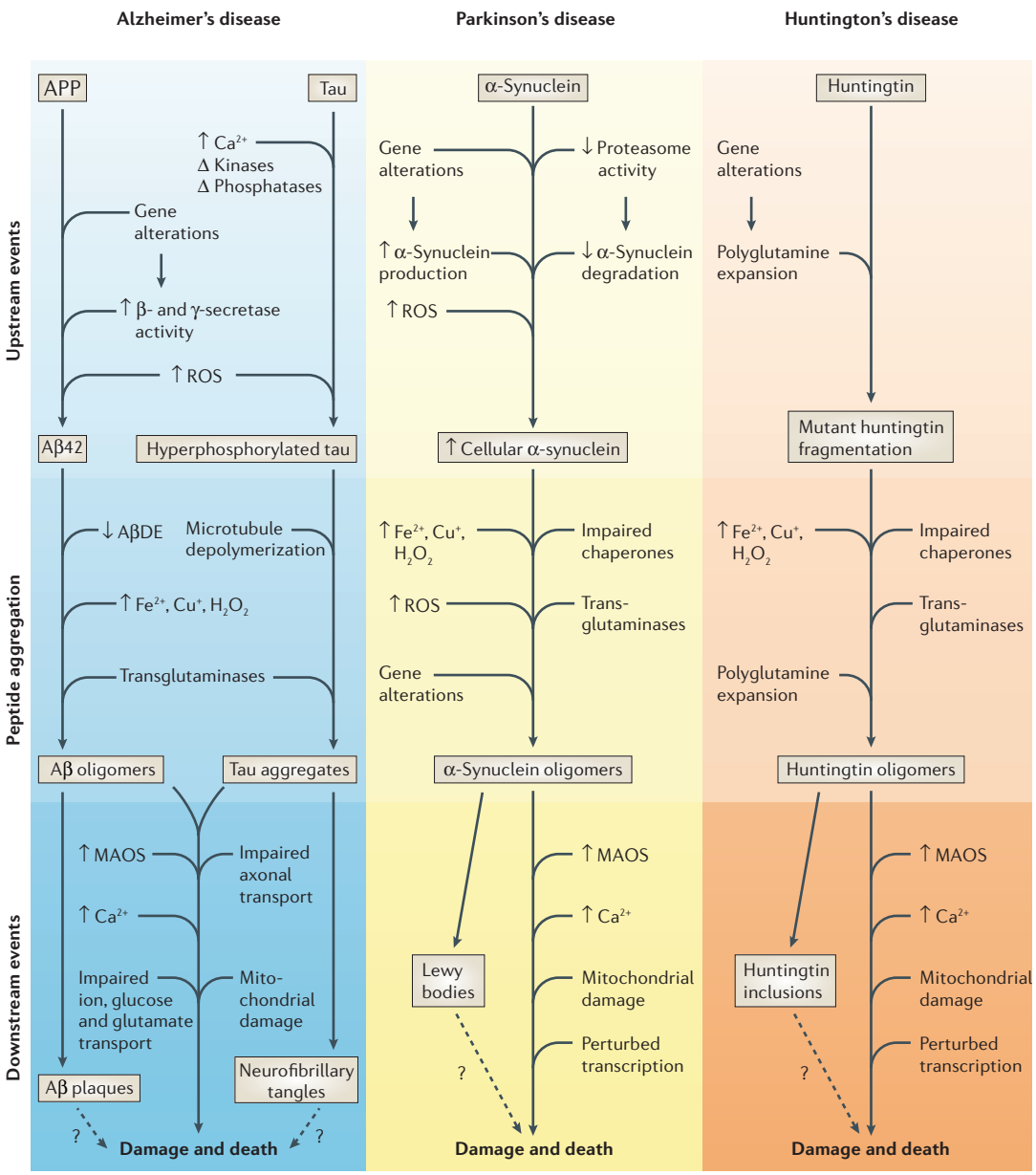
Selective neuronal vulnerability

Why do hippocampal and frontal lobe pyramidal neurons die in AD, whereas dentate gyrus granule neurons and cortical interneurons are spared? Why do dopaminergic neurons in the substantia nigra, medium spiny neurons in the striatum and lower motor neurons in the spinal cord succumb in PD, HD and ALS, respectively? Once the most vulnerable neurons are affected, what determines which neuronal populations degenerate later in the course of the disease (for example, upper motor neurons in ALS and cortical neurons in PD)? Unfortunately, the mechanism underlying SNV in any of these age-related neurodegenerative disorders is not known, and although many different genetic abnormalities have been identified that can cause a neurodegenerative disorder (FIG. 2), in no case is it known why the mutant gene causes SNV. Nevertheless, a rapidly growing literature provides many clues as to the molecular and cellular factors that determine whether a particular neuron succumbs to or resists an age-related disease. The physical and molecular characteristics of neurons, their functional properties and their location in neural circuits are all likely to influence their fate during ageing[40]. Vulnerable neurons are typically large with myelinated axons that extend relatively long distances, from one region of the nervous system to another or from the CNS to peripheral targets. This is true for the hippocampal and cortical pyramidal neurons, upper and lower motor neurons and striatal medium

Box 1 | **Mechanisms of abnormal protein accumulation in neurodegenerative disorders**

Differences among neuronal populations in the production and/or clearance of abnormal proteins might be determinants of age-related neuronal vulnerability in Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD). The pathogenic proteins are amyloid β-peptide (Aβ) and tau in AD, α-synuclein in PD and huntingtin in HD. Genetic and age-related factors that can increase the amounts of pathogenic proteins (upstream events) include: in AD, increased levels of Aβ42 that are caused by mutations in amyloid precursor protein or presenilins (for example, γ-secretase), by reactive oxygen species (ROS) and by reductions in Aβ-degrading enzymes (AβDE), such as neprilysin and insulin-degrading enzyme, increases in tau concentrations that are effected by ROS, phosphorylation and calcium; in PD, increased levels of α-synuclein caused by triplication of its gene or mutations in parkin, DJ1, ubiquitin carboxy-terminal hydrolase 1 (UCHL1), phosphatase and tensin homologue-induced kinase 1 (PINK1) or leucine-rich repeat kinase 2 (LRKK2), as well as proteasome impairment and ROS; in HD, polyglutamine expansions in huntingtin (HTT).

The protein aggregation process itself is enhanced by: increasing protein concentration; the action of transglutaminases; protein chaperone insufficiency; mutations in α-synuclein (PD) and polyglutamine expansions in huntingtin (HD); and/or post-translational modifications, such as oxidations induced by, for example, hydrogen peroxide (H_2O_2), Fe^{2+} and Cu^{+}, and phosphorylation. Although the proteins involved can differ, there is considerable overlap in the mechanisms by which they damage and kill neurons. Oligomers of Aβ, α-synuclein and HTT might damage and kill neurons by inducing membrane-associated oxidative stress (MAOS), thereby impairing mitochondrial function and disrupting calcium homeostasis (see REFS 2–11). Δ, change.



Trans-entorhinal region
An area of the brain — located between association cortices and the hippocampus — that is important in the integration of information and learning and memory processes.

spiny neurons that are affected in AD, ALS and HD, respectively[2–6]. The dopaminergic neurons in the substantia nigra that succumb to PD, although smaller than the aforementioned neurons, are also projection neurons with relatively long axons[41]. There are several reasons why large projection neurons might be particularly vulnerable to ageing, including a high energy requirement, reliance on axonal transport (anterograde and retrograde) for sustained function and trophic support, and a large cell-surface area that increases exposure of the cells to toxic environmental conditions. The cytoskeleton of large neurons might be particularly prone to dysfunction, as suggested by the aggregation and displacement of axonal neurofilaments and the microtubule-associated protein tau, which is observed in motor neurons in ALS[5] and pyramidal neurons in AD[42].

Degeneration is often limited to subpopulations of neurons with a particular neurotransmitter phenotype. For example, ALS strikes cholinergic motor neurons, and GABA (γ-aminobutyric acid)-containing striatal neurons and dopaminergic neurons are most vulnerable in HD and PD, respectively. However, if the cumulative neurodegenerative topography among disorders is considered, it is clear that ageing endangers neurons of all the main neurotransmitter phenotypes (TABLE 1). Among the different neurotransmitters, glutamate might have an active and essential role in neuronal damage and death in all neurodegenerative disorders (see section on excitotoxicity, below). By contrast, in PD, dopamine itself might contribute to the demise of the neurons that produce it by inducing oxidative stress in presynaptic terminals[3]. The signalling pathways of various neuropeptides, including corticotropin-releasing hormone[43], vasopressin and oxytocin[44], might also be disrupted, particularly in later stages of neurodegenerative disorders.

Dysfunction and death of neurons adversely affects both the pre- and post-synaptic neurons with which they communicate. Therefore, patterns of neuronal degeneration are often domino-like. In the case of AD, neurons in the entorhinal cortex that provide input to the hippocampus degenerate early in the course of the disease, followed by hippocampal neurons and then cortical neurons that communicate with hippocampal neurons[45]. Although substantia nigra dopaminergic neurons have been the primary focus of PD research, they might not be the first affected. Instead, neurons in the dorsal motor nuclei of the medulla oblongata, and the raphe nucleus and locus coeruleus of the brainstem, could succumb first[46]. Substantia nigra damage is followed by degeneration of neurons in the trans-entorhinal region, motor and sensory cortex and prefrontal cortex. The degeneration of motor neurons in ALS often follows a progression from lower to upper spinal cord, followed by loss of upper motor neurons in the cerebral cortex, although there is considerable variability among patients[47]. It is increasingly appreciated that synapses are the most vulnerable regions of neurons (FIG. 3). Differences among synapse structure, metabolism and signalling mechanisms might, therefore, be determinants of neuronal vulnerability. Finally, changes that occur in the cellular milieu in which neurons reside, including phenotypes of astrocytes, oligodendrocytes, microglia and vascular cells, probably influence the fate of neurons during ageing.

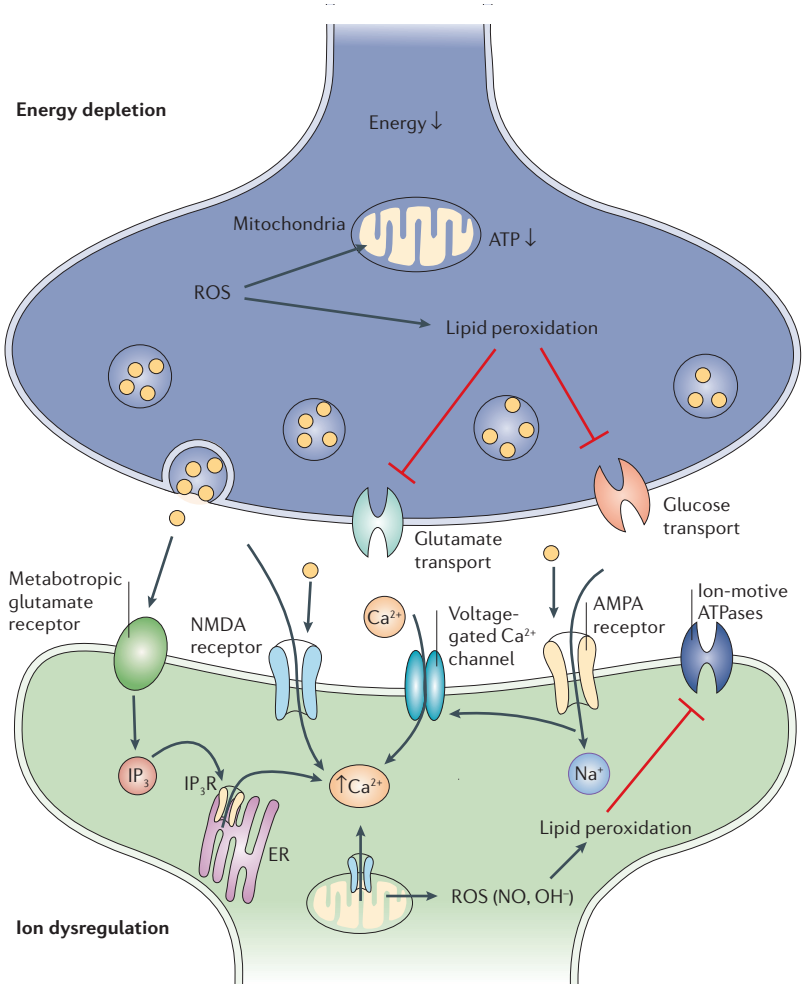


Figure 3 | **The sensitive synapse.** Age- and disease-related stressors promote the activation of biochemical cascades that result in ion dysregulation and energy depletion in synaptic terminals and neurites. One example is the stimulation of glutamate receptors that, under conditions of reduced energy availability or increased oxidative stress, leads to Ca^{2+} influx into postsynaptic regions of dendrites. This, in turn, can trigger apoptosis (FIG. 4). In addition, among other processes, reactive oxygen species (ROS) can induce lipid peroxidation, which results in the dysfunction of ion-motive ATPases, as well as glucose and glutamate transporters. This leads to further ion dysregulation, energy depletion and excitotoxicity. Perturbations in energy metabolism and ion homeostasis are likely to occur in both pre- and post-synaptic compartments during ageing and in neurodegenerative disorders. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; ER, endoplasmic reticulum; IP_3, inositol-1,4,5-trisphosphate; IP_3R, IP_3 receptor; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide.

Pathways to neuronal death

Apoptosis. The fact that mutations in specific genes can cause one neurodegenerative disorder, but not others, is evidence for multiple mechanisms of neuronal death. However, the development and analyses of animal and cell culture models of neurodegenerative disorders, based on the expression of disease-causing mutant human genes, suggest a convergence of disease-specific

Table 1 | **Phenotypes of neurons vulnerable to age-related neurodegenerative disorders**

Disorder	Affected regions	Phenotypes	Refs
Alzheimer's disease	Entorhinal cortex, hippocampus, frontal cortex, basal forebrain, parietal lobe, occipital lobe, amygdala, locus coeruleus* and raphe nucleus*	Projection neurons; multiple transmitters (for example, glutamate, acetylcholine, noradrenaline and serotonin); and low CBPs	2
Parkinson's disease	Substantia nigra, frontal cortex, locus coeruleus* and raphe nucleus*	Projection neurons; primarily dopaminergic neurons; and low CBPs	3
Huntington's disease	Striatum, frontal cortex and locus coeruleus*	Projection neurons; and GABA-containing and glutamatergic neurons	5
Amyotrophic lateral sclerosis	Motor cortex and spinal cord	Projection neurons; cholinergic and glutamatergic neurons; and low CBPs	6
Stroke	Most CNS regions	Large neurons; and low CBPs	223

*These neuronal populations are typically affected late in the disease process. CBPs, calcium-binding proteins; GABA, γ-aminobutyric acid.

upstream factors on well-known cell death cascades. The most widely studied type of programmed cell death in the nervous system is apoptosis, a process that is regulated by specific cysteine proteases called caspases[48] (FIG. 4). Many different triggers of neuronal apoptosis have been documented, including oxidative stress, overactivation of glutamate receptors, trophic factor insufficiency, DNA damage and accumulation of damaged proteins[48–51]. In this section, we briefly review key subcellular molecular cascades in apoptosis, and describe evidence supporting the involvement of such cascades in age-related neuronal death.

Two major groups of proteins in the BCL2 (B-cell leukaemia/lymphoma 2) family have pivotal roles in most types of apoptosis: pro-apoptotic proteins such as BCL2-associated protein X (BAX) and BCL-associated death promoter (BAD); and anti-apoptotic proteins such as BCL2 and BCL-X_L[52]. These proteins control the fate of cells by interacting with the membranes of mitochondria and the endoplasmic reticulum. BAX and BAD increase mitochondrial membrane permeability and the release of apoptotic factors, whereas BCL2 and BCL-X_L stabilize the membranes[48,53]. Proteases such as caspases and calpains trigger apoptosis by degrading various structural proteins[54,55]. Both caspases and calpains have been implicated in the death of neurons that occurs in AD[48,56], PD[57,58], HD[59,60] and ALS[60]. Mitochondrial changes that occur in most instances of neuronal death include Ca^{2+} uptake, formation of permeability transition pores and release of cytochrome *c* and apoptosis inducing factor (AIF)[61]. The endoplasmic reticulum also releases Ca^{2+}, and factors that modulate the expression of pro- and anti-apoptotic genes, and so is also actively involved in many cases of neuronal death[62,63]. Cytochrome *c*-mediated Ca^{2+} release from the endoplasmic reticulum[64] suggests that the mitochondria and endoplasmic reticulum interact during apoptosis.

Oxidative stress can trigger apoptosis by several different mechanisms. ROS produced in the mitochondria promote Ca^{2+} uptake and increased membrane permeability, which results in the release of cytochrome *c* and initiates apoptosis[61]. Hydroxyl radicals can directly attack DNA bases, and if the damage is extensive, a cell death pathway is activated that involves ATM (ataxia-telangiectasia mutated) kinase, p53 and BAX translocation to the mitochondria[65]. Membrane-associated oxidative stress can trigger apoptosis by several mechanisms. For example, lipid peroxidation generates the aldehyde 4-hydroxynonenal, which can induce apoptosis by perturbing ion homeostasis and inducing mitochondrial permeability transition; this mechanism might mediate neuronal death resulting from neurotrophic factor deprivation, AD or ALS[20,66,67]. Oxidative stress also activates sphingomyelinases, which, in turn, leads to the release of ceramides from membrane sphingomyelin; ceramides can trigger apoptosis by activating kinases and by interacting with mitochondrial membranes[68]. Increased ceramide production has been linked to neuronal death in AD, HIV dementia and ALS[69–71].

After the period of developmental cell death, in which large numbers of brain cells undergo apoptosis, the rate of apoptosis is relatively low during adult life[72]. However, the rate of apoptosis might accelerate during later life, and the involvement of apoptotic cascades in age-related neuronal death is suggested by studies of normal ageing, and of neurodegenerative disorders in humans and animal models. The activities of the pro-apoptotic proteins caspase 3 and poly(ADP-ribose) polymerase (PARP) are increased in brain cells during normal ageing, but might be counteracted by the upregulation of anti-apoptotic proteins such as X-linked inhibitor of apoptosis protein (XIAP) and nerve growth factor (NGF); dietary restriction can suppress the age-related increase in caspase 3 and PARP, whereas it enhances the expression of anti-apoptotic proteins[73]. Old neurons might die during ageing and in neurodegenerative disorders, and neurons arising from stem cells might also succumb. For example, hippocampal neurogenesis is reduced during ageing, apparently as the result of reduced stem cell proliferation and increased apoptosis of newly generated neurons[74,75]. Neurogenesis might be impaired in AD, possibly as a result of increased death of newly generated neurons[76], although evidence for a compensatory increase in neurogenesis in AD has also been reported[77]. Whether they are mature or young, neurons seem to become more vulnerable to death with ageing, and the cell death cascades of ageing are exacerbated in age-related neurodegenerative disorders.

Caspases
A family of cysteine proteases that cleave proteins at specific aspartate residues and have a key role in inflammation and mammalian apoptosis.

BCL2
A protein that promotes the survival of neurons by stabilizing mitochondrial membranes and decreasing oxidative stress.

Calpains
Cysteine proteases activated by calcium that cleave various substrates, including cytoskeletal proteins.

Permeability transition pores
Pores in the mitochondrial membranes that are formed by proteins in response to signals that trigger apoptosis.

Ceramides
Membrane lipids that are incorporated into sphingomyelin and are released in response to the activation of sphingomyelinases.

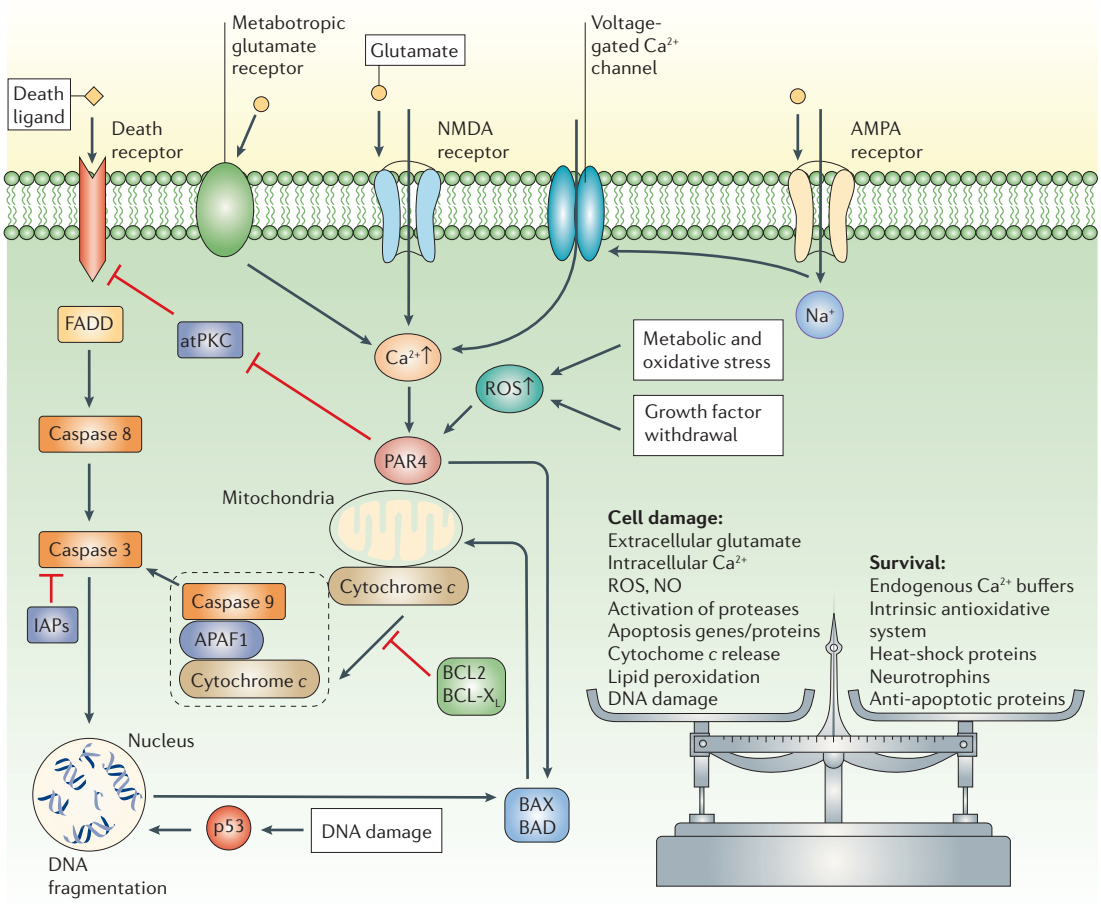


Figure 4 | **Once triggered, the death of neurons is programmed.** Excitotoxic (excessive glutamate) and other death signals activate intracellular cascades involving increased levels of reactive oxygen species (ROS) and Ca^{2+}, production of prostate apoptosis response 4 (PAR4) and p53, and translocation of pro-apoptotic B-cell leukaemia/lymphoma 2 (BCL2) family members (BCL2-associated protein X (BAX) and BCL-associated death promoter (BAD)) to the mitochondrial membrane. These events are followed by increased mitochondrial dysregulation and release of cytochrome *c* into the cytosol. Cytochrome *c* forms a complex with apoptotic protease-activating factor 1 (APAF1) and caspase 9. Activated caspase 9 cleaves and activates caspase 3 which, in turn, cleaves protein substrates that effect changes in the plasma membrane, cytoskeleton and nucleus. Certain caspases (for example, caspase 8) can also be directly activated through death ligands and can act independently of mitochondrial changes. The process of apoptosis can be inhibited at different stages through anti-apoptotic mechanisms, such as inhibitor of apoptosis proteins (IAPs) or BCL2 and BCL-X_L. In general, cell fate is decided by a balance between survival factors and potentially harmful or destructive factors. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; atPKC, atypical protein kinase C; FADD, Fas-associated death domain protein; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide.

Excitotoxicity. Glutamate is the main excitatory neurotransmitter in the CNS, with most neurons receiving synaptic inputs from glutamatergic neurons. Glutamate therefore has essential roles in the synaptic transmission and plasticity that underlie all behaviours, including learning and memory, emotions, and sensory and motor activities. These actions of glutamate are mediated by cell-surface receptors that flux Na^+ and Ca^{2+}, of which AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and NMDA (*N*-methyl-D-aspartate) receptors are the most abundant. Excessive activation of glutamate receptors causes sustained Ca^{2+} influx and ROS production, which leads to excitotoxicity and can result in damage to dendrites, and even cell death[78]. Molecular and cellular changes that occur during ageing are known to render neurons vulnerable to excitotoxicity. For example, impairing the function of ion-motive ATPases and glutamate and glucose transporters leads to oxidative and metabolic stress, and impaired cellular energy metabolism increases the susceptibility of neurons to excitotoxicity. Disease-specific abnormalities might compound the adverse effects of glutamate on neurons. Indeed, Aβ, dopamine, mutant huntingtin and mutant Cu/Zn-SOD have each been shown to sensitize neurons to excitotoxic death. Other studies of mouse models of AD, PD, HD and ALS support a role for excitotoxicity in these disorders[2–6]. Characteristics of neurons that make them particularly prone to excitotoxicity include high numbers of NMDA and AMPA receptors, and low levels of protective calcium-binding proteins[78].

Ion-motive ATPases
Energy-dependent ion pumps in membranes that are essential for the restoration and maintenance of the Na^+ and Ca^{2+} gradients.

Box 2 | **Environmental neurotoxins and age-related neurodegenerative disorders**

An incident in which several drug users in California, USA, rapidly developed a Parkinson's disease (PD)-like syndrome led to the discovery of the dopaminergic neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)[82]. The effects of the excitotoxic neurotoxin domoic acid came to light in 1987 when more than 100 individuals who had recently eaten shellfish at restaurants in Canada became ill, with 25% of them suffering short-term memory loss that was clinically similar to that seen in patients with Alzheimer's disease (AD). Subsequent investigations established that the shellfish contained unusually high amounts of domoic acid, which was produced by the algal food source of the shellfish[220]. In another case, studies of several children in China who rapidly developed symptoms similar to those of Huntington's disease (HD) led to the discovery of 3-nitropropionic acid, a potent inhibitor of mitochondrial complex II (REF. 84). An amyotrophic lateral sclerosis (ALS)-like syndrome was discovered in native populations in islands of Guam that, based on epidemiological and genetic studies, appears to have had an environmental cause. Evidence suggests that the cycad seed, a staple of the natives' diet, is a source of the putative toxin known as β-methylamino-L-alanine (BMAA)[81]. In rodents and monkeys, MPTP, domoic acid, 3-nitropropionic acid and BMAA can destroy the specific populations of neurons that die in PD, AD, HD and ALS. Moreover, the vulnerability of neurons to excitotoxins and mitochondrial toxins described above increases with advancing age, suggesting that they can act on neurodegenerative pathways similar to those involved in age-related neurodegenerative disorders.

Neurotoxin-based models have provided important evidence supporting the involvement of mitochondrial compromise and excitotoxicity in neurodegenerative disorders. This information has led to the search for novel environmental toxins that could determine whether individuals develop a neurodegenerative disorder as they age. Several such toxins have been identified, but their contributions to disease are not yet clear. For example, the widely used pesticide rotenone and the herbicide paraquat, which epidemiological data suggest are involved in some cases of PD, can induce PD-like pathology in rodents[222]. It is probable that multiple genetic and environmental factors determine whether exposure to a neurotoxin results in disease. Indeed, when rats or mice are maintained on dietary restriction regimens, they exhibit increased resistance to several different neurotoxins, including kainic acid, MPTP and 3-nitropropionic acid[116,117], which is consistent with epidemiological findings suggesting that high calorie diets are associated with an increased risk of PD

The discovery and study of environmental neurotoxins, and the involvement of an excitotoxic mechanism in their cell death-inducing actions, have made valuable contributions to neurodegenerative disorder research (BOX 2). Several such toxins bind and activate glutamate receptors directly. Kainic acid and domoic acid, which are potent agonists of the kainic acid subtype of glutamate receptor, can induce epileptic seizures that result in damage to hippocampal pyramidal neurons and cognitive deficits that are reminiscent of AD[79,80]. β-Methylamino-L-alanine — an excitotoxin that can kill spinal cord motor neurons — has been implicated in the pathogenesis of some cases of ALS[81]. Other disease-relevant neurotoxins render neurons vulnerable to excitotoxicity by impairing mitochondrial function. For example, exposure of humans, monkeys and/or rodents to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) or rotenone causes PD-like pathology and symptoms, whereas exposure to 3-nitropropionic acid can cause HD-like damage to striatal neurons[82–84]. The MPTP metabolite MPP^+ (1-methyl-4-phenyl-pyridinium) and rotenone are potent inhibitors of mitochondrial complex I, whereas 3-nitropropionic acid inhibits succinate dehydrogenase.

The fact that such toxins are capable of causing AD-, PD-, HD- and ALS-like syndromes in animals, together with the reports of the effects of exposure to high levels of these toxins in humans[80–84], suggests that they might act on mechanisms that are operative in these diseases, and that neurotoxins might have a role in some cases of age-related neurodegeneration.

Calcium dysregulation. The concentration of Ca^{2+} in the cytosol is tightly regulated in all cells: under resting conditions the Ca^{2+} concentration is typically in the range 75–200 nM, and transiently increases to 1–10 μM in response to membrane depolarization and the opening of voltage-dependent Ca^{2+} and NMDA receptor channels[85]. In addition, Ca^{2+} is released from inositol-1,4,5-trisphosphate- and ryanodine-sensitive stores in response to extracellular signals or increased cytosolic Ca^{2+} concentrations (Ca^{2+}-induced Ca^{2+} release). Mitochondria are also capable of sequestering Ca^{2+} and then releasing these ions into the cytosol. Ca^{2+} is removed from the cytosol by plasma membrane and endoplasmic reticulum Ca^{2+} ATPases, and by sequestration by Ca^{2+}-binding proteins. Perturbations of neuronal Ca^{2+} homeostasis have been documented during normal ageing, including increased Ca^{2+}-dependent afterhyperpolarizations in hippocampal CA1 neurons and alterations in the Ca^{2+}-handling properties of mitochondria and the endoplasmic reticulum[86]. It is now well established that sustained elevations of intracellular Ca^{2+} concentrations can cause neuritic degeneration and cell death by activating proteases and inducing ROS production. Studies of mutations in the genes that cause HD and familial cases of AD, PD and ALS suggest that perturbed neuronal Ca^{2+} homeostasis is a consequence of those mutations that contribute to the degeneration of neurons. For example, mutations in presenilin 1 and APP promote neuronal Ca^{2+} overload and cell death under conditions of oxidative and metabolic stress[87,88], and mutations in α-synuclein and huntingtin have been associated with perturbed Ca^{2+} regulation in PD and HD, respectively[89,90]. Spinal cord motor neurons might die in ALS as the result of overactivation of glutamate receptors or autoimmune attack on voltage-dependent Ca^{2+} channels[91,92].

Afterhyperpolarization
The membrane hyperpolarization that follows the occurrence of an action potential.

Alterations in cellular Ca^{2+} homeostasis might have a role in SNV during ageing. In this regard, studies of the hippocampus have been particularly informative. CA1 and CA3 pyramidal neurons are vulnerable in AD, severe epileptic seizures and ischaemia, whereas dentate granule neurons are relatively unaffected. This differential neuronal vulnerability might be explained, in part, by the fact that dentate granule neurons express high concentrations of the neuroprotective Ca^{2+}-binding protein calbindin, whereas pyramidal neurons contain little or no calbindin[93,94]. Age-related reductions in calbindin expression have been implicated in the SNV of basal forebrain cholinergic neurons[95] and entorhinal cortex layer II neurons[96] in AD, dopaminergic neurons in PD and striatal neurons in HD[97]. Spinal cord motor neurons with low levels of calbindin and parvalbumin are vulnerable in ALS, whereas cranial nerve motor neurons, which express high levels of these calcium-binding proteins, are relatively resistant[98]. Neurons expressing high levels of NMDA receptors (for example, CA1 hippocampal neurons in AD)[99] and/or Ca^{2+}-permeable AMPA receptors (for example, spinal cord motor neurons in ALS)[100] might be prone to age-related degeneration.

Mitochondrial perturbations. Decreases in mitochondrial function have often been associated with ageing in general, and ageing of the nervous system in particular[101]. Positron emission tomography imaging of radiolabelled glucose uptake in the brains of normal human participants aged 20–67 years indicated widespread age-dependent reductions in glucose utilization in most brain regions, with the exception of the cerebellum and occipital cortex[102]. Similar analyses of patients with AD, PD and HD reveal dramatic reductions in glucose utilization in the brain regions most severely affected; these abnormalities can be detected before the onset of clinical disease[103–105]. Measurements of the activities of mitochondrial enzyme activities in brain tissue samples revealed significant decreases in the activities of the pyruvate dehydrogenase complex, isocitrate dehydrogenase and the α-ketoglutarate dehydrogenase complex in patients with AD compared with control subjects[106]. Mitochondrial complex I activity declines in the brain during normal ageing, but much more so in PD[107]. Patients with HD lose weight progressively, despite maintaining a high caloric intake, an abnormality that might result from impaired mitochondrial function[108]. Deficits in mitochondrial function might also occur early in the course of ALS, perhaps first in the axons and presynaptic terminals of the motor neurons[109].

Studies of normal ageing and animal models of neurodegenerative disorders have provided further insights into the nature of perturbed neuronal energy metabolism that might predispose neurons to SNV. Analyses of mitochondria isolated from different brain regions of young, middle-aged and old rats revealed that mitochondria from the cerebral cortex of old rats show enhanced ROS production and mitochondrial swelling in response to increasing Ca^{2+} loads compared with cortical mitochondria from younger rats[110]. By contrast, the sensitivity of cerebellar mitochondria to Ca^{2+} was unaffected by ageing. The capacity of mitochondria to respond appropriately to excitation might be impaired during ageing, as suggested by reduced buffering of voltage-gated Ca^{2+} influx in basal forebrain neurons from aged rats[111]. Moreover, ageing increases the vulnerability of mitochondria to toxins such as 3-nitropropionic acid[112]. In addition to alterations in mitochondria, neurons also show impaired glucose uptake during normal ageing[113], further compromising their ability to maintain ion homeostasis and other energy-dependent cellular processes. Many of the age-related deficits in energy metabolism might be a consequence of oxidative stress. As evidence, neurons in mice deficient in glutathione peroxidase are more vulnerable to being killed by 3-nitropropionic acid and MPTP[114]. Similarly, mitochondrial manganese superoxide dismutase protects neurons against oxidative damage[115]. Finally, caloric restriction can preserve mitochondrial function during ageing, apparently by reducing ROS production[38], and can protect neurons from being killed by mitochondrial toxins[116,117].

Several abnormalities in mitochondrial function and energy homeostasis have been observed in mice expressing mutant forms of APP and/or presenilin 1 that cause AD in humans. APP-mutant mice show reduced cerebral glucose utilization and cerebral blood flow, which correlates with Aβ accumulation[118]. Aβ has been shown to impair mitochondrial function, and studies of APP-mutant mice suggest a key role for an Aβ-binding alcohol dehydrogenase in this pathogenic action[119]. Mitochondria in neurons of mutant presenilin 1-knockin mice show increased sensitivity to toxins[120] and cellular Ca^{2+} overload[121]. Huntingtin-mutant mice also manifest alterations in mitochondrial function and energy metabolism. For example, Panov *et al.*[122] found that mitochondria from huntingtin-mutant mice maintain an abnormally low resting membrane potential and are hypersensitive to Ca^{2+}. Mutant huntingtin might also perturb energy metabolism indirectly by impairing the transport of mitochondria along axons[123]. ALS (Cu/Zn-SOD mutant) mice exhibit impaired mitochondrial function in spinal cord neurons[109], and treatment of the mice with creatine, which enhances cellular energy metabolism, suppresses the neurodegenerative process and improves survival of these mice[124]. Administration of agents that enhance cellular energy metabolism (for example, creatine, coenzyme Q10 and nicotinamide) delays disease onset and progression in mouse models of neurodegenerative disorders, which suggests a key role for cellular energy deficits in the disease process[125]. Collectively, the available data suggest that the ageing process is associated with impaired mitochondrial function and energy metabolism in neurons, and that environmental and genetic factors can exacerbate or protect against these adverse effects of ageing.

Accumulation of damaged molecules

One of the most widely documented and obvious alterations that occur in neurons during ageing is the accumulation of damaged molecules within the cells. A conspicuous example is lipofuscin, an autofluorescent material that consists of oxidatively damaged proteins

Glutathione peroxidase
An antioxidant enzyme that converts hydrogen peroxide to water.

Mitochondrial manganese superoxide dismutase
An antioxidant enzyme located in mitochondria that converts superoxide anion radicals to hydrogen peroxide.

and lipids that could accumulate as a result of impaired mechanisms for their removal[10,126,127]. In addition, ageing is associated with increased amounts of damaged DNA in neurons, which could result from impaired DNA repair systems[13]. Mutations in DNA repair proteins can cause premature ageing syndromes with neurodegenerative phenotypes[12], which is consistent with a role for impairment of these systems in the normal ageing of the nervous system.

A major problem encountered by neurons during ageing that is strongly linked to neurodegenerative disorders is the accumulation of damaged proteins that form insoluble aggregates that accumulate in and/or outside of the cells (BOX 1). Damaged proteins are removed by enzymatic degradation by cytosolic proteases, lysosomes and the proteasome, and there is evidence that these three mechanisms are altered in neurons during ageing[128–130]. In rats, proteasome activity decreases with advancing age in the cerebral cortex, hippocampus and spinal cord, but not in the cerebellum or brainstem[131]. Analyses of brain tissue samples suggest a much more severe malfunction of the proteasomal system in AD[132] and PD[133]. Several of the adverse consequences of ageing on neuronal function and survival can be mimicked by pharmacological inhibition of proteasomes[134] or lysosomes[135]. In addition, increasing evidence suggests that impaired autophagy is important in neuronal dysfunction and death in ageing and age-related disease[136]. It has been shown that autophagy disrupted during normal ageing can be restored by dietary restriction, which is consistent with a possible role for impaired removal of damaged organelles in neuropathologies of ageing[137].

Four major neuronal proteins that are prone to aggregation and contribute to neuronal dysfunction and death in neurodegenerative disorders are Aβ, tau, α-synuclein and huntingtin. Variations in the amino acid sequence of Aβ have a serious effect on its self-aggregating properties; for example, sequence differences among species are associated with either the presence (for example, in humans and dogs) or absence (for example, in rats and mice) of Aβ deposits in the brains of old animals, as well as with the propensity of the peptides to self aggregate[138]. In addition, subtle variations in peptide structure influence the capacity of Aβ to recruit soluble Aβ into fibrillar aggregates[139]. Aβ can be degraded by several enzymes, including neprilysin, insulin-degrading enzyme and the proteasome[130,140]. Impairments of one or more of these protein degradation systems by age-related increases in oxidative stress and protein damage might contribute to the formation of intracellular and extracellular Aβ aggregates in ageing and AD. Oxidative processes involving hydrogen peroxide, Fe^{2+} and Cu^{+} might promote the aggregation of Aβ and toxic effects on neurons[2].

Tau forms fibrillar aggregates within neurons (neurofibrillary tangles) during normal ageing and more so in AD, frontotemporal lobe dementia and related neurodegenerative disorders[141]. Different isoforms of tau are produced by neurons, and studies of mutations that cause tangle disorders, such as frontotemporal lobe dementia associated with Parkinsonism linked to chromosome 17 (FTDP-17), suggest that the ratio of three-repeat isoforms to four-repeat isoforms is crucial in the aggregation of tau to form neurofibrillary tangles[141]. Age-related alterations in tau kinases and phosphatases might result in the accumulation of aggregation-prone hyperphosphorylated forms of tau[142]. In addition, oxidative stress and impaired protein clearance mechanisms probably contribute to the accumulation of tau[142,143]. Tau normally has a key role in neuronal plasticity and axonal transport through its contribution to the regulation of the polymerization of microtubules. Hyperphosphorylation and aggregation of tau therefore disrupts microtubule functions, which might be important in the death of neurons in tauopathies and, to a lesser extent, in neuronal degeneration associated with normal ageing.

Cytoplasmic and intranuclear inclusions containing α-synuclein are prominent features of PD and might also occur in normal ageing. The identification of genetic aberrancies responsible for early-onset inherited forms of PD, and the elucidation of their metabolism and normal functions, has resulted in strong evidence for impaired proteolytic clearance of α-synuclein as a fundamental abnormality that occurs in dopaminergic neurons in PD[3,144]. Mutations in α-synuclein, parkin and ubiquitin carboxy-terminal hydrolase 1 result in reduced degradation of α-synuclein. Moreover, a triplication of the α-synuclein gene is sufficient to cause PD, further supporting an impaired ability of dopaminergic neurons to degrade α-synuclein during ageing[145]. Although the mechanism (or mechanisms) by which impaired clearance of α-synuclein promotes neuronal degeneration is unknown, emerging evidence suggests the involvement of perturbed dopamine storage and release from presynaptic terminals[146].

Polyglutamine expansions in the huntingtin protein cause HD, and these pathogenic proteins self-aggregate and are neurotoxic[147]. Although a genetic cause underlies HD, those affected typically develop symptoms after the age of 50 years, which suggests that changes that occur during ageing might facilitate the aggregation and neurotoxicity of mutant huntingtin. Indeed, two age-related processes — oxidative stress and perturbations in protein chaperones — can promote aggregation and cytotoxicity of mutant huntingtin[148,149]. Moreover, when huntingtin-mutant mice are maintained on dietary restriction the formation of intraneuronal huntingtin inclusions and the degeneration of striatal and cortical neurons is retarded and lifespan is extended[32]. Dietary restriction is known to reduce oxidative stress and increase the production of protein chaperones, suggesting mechanisms by which dietary restriction might counteract pathogenic processes in HD. Protein chaperones such as heat-shock protein 70 (HSP70) and glucose-regulated protein 78 (GRP78) can protect neurons against death in cell culture and animal models of neurodegenerative disorders[150]. Abnormalities in protein chaperone mechanisms have been documented in studies of several neurodegenerative disorders, in addition to HD, AD, PD and ALS[151–153]. In the case of ALS, an impaired ability of motor neurons to upregulate HSP70 in response to stress might have a role in their selective vulnerability[154].

Lysosome
A membrane-bound organelle with a low pH that contains high concentrations of enzymes that degrade proteins.

Frontotemporal dementia
A neurodegenerative disorder resulting from the degeneration of neurons in the frontal lobe.

Repeat isoform
An isoform of the microtubule-associated protein tau that contains either three or four microtubule-binding domains.

Neurotrophic factors

Cells of the nervous system, as well as peripheral targets such as muscle cells, produce neurotrophic factors that promote neuronal survival, neurite outgrowth and synaptic plasticity. Here, we focus on neurotrophic factor signalling pathways that might be important in determining whether neurons resist or succumb to a neurodegenerative disorder. Neuronal populations vulnerable to age-related disease are believed to be protected by one or more neurotrophic factors. For example: hippocampal pyramidal neurons (affected in AD) respond to BDNF, NGF, insulin-like growth factors (IGF) 1 and 2 and basic fibroblast growth factor (bFGF); basal forebrain cholinergic neurons (AD) respond to NGF and bFGF; substantia nigra dopaminergic neurons (PD) respond to glial cell line-derived neurotrophic factor (GDNF) and BDNF; striatal medium spiny neurons (HD) respond to BDNF and NGF; and motor neurons (ALS) respond to IGF1 and BDNF[155–160]. Declining production of a neurotrophic factor (or factors) or impaired signal transduction during ageing could have a role in SNV. Age-related decreases in the expression of BDNF in the hippocampus have been reported[161] and might contribute to age-related cognitive impairment[162]. The responsiveness of BDNF signalling to environmental stimuli might be compromised during ageing. For example, the abilities of cognitive challenges[163], exercise[164] and brain injury[165] to upregulate BDNF signalling are impaired in aged rats. Although levels of receptors for IGF1 or IGF2 were not different in aged memory-impaired rats compared with unimpaired rats[166], the ability of IGF1 to stimulate protein synthesis in the cerebral cortex was diminished[167] and deafferentation-induced IGF1 expression was attenuated[168] in old rats. Moreover, infusion of IGF1 into the brain can restore cognitive function in old rats[169]. GDNF infusion in aged monkeys led to increases in stimulus-evoked dopamine release and improvements in age-related decreases in motor function[170]. Considerable evidence suggests a role for deficits in NGF signalling in age-related atrophy of basal forebrain cholinergic neurons, and age-dependent cognitive deficits in rats can be reversed by transplantation of NGF-secreting fibroblasts[171]. In addition to direct actions on neurons themselves, neurotrophic factors might affect other cell types, including glia and vascular cells[172].

Data from patients and animal models suggest that compromised neurotrophic factor signalling is involved in age-related neurodegeneration. BDNF signalling might be compromised early in the course of AD[173], whereas the role of impaired NGF signalling in AD appears to be more complex[174]. Studies of patients with HD and huntingtin-mutant mice have revealed reduced levels of BDNF in the striatum and cortex[175], and some manipulations that suppress the disease process in HD mouse models (dietary restriction and paroxetine) also increase BDNF expression[29,172,176]: mechanisms by which neurotrophic factors might prevent age- and disease-related neuronal degeneration have been reviewed in detail previously[78] and include suppression of oxidative and metabolic stress, excitotoxicity and calcium overload, and protein and DNA damage. The neuroprotective signal transduction pathways for neurotrophic factors often involve receptor tyrosine kinases, phosphatidylinositol-3-kinase, Akt kinase, mitogen-activated protein kinases, and transcription factors such as CREB (cyclic AMP responsive element-binding protein) and nuclear factor-κB[78]. Examples of neuroprotective genes upregulated by these signalling pathways include BCL2, inhibitor of apoptosis proteins (IAP), Mn-SOD and calbindin[78].

Cytoskeletal disruption

The complex morphologies of neurons, with long axons and elaborate dendritic arbors, are maintained and modified by the cytoskeleton (microtubules, microfilaments and intermediate filaments) and associated proteins (for example, microtubule-associated proteins and actin-binding proteins)[177,178]. The shafts of axons and dendrites contain large numbers of microtubules, whereas the more dynamic growth cones and synaptic terminals are actin-rich; neurofilaments are concentrated in axons. The cytoskeletal organization is disrupted in neurons that degenerate during ageing and in neurodegenerative disorders. In particular, microtubules depolymerize and the microtubule-associated protein tau, which is normally present only in axons, accumulates in the cell body[179]. Axonal neurofilament pathology is prominent in motor neurons in ALS, but also occurs in hippocampal neurons in AD and dopaminergic neurons in PD[178]. Hyperphosphorylation of tau on specific amino-acid residues occurs in vulnerable neurons in AD as the result of alterations in tau kinases and phosphatases; data suggest that such alterations decrease the affinity of tau for microtubules and promote its self-aggregation[179]. Events upstream of cytoskeletal abnormalities in ageing and disease might include oxidative stress and perturbed calcium homeostasis[180,181]. In AD, Aβ abnormalities are believed to cause the tau pathology. Many of the cytoskeletal abnormalities present in human neurodegenerative disorders are also manifest in animal models. For example, hippocampal and cortical neurons show neurofibrillary tangle-like tau pathology in a mouse model of AD[182], axonal transport of BDNF is disrupted in cortical neurons from huntingtin-mutant-knockin mice[183], and motor neurons suffer severe neurofilament pathology in Cu/Zn-SOD-mutant mice[184].

Although cytoskeletal abnormalities are prominent in vulnerable neuronal populations in a range of neurodegenerative disorders, until recently it was not clear whether the alterations were pivotal in the cell death process. The identification of tau mutations as the causal genetic factor in individuals with the inherited disorder FTDP-17 firmly established the sufficiency of tau pathology for SNV[185]. Transgenic mice engineered to mimic the FTDP-17 defect exhibit age-dependent filamentous tau pathology in cortical, brainstem and spinal cord neurons[186]. Why pyramidal neurons in the frontal cortex are particularly vulnerable in FTDP-17 is not known, but it is thought that the ratios of different tau isoforms

Table 2 | **Examples of approaches to preventing and treating age-related neurodegeneration**

Approach	Mechanism of action/target	Disorders	Refs
Dietary restriction	Decrease ROS concentration, neurotrophic factors, hormesis*	AD, PD, HD	30–33, 200
Exercise	Neurotrophins, hormesis	AD, PD	36,217,218
Cognitive stimulation	Neurotrophins, hormesis	AD, PD	201
Dietary phytochemicals	Antioxidants, hormesis	AD, PD, HD, ALS	224
Dietary lipid modification	Decrease ROS concentration, membrane homeostasis	AD, PD	69,202,203,213
Antioxidants	Decrease ROS concentration	AD, PD, HD, ALS	225
Anti-inflammatory agents	Decrease concentrations of ROS and neurotoxic cytokines	AD, PD, HD, ALS	188
Anti-excitotoxic agents	Decrease calcium influx and ROS concentration	AD, PD	78,204
Calcium-stabilizing agents	Prevent cellular calcium overload	AD, PD, HD, ALS	78
Amyloid β-modulating agents	β- or γ-secretase inhibitors, amyloid β-degrading agents	AD	2
Energy modulation	Increase cellular energy availability	AD, PD, HD, ALS	207
Inhibitors of apoptosis	Caspases, BCL2 proteins, mitochondrial and endoplasmic reticulum membranes	AD, PD, HD, ALS	205,206
Neurotrophic factors	Neuronal survival and plasticity, neurogenesis	AD, PD, HD, ALS	208–210
Immunotherapy	Active and/or passive immune attack on diseased protein	AD, others?	211
RNA interference	Suppress production of diseased protein	HD, familial disease	212

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BCL2, B-cell leukaemia/lymphoma 2; HD, Huntington's disease; PD, Parkinson's disease; ROS, reactive oxygen species.

or the mechanisms of tau degradation or aggregation in vulnerable neurons could influence this SNV[187]. However, the determinants of SNV to cytoskeletal pathology during ageing are likely to be the same as those that determine whether a neuron lives or dies. For example, aberrant processing of APP in AD results in the production of neurotoxic forms of Aβ that induce oxidative stress and Ca^{2+} dysregulation in neurons, which results in microtubule depolymerization and tau pathology (BOX 1). Axonal microtubule and neurofilament pathologies in motor neurons in ALS might also be secondary to oxidative stress and neurotrophic insufficiency.

Inflammation

There is considerable evidence for both local and humoral inflammatory and immune responses in ageing and neurodegenerative disorders. This has been perhaps best studied in regards to AD, in which activated microglia and astrocytes are associated with Aβ plaques and neurofibrillary pathology[188]. Pro-inflammatory cytokines are produced by the activated glial cells and might contribute to the neurodegenerative process[189]. In addition, complement factors that can damage cells are localized to Aβ plaques[190]. Epidemiological findings, and studies of the effects of anti-inflammatory agents in cell culture and animal models of AD suggest a role for inflammatory processes in neuronal degeneration and disease progression[188]. Humoral immune responses to the neuronal and glial pathologies in the brain appear to occur in AD, which is indicated by increased levels of leukocyte adhesion molecules and the presence of cells that express lymphocyte markers in association with amyloid pathology[190,191]. Interestingly, antibodies against Aβ have been detected in association with Aβ deposits and circulating in the blood of patients with AD; such antibodies might either function adaptively, removing Aβ from the brain, or might contribute to the neurodegenerative process[192–194]. Other neurodegenerative disorders also manifest inflammatory processes in association with the pathology, including PD[195] and ALS[196]. In addition, it has been proposed that autoantibodies directed against motor neuron antigens have a role in the pathogenesis of ALS[197]. When taken together, the available data suggest that immune-based processes can be targeted for therapeutic intervention to promote healthy brain ageing and treat neurodegenerative disease.

Therapeutic implications

There are currently no treatments available for those with neurodegenerative disorders that will halt the disease process. However, a few treatments have been shown to slow the course of the disease, including riluzole in patients with ALS[198], and possibly memantine in patients with AD[199]. Recent advances in early diagnosis and preclinical studies suggest that effective treatments that slow the disease course in different neurodegenerative disorders will be found. Based on their site of action in the ageing process and/or neurodegenerative cascade (FIG. 2), treatments might be either disorder-specific or might be useful for more than one disorder (TABLE 2). For

Cytokines
A large class of intercellular signalling proteins that are important in neural–immune system interactions and inflammatory processes.

Complement factors
Proteins that function in innate immunity, often forming pores in membranes, which results in cell death.

Leukocyte adhesion molecules
Proteins located on the surface of vascular endothelial cells that bind to leukocytes, thereby facilitating the passage of the leukocytes across the blood–brain barrier.

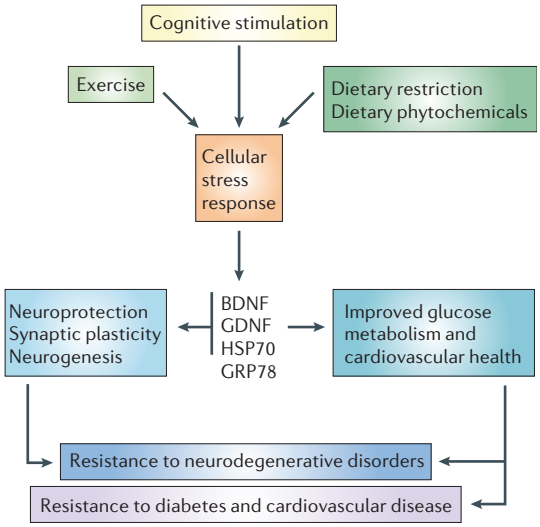


Figure 5 | **Counteracting ageing by stimulating beneficial cellular stress responses.** Exercise, dietary energy restriction and cognitive stimulation have all been shown to protect neurons against dysfunction and death in animal models of neurodegenerative disorders. This occurs, in part, by induction of a mild stress response that induces the production of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glia cell line-derived neurotrophic factor (GDNF), as well as protein chaperones such as heat-shock protein 70 (HSP70) and glucose-regulated protein 78 (GRP78). In addition, exercise and dietary restriction improve energy metabolism (increased insulin sensitivity) and cardiovascular health (decreased blood pressure and enhanced cardiovascular stress adaptation). This model is based largely on the results of studies in animals and, although such studies have been promising, it is not yet clear whether exercise, dietary restriction and cognitive stimulation can protect against neurodegeneration in humans.

example, γ- and β-secretase inhibitors selectively target a mechanism (APP processing) that is abnormal in AD, but might not be operative in other disorders (PD, HD or ALS). By contrast, antioxidants and anti-inflammatory agents target a pathogenic process that is common to all neurodegenerative disorders. Because extensive neuronal degeneration and death occurs prior to diagnosis, treatments that can restore function are unlikely. Instead, there is a great potential for preventing, or at least delaying, disease onset in those at risk due to genetic and/or environmental factors. Indeed, everyone is at a high risk of AD and PD as they enter their seventh and eighth decades of life.

Evidence is emerging that age-related neuronal dysfunction can be delayed — the risk of neurodegenerative disorders can be modified by diet and lifestyle (FIG. 5). For example, dietary restriction extends brain longevity and suppresses the disease process in animal models of AD, PD, HD and stroke[30–33,200]. Exercise and cognitive stimulation slow the pathogenic cascades in AD mice[201]. However, although studies with animal models have been promising, the extent to which such approaches might counteract ageing and neurodegenerative disease in humans remains to be determined. Dietary and pharmacological manipulations of lipid metabolism have proven to be effective in preclinical studies of AD, findings that are supported by epidemiological data[202,203]. Other approaches include glutamate receptor modulating agents for AD[204], anti-apoptotic agents for PD and HD[205,206], agents that enhance energy metabolism for HD[207], and neurotrophic factor therapies for PD, HD and ALS[208–210]. Particularly exciting are the possibilities that pathogenic proteins, such as Aβ and tau, and polyglutamine repeat proteins, such as huntingtin, could be targeted by active or passive immunization[211], or by RNA interference technology[212].

Conclusions and perspectives

A major goal of research into ageing is to extend 'healthspan' by identifying approaches for delaying or preventing age-related diseases. The fact that many individuals maintain a well-functioning nervous system and continue productive lives through their seventies, eighties and even nineties is encouraging. The implication is that if the cellular and molecular mechanisms that determine whether nervous systems adapt positively or develop a disease during ageing can be identified, then disease processes can be averted. In this regard, oxidative and metabolic stress, and impaired cellular stress adaptation, are mechanisms of ageing that render neurons vulnerable to degeneration. On this background of age-related endangerment, genetic and environmental factors determine whether a disease process develops. These include causal mutations, more subtle genetic risk factors and environmental factors, including aspects of diet and lifestyle. Because of the cellular and molecular complexity of the nervous system, and the signalling mechanisms that influence neuronal plasticity and survival, the basis of SNV remains elusive. Nevertheless, the proposed mechanisms of age-related neuronal vulnerability described above are apparently operative in multiple neurodegenerative disorders. Disorder-specific differences in the phenotypes of neurons determine which neurons succumb. For example, in AD, the amounts and location of APP in neurons, levels of α- and β-secretase activities, and factors that affect APP processing (oxidative stress, lipid metabolism and calcium dynamics) might determine SNV.

Currently, most efforts to prevent and treat neurodegenerative disorders focus on diet and lifestyle modification and drugs that target disease processes. Although data on humans is still limited, the emerging evidence that dietary restriction, exercise and cognitive stimulation can bolster neuroprotective mechanisms suggests that diet and lifestyle changes could reduce the risk of neurodegenerative disorders[213–221]. An understanding of the mechanisms of action of such environmental risk-reduction factors has led to efforts to develop dietary supplements and drugs that mimic their action. Together with advances in the development of drugs that target specific molecular events in neurodegenerative cascades, it seems likely that extension of neural healthspan is possible for most individuals.

1. Hofer, S. M., Berg, S. & Era, P. Evaluating the interdependence of aging-related changes in visual and auditory acuity, balance, and cognitive functioning. *Psychol. Aging* **18**, 285–305 (2003).
2. Mattson, M. P. Pathways towards and away from Alzheimer's disease. *Nature* **430**, 631–639 (2004). **This review integrates information on the molecular pathogenesis of AD and efforts to prevent and treat this disorder.**
3. Cookson, M. R. The biochemistry of Parkinson's disease. *Annu. Rev. Biochem.* **74**, 29–52 (2005).
4. Moore, D. J., West, A. B., Dawson, V. L. & Dawson, T. M. Molecular pathophysiology of Parkinson's disease. *Annu. Rev. Neurosci.* **27**, 57–87 (2005). **Reviews the involvement of mitochondrial dysfunction and perturbed ubiquitin-mediated proteolysis in PD.**
5. Sieradzan, K. A. & Mann, D. M. The selective vulnerability of nerve cells in Huntington's disease. *Neuropathol. Appl. Neurobiol.* **27**, 1–21 (2001).
6. Cleveland, D. W. & Rothstein, J. D. From Charcot to Lou Gehrig: deciphering selective motor neuron death in ALS. *Nature Rev. Neurosci.* **2**, 806–819 (2001).
7. Serrano, F. & Klann, E. Reactive oxygen species and synaptic plasticity in the aging hippocampus. *Ageing Res. Rev.* **3**, 431–443 (2004).
8. Zecca, L., Youdim, M. B., Riederer, P., Connor, J. R. & Crichton, R. R. Iron, brain ageing and neurodegenerative disorders. *Nature Rev. Neurosci.* **5**, 863–873 (2004).
9. Ames, B. N. Delaying the mitochondrial decay of aging. *Ann. NY Acad. Sci.* **1019**, 406–411 (2004).
10. Gray, D. A., Tsirigotis, M. & Woulfe, J. Ubiquitin, proteasomes, and the aging brain. *Sci. Aging Knowledge Environ.* RE6 27 Aug 2003.
11. Trojanowski, J. Q. & Mattson, M. P. Overview of protein aggregation in single, double, and triple neurodegenerative brain amyloidoses. *Neuromolecular Med.* **4**, 1–6 (2003).
12. Kyng, K. J. & Bohr, V. A. Gene expression and DNA repair in progeroid syndromes and human aging. *Ageing Res. Rev.* **4**, 579–602 (2005).
13. Lu, T. *et al.* Gene regulation and DNA damage in the ageing human brain. *Nature* **429**, 883–891 (2004).
14. Butler, R. N. *et al.* Longevity genes: from primitive organisms to humans. *J. Gerontol. A Biol. Sci. Med. Sci.* **58**, 581–584 (2003).
15. Wolkow, C. A. Life span: getting the signal from the nervous system. *Trends Neurosci.* **25**, 212–216 (2002). **Describes how insulin-like signalling in the nervous system might regulate ageing and determine lifespan.**
16. Mattson, M. P. Methylation and acetylation in nervous system development and neurodegenerative disorders. *Ageing Res. Rev.* **2**, 329–342 (2003).
17. Yehuda, S., Rabinovitz, S., Carasso, R. L. & Mostofsky, D. I. The role of polyunsaturated fatty acids in restoring the aging neuronal membrane. *Neurobiol. Aging* **23**, 843–853 (2002).
18. Floyd, R. A. & Hensley, K. Oxidative stress in brain aging. Implications for therapeutics of neurodegenerative diseases. *Neurobiol. Aging* **23**, 795–807 (2002).
19. Jenner, P. Oxidative stress in Parkinson's disease. *Ann. Neurol.* **53**, S26–S36 (2003).
20. Pedersen, W. A. *et al.* Protein modification by the lipid peroxidation product 4-hydroxynonenal in the spinal cords of amyotrophic lateral sclerosis patients. *Ann. Neurol.* **44**, 819–824 (1998).
21. Rakhit, R. *et al.* Monomeric Cu,Zn-superoxide dismutase is a common misfolding intermediate in the oxidation models of sporadic and familial amyotrophic lateral sclerosis. *J. Biol. Chem.* **279**, 15499–15504 (2004).
22. Cuervo, A. M., Stefanis, L., Fredenburg, R., Lansbury, P. T. & Sulzer, D. Impaired degradation of mutant α-synuclein by chaperone-mediated autophagy. *Science* **305**, 1292–1295 (2004). **Describes the degradation of wild-type α-synuclein by chaperone-mediated autophagy, and the impairment of this process by mutant forms of the protein.**
23. Grondin, R. *et al.* Chronic, controlled GDNF infusion promotes structural and functional recovery in advanced parkinsonian monkeys. *Brain* **125**, 2191–2201 (2002).
24. Zuccato, C. *et al.* Huntingtin interacts with REST/NRSF to modulate the transcription of NRSE-controlled neuronal genes. *Nature Genet.* **35**, 76–83 (2003).
25. Weindruch, R. & Sohal, R. S. Seminars in medicine of the Beth Israel Deaconess Medical Center. Caloric intake and aging. *N. Engl. J. Med.* **337**, 986–994 (1997).
26. Heilbronn, L. K. & Ravussin, E. Calorie restriction and aging: review of the literature and implications for studies in humans. *Am. J. Clin. Nutr.* **78**, 361–369 (2003).
27. Mattison, J. A., Lane, M. A., Roth, G. S. & Ingram, D. K. Calorie restriction in rhesus monkeys. *Exp. Gerontol.* **38**, 35–46 (2003).
28. Fontana, L., Meyer, T. E., Klein, S. & Holloszy, J. O. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. *Proc. Natl Acad. Sci. USA* **101**, 6659–6663 (2004).
29. Mattson, M. P. Energy intake, meal frequency, and health: a neurobiological perspective. *Annu. Rev. Nutr.* **25**, 237–260 (2005).
30. Patel, N. V. *et al.* Caloric restriction attenuates Aβ-deposition in Alzheimer transgenic models. *Neurobiol. Aging* **26**, 995–1000 (2005).
31. Maswood, N. *et al.* Caloric restriction increases neurotrophic factor levels and attenuates neurochemical and behavioral deficits in a primate model of Parkinson's disease. *Proc. Natl Acad. Sci. USA* **101**, 18171–18176 (2004).
32. Duan, W. *et al.* Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice. *Proc. Natl Acad. Sci. USA* **100**, 2911–2916 (2003).
33. Yu, Z. F. & Mattson, M. P. Dietary restriction and 2-deoxyglucose administration reduce focal ischemic brain damage and improve behavioral outcome: evidence for a preconditioning mechanism. *J. Neurosci. Res.* **57**, 830–839 (1999).
34. Mattson, M. P., Maudsley, S. & Martin, B. BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. *Trends Neurosci.* **27**, 589–594 (2004).
35. Barja, G. Free radicals and aging. *Trends Neurosci.* **27**, 595–600 (2004).
36. Cotman, C. W. & Berchtold, N. C. Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci.* **25**, 295–301 (2002).
37. Spires, T. L. Environmental enrichment rescues protein deficits in a mouse model of Huntington's disease, indicating a possible disease mechanism. *J. Neurosci.* **24**, 2270–2276 (2004).
38. Liu, D. *et al.* Mitochondrial UCP4 induces a glycolytic shift in energy metabolism and increases the resistance of neurons to oxidative stress. *Neuromolecular Med.* (in the press).
39. Parker, J. A. *et al.* Resveratrol rescues mutant polyglutamine cytotoxicity in nematode and mammalian neurons. *Nature Genet.* **37**, 349–350 (2005).
40. Morrison, B. M., Hof, P. R. & Morrison, J. H. Determinants of neuronal vulnerability in neurodegenerative diseases. *Ann. Neurol.* **44**, S32–S44 (1998).
41. Smith, D. E., Saji, M., Joh, T. H., Reis, D. J. & Pickel, V. M. Ibotenic acid-induced lesions of striatal target and projection neurons: ultrastructural manifestations in dopaminergic and non-dopaminergic neurons and in glia. *Histol. Histopathol.* **2**, 251–263 (1987).
42. Mandelkow, E. M., Stamer, K., Vogel, R., Thies, E. & Mandelkow, E. Clogging of axons by tau, inhibition of axonal traffic and starvation of synapses. *Neurobiol. Aging* **24**, 1079–1085 (2003).
43. Bayatti, N. & Behl, C. The neuroprotective actions of corticotropin releasing hormone. *Ageing Res. Rev.* **4**, 258–270 (2005).
44. Ishunina, T. A. & Swaab, D. F. Neurohypophyseal peptides in aging and Alzheimer's disease. *Ageing Res. Rev.* **1**, 537–558 (2002).
45. Braak, H. & Braak, E. Evolution of neuronal changes in the course of Alzheimer's disease. *J. Neural Transm. Suppl.* **53**, 127–140 (1998).
46. Braak, H. *et al.* Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol. Aging* **24**, 197–211 (2003).
47. Mills, K. R. The natural history of central motor abnormalities in amyotrophic lateral sclerosis. *Brain* **126**, 2558–2566 (2003).
48. Yuan, J. & Yankner, B. A. Apoptosis in the nervous system. *Nature* **407**, 802–809 (2000). **Reviews evidence that supports a role for apoptosis in the pathogenesis of neurodegenerative disorders.**
49. Mattson, M. P. Apoptosis in neurodegenerative disorders. *Nature Rev. Mol. Cell Biol.* **1**, 120–129 (2000).
50. Miller, F. D., Pozniak, C. D. & Walsh, G. S. Neuronal life and death: an essential role for the p53 family. *Cell Death Differ.* **7**, 880–888 (2000).
51. Tanaka, Y. *et al.* Inducible expression of mutant α-synuclein decreases proteasome activity and increases sensitivity to mitochondria-dependent apoptosis. *Hum. Mol. Genet.* **10**, 919–926 (2001).
52. Akhtar, R. S., Ness, J. M. & Roth, K. A. Bcl-2 family regulation of neuronal development and neurodegeneration. *Biochim. Biophys. Acta* **1644**, 189–203 (2004).
53. Cheung, E. C. *et al.* Apoptosis-inducing factor is a key factor in neuronal cell death propagated by BAX-dependent and BAX-independent mechanisms. *J. Neurosci.* **25**, 1324–1334 (2005).
54. Wang, K. K. Calpain and caspase: can you tell the difference? *Trends Neurosci.* **23**, 20–26 (2000).
55. Stefanis, L. Caspase-dependent and -independent neuronal death: two distinct pathways to neuronal injury. *Neuroscientist* **11**, 50–62 (2005).
56. Chan, S. L. *et al.* Presenilin-1 mutations sensitize neurons to DNA damage-induced death by a mechanism involving perturbed calcium homeostasis and activation of calpains and caspase-12. *Neurobiol. Dis.* **11**, 2–19 (2002).
57. Brown, D. & Tatton, N. Apoptosis in Parkinson's disease: signals for neuronal degradation. *Ann. Neurol.* **53** (Suppl. 3), S61–S70 (2003).
58. Crocker, S. J. *et al.* Inhibition of calpains prevents neuronal and behavioral deficits in an MPTP mouse model of Parkinson's disease. *J. Neurosci.* **23**, 4081–4091 (2003).
59. Gafni, J. & Ellerby, L. M. Calpain activation in Huntington's disease. *J. Neurosci.* **22**, 4842–4849 (2002).
60. Friedlander, R. M. Apoptosis and caspases in neurodegenerative diseases. *N. Engl. J. Med.* **348**, 1365–1375 (2003).
61. Mattson, M. P. & Kroemer, G. Mitochondria in cell death: novel targets for neuroprotection and cardioprotection. *Trends Mol. Med.* **9**, 196–205 (2003).
62. Glazner, G. W. *et al.* Endoplasmic reticulum D-*myo*-inositol 1,4,5-trisphosphate-sensitive stores regulate nuclear factor-κB binding activity in a calcium-independent manner. *J. Biol. Chem.* **276**, 22461–22467 (2001).
63. Milhavet, O. *et al.* Involvement of Gadd153 in the pathogenic action of presenilin-1 mutations. *J. Neurochem.* **83**, 673–681 (2002).
64. Boehning, D. *et al.* Cytochrome c binds to inositol (1,4,5) trisphosphate receptors, amplifying calcium-dependent apoptosis. *Nature Cell Biol.* **5**, 1051–1061 (2003).
65. Culmsee, C. & Mattson, M. P. p53 in neuronal apoptosis. *Biochem. Biophys. Res. Commun.* **331**, 761–777 (2005).
66. Kruman, I. *et al.* Evidence that 4-hydroxynonenal mediates oxidative stress-induced neuronal apoptosis. *J. Neurosci.* **17**, 5089–5100 (1997).
67. Bruckner, S. R., Perry, G. & Estus, S. 4-hydroxynonenal contributes to NGF withdrawal-induced neuronal apoptosis. *J. Neurochem.* **85**, 999–1005 (2003).
68. Zhou, H., Li, X. M., Meinkoth, J. & Pittman, R. N. Akt regulates cell survival and apoptosis at a postmitochondrial level. *J. Cell Biol.* **151**, 483–494 (2000).
69. Cutler, R. G. *et al.* Involvement of oxidative stress-induced abnormalities in ceramide and cholesterol metabolism in brain aging and Alzheimer's disease. *Proc. Natl Acad. Sci. USA* **101**, 2070–2075 (2004). **Links age-related alterations in the metabolism of membrane lipids to oxidative stress and neuronal degeneration in AD.**
70. Haughey, N. J. *et al.* Perturbation of sphingolipid metabolism and ceramide production in HIV-dementia. *Ann. Neurol.* **55**, 257–267 (2004).
71. Cutler, R. G. *et al.* Evidence that accumulation of ceramides and cholesterol esters mediates oxidative stress-induced death of motor neurons in amyotrophic lateral sclerosis. *Ann. Neurol.* **52**, 448–457 (2002).
72. White, L. D. & Barone, S. Jr Qualitative and quantitative estimates of apoptosis from birth to senescence in the rat brain. *Cell Death Differ.* **8**, 345–356 (2001).
73. Hiona, A. & Leeuwenburgh, C. Life-long caloric restriction counteracts apoptotic effects of aging in the brain and bolsters the action of apoptosis inhibitors.

Neurobiol. Aging. 26 Sep 2006 (doi:10.1016/j.neurobiolaging.2005.08.006).
74. Kempermann, G., Kuhn, H. G. & Gage, F. H. Experience-induced neurogenesis in the senescent dentate gyrus. *J. Neurosci.* **18**, 3206–3212 (1998). **Evidence that age-related declines in hippocampal neurogenesis can be counteracted by cognitive stimulation.**
75. Sun, W. *et al.* Programmed cell death of adult-generated hippocampal neurons is mediated by the proapoptotic gene Bax. *J. Neurosci.* **24**, 11205–11213 (2004).
76. Haughey, N. J. *et al.* Disruption of neurogenesis by amyloid β-peptide, and perturbed neural progenitor cell homeostasis, in models of Alzheimer's disease. *J. Neurochem.* **83**, 1509–1524 (2002).
77. Jin, K. *et al.* Increased hippocampal neurogenesis in Alzheimer's disease. *Proc. Natl Acad. Sci. USA* **101**, 343–347 (2004).
78. Mattson, M. P. Excitotoxic and excitoprotective mechanisms: abundant targets for the prevention and treatment of neurodegenerative disorders. *Neuromolecular Med.* **3**, 65–94 (2003).
79. Ben-Ari, Y. & Cossart, R. Kainate, a double agent that generates seizures: two decades of progress. *Trends Neurosci.* **23**, 580–587 (2000).
80. Perl, T. M. *et al.* An outbreak of toxic encephalopathy caused by eating mussels contaminated with domoic acid. *N. Engl. J. Med.* **323**, 1631–1633 (1990).
81. Kisby, G. E., Ellison, M. & Spencer, P. S. Content of the neurotoxins cycasin (methylazoxymethanol β-D-glucoside) and BMAA (β-*N*-methylamino-L-alanine) in cycad flour prepared by Guam Chamorros. *Neurology* **42**, 1336–1340 (1992).
82. Langston, J. W., Ballard, P., Tetrud, J. W. & Irwin, I. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* **219**, 979–980 (1983). **First direct evidence that an environmental neurotoxin can cause parkinsonism.**
83. Panov, A. *et al.* Rotenone model of Parkinson disease: multiple brain mitochondria dysfunctions after short term systemic rotenone intoxication. *J. Biol. Chem.* **280**, 42026–42035 (2005).
84. Ludolph, A. C., He, F., Spencer, P. S., Hammerstad, J. & Sabri, M. 3-Nitropropionic acid-exogenous animal neurotoxin and possible human striatal toxin. *Can. J. Neurol. Sci.* **18**, 492–498 (1991).
85. Berridge, M. J., Bootman, M. D. & Roderick, H. L. Calcium signalling: dynamics, homeostasis and remodelling. *Nature Rev. Mol. Cell Biol.* **4**, 517–529 (2003).
86. Toescu, E. C., Verkhratsky, A. & Landfield, P. W. Ca^{2+} regulation and gene expression in normal brain aging. *Trends Neurosci.* **27**, 614–620 (2004).
87. Guo, Q. *et al.* Increased vulnerability of hippocampal neurons to excitotoxic necrosis in presenilin-1 mutant knock-in mice. *Nature Med.* **5**, 101–106 (1999).
88. Schneider, I. *et al.* Mutant presenilins disturb neuronal calcium homeostasis in the brain of transgenic mice, decreasing the threshold for excitotoxicity and facilitating long-term potentiation. *J. Biol. Chem.* **276**, 11539–11544 (2001).
89. Martinez, J., Moeller, I., Erdjument-Bromage, H., Tempst, P. & Lauring, B. Parkinson's disease-associated α-synuclein is a calmodulin substrate. *J. Biol. Chem.* **278**, 17379–17387 (2003).
90. Tang, T. S. *et al.* Disturbed Ca^{2+} signaling and apoptosis of medium spiny neurons in Huntington's disease. *Proc. Natl Acad. Sci. USA* **102**, 2602–2607 (2005).
91. Smith, R. G. *et al.* Altered muscle calcium channel binding kinetics in autoimmune motoneuron disease. *Muscle Nerve* **18**, 620–627 (1995).
92. Von Lewinski, F. & Keller, B. U. Ca^{2+}, mitochondria and selective motoneuron vulnerability: implications for ALS. *Trends Neurosci.* **28**, 494–500 (2005).
93. Mattson, M. P., Rychlik, B., Chu, C. & Christakos, S. Evidence for calcium-reducing and excito-protective roles for the calcium-binding protein calbindin-D28k in cultured hippocampal neurons. *Neuron* **6**, 41–51 (1991).
94. Magloczky, Z. & Freund, T. F. Selective neuronal death in the contralateral hippocampus following unilateral kainate injections into the CA3 subfield. *Neuroscience* **56**, 317–335 (1993).
95. Guela, C. *et al.* Loss of calbindin-D28k from aging human cholinergic basal forebrain: relation to neuronal loss. *J. Comp. Neurol.* **455**, 249–259 (2003).
96. Thorns, V., Licastro, F. & Masliah, E. Locally reduced levels of acidic FGF lead to decreased expression of 28-kDa calbindin and contribute to the selective vulnerability of the neurons in the entorhinal cortex in Alzheimer's disease. *Neuropathology* **21**, 203–211 (2001).
97. Iacopino, A. M. & Christakos, S. Specific reduction of calcium-binding protein (28-kilodalton calbindin-D) gene expression in aging and neurodegenerative diseases. *Proc. Natl Acad. Sci. USA* **87**, 4078–4082 (1990). **Evidence that age- and neuron-specific changes in calcium-binding proteins are associated with SNV.**
98. Alexianu, M. E. *et al.* The role of calcium-binding proteins in selective motoneuron vulnerability in amyotrophic lateral sclerosis. *Ann. Neurol.* **36**, 846–858 (1994).
99. Ikonomovic, M. D. *et al.* Distribution of glutamate receptor subunit NMDAR1 in the hippocampus of normal elderly and patients with Alzheimer's disease. *Exp. Neurol.* **160**, 194–204 (1999).
100. Williams, T. L., Day, N. C., Ince, P. G., Kamboj, R. K. & Shaw, P. J. Calcium-permeable α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors: a molecular determinant of selective vulnerability in amyotrophic lateral sclerosis. *Ann. Neurol.* **42**, 200–207 (1997).
101. Melov, S. Modeling mitochondrial function in aging neurons. *Trends Neurosci.* **27**, 601–606 (2004).
102. Petit-Taboue, M. C., Landeau, B., Desson, J. F., Desgranges, B. & Baron, J. C. Effects of healthy aging on the regional cerebral metabolic rate of glucose assessed with statistical parametric mapping. *Neuroimage* **7**, 176–184 (1998).
103. Masconi, L. Brain glucose metabolism in the early and specific diagnosis of Alzheimer's disease. FDG-PET studies in MCI and AD. *Eur. J. Nucl. Med. Mol. Imaging* **32**, 486–510 (2005).
104. Dagher, A. Functional imaging in Parkinson's disease. *Semin. Neurol.* **21**, 23–32 (2001).
105. Feigin, A. *et al.* Metabolic network abnormalities in early Huntington's disease: an [^{18}F]FDG PET study. *J. Nucl. Med.* **42**, 1591–1595 (2001).
106. Bubber, P., Haroutunian, V., Fisch, G., Blass, J. P. & Gibson, G. E. Mitochondrial abnormalities in Alzheimer brain: mechanistic implications. *Ann. Neurol.* **57**, 695–703 (2005).
107. Smigrodzki, R., Parks, J. & Parker, W. D. High frequency of mitochondrial complex I mutations in Parkinson's disease and aging. *Neurobiol. Aging* **25**, 1273–1281 (2004).
108. Seong, I. S. *et al.* HD CAG repeat implicates a dominant property of huntingtin in mitochondrial energy metabolism. *Hum. Mol. Genet.* **14**, 2871–2880 (2005).
109. Manfredi, G. & Xu, Z. Mitochondrial dysfunction and its role in motor neuron degeneration in ALS. *Mitochondrion* **5**, 77–87 (2005).
110. Brown, M. R., Geddes, J. W. & Sullivan, P. G. Brain region-specific, age-related, alterations in mitochondrial responses to elevated calcium. *J. Bioenerg. Biomembr.* **36**, 401–406 (2004).
111. Murchison, D., Zawieja, D. C. & Griffith, W. H. Reduced mitochondrial buffering of voltage-gated calcium influx in aged rat basal forebrain neurons. *Cell Calcium* **36**, 61–75 (2004).
112. Kim, G. W. & Chan, P. H. Oxidative stress and neuronal DNA fragmentation mediate age-dependent vulnerability to the mitochondrial toxin, 3-nitropropionic acid, in the mouse striatum. *Neurobiol. Dis.* **8**, 114–126 (2001). **Evidence that neuronal vulnerability to mitochondrial toxins increases with advancing age.**
113. Patel, J. R. & Brewer, G. J. Age-related changes in neuronal glucose uptake in response to glutamate and β-amyloid. *J. Neurosci. Res.* **72**, 527–536 (2003).
114. Klivenyi, P. *et al.* Mice deficient in cellular glutathione peroxidase show increased vulnerability to malonate, 3-nitropropionic acid, and 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. *J. Neurosci.* **20**, 1–7 (2000).
115. Keller, J. N. *et al.* Mitochondrial manganese superoxide dismutase prevents neural apoptosis and reduces ischemic brain injury: suppression of peroxynitrite production, lipid peroxidation, and mitochondrial dysfunction. *J. Neurosci.* **18**, 687–697 (1998).
116. Bruce-Keller, A. J., Umberger, G., McFall, R. & Mattson, M. P. Food restriction reduces brain damage and improves behavioral outcome following excitotoxic and metabolic insults. *Ann. Neurol.* **45**, 8–15 (1999).
117. Duan, W. & Mattson, M. P. Dietary restriction and 2-deoxyglucose administration improve behavioral outcome and reduce degeneration of dopaminergic neurons in models of Parkinson's disease. *J. Neurosci. Res.* **57**, 195–206 (1999).
118. Niwa, K., Kazama, K., Younkin, S. G., Carlson, G. A. & Iadecola, C. Alterations in cerebral blood flow and glucose utilization in mice overexpressing the amyloid precursor protein. *Neurobiol. Dis.* **9**, 61–68 (2002).
119. Lustbader, J. W. *et al.* ABAD directly links Aβ to mitochondrial toxicity in Alzheimer's disease. *Science* **304**, 448–452 (2004).
120. Keller, J. N. *et al.* Increased sensitivity to mitochondrial toxin-induced apoptosis in neural cells expressing mutant presenilin-1 is linked to perturbed calcium homeostasis and enhanced oxyradical production. *J. Neurosci.* **18**, 4439–4450 (1998).
121. Guo, Q., Christakos, S., Robinson, N. & Mattson, M. P. Calbindin D28k blocks the proapoptotic actions of mutant presenilin 1: reduced oxidative stress and preserved mitochondrial function. *Proc. Natl Acad. Sci. USA* **95**, 3227–3232 (1998).
122. Panov, A. V. *et al.* Early mitochondrial calcium defects in Huntington's disease are a direct effect of polyglutamines. *Nature Neurosci.* **5**, 731–736 (2002).
123. Trushina, E. *et al.* Mutant huntingtin impairs axonal trafficking in mammalian neurons *in vivo* and *in vitro*. *Mol. Cell Biol.* **24**, 8195–8209 (2004).
124. Klivenyi, P. *et al.* Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis. *Nature Med.* **5**, 347–350 (1999).
125. Tarnopolsky, M. A. & Beal, M. F. Potential for creatine and other therapies targeting cellular energy dysfunction in neurological disorders. *Ann. Neurol.* **49**, 561–574 (2001). **Reviews evidence that a cellular energy deficit has a key role in the degeneration of motor neurons in HD and ALS.**
126. Szweda, P. A., Camouse, M., Lundberg, K. C., Oberley, T. D. & Szweda, L. I. Aging, lipofuscin formation, and free radical-mediated inhibition of cellular proteolytic systems. *Ageing Res. Rev.* **2**, 383–405 (2003).
127. Gray, D. A. & Woulfe, J. Lipofuscin and aging: a matter of toxic waste. *Sci. Aging Knowledge Environ.* RE1 2 Feb 2005.
128. Nixon, R. A. The calpains in aging and aging-related diseases. *Ageing Res. Rev.* **2**, 407–418 (2003).
129. Bi, X., Yong, A. P., Zhou, J., Gall, C. M. & Lynch, G. Regionally selective changes in brain lysosomes occur in the transition from young adulthood to middle age in rats. *Neuroscience* **97**, 395–404 (2000).
130. Keller, J. N., Gee, J. & Ding, Q. The proteasome in brain aging. *Ageing Res. Rev.* **1**, 279–293 (2002).
131. Keller, J. N., Hanni, K. B. & Markesbery, W. R. Possible involvement of proteasome inhibition in aging: implications for oxidative stress. *Mech. Ageing Dev.* **113**, 61–70 (2000).
132. Lam, Y. A. *et al.* Inhibition of the ubiquitin-proteasome system in Alzheimer's disease. *Proc. Natl Acad. Sci. USA* **97**, 9902–9906 (2000).
133. McNaught, K. S., Olanow, C. W., Halliwell, B., Isacson, O. & Jenner, P. Failure of the ubiquitin-proteasome system in Parkinson's disease. *Nature Rev. Neurosci.* **2**, 589–594 (2001).
134. Sullivan, P. G. *et al.* Proteasome inhibition alters neural mitochondrial homeostasis and mitochondria turnover. *J. Biol. Chem.* **279**, 20699–20707 (2004).
135. Bednarski, E., Ribak, C. E. & Lynch, G. Suppression of cathepsins B and L causes a proliferation of lysosomes and the formation of meganeurites in hippocampus. *J. Neurosci.* **17**, 4006–4021 (1997).
136. Nixon, R. A. *et al.* Extensive involvement of autophagy in Alzheimer disease: an immuno-electron microscopy study. *J. Neuropathol. Exp. Neurol.* **64**, 113–122 (2005).
137. Bergamini, E., Cavallini, G., Donati, A. & Gori, Z. The anti-ageing effects of caloric restriction may involve stimulation of macroautophagy and lysosomal degradation, and can be intensified pharmacologically. *Biomed. Pharmacother.* **57**, 203–208 (2003).
138. Maggio, J. E. *et al.* Reversible *in vitro* growth of Alzheimer disease β-amyloid plaques by deposition of labeled amyloid peptide. *Proc. Natl Acad. Sci. USA* **89**, 5462–5466 (1992).
139. Petkova, A. T. *et al.* Self-propagating, molecular-level polymorphism in Alzheimer's β-amyloid fibrils. *Science* **307**, 262–265 (2005). **Shows that subtle variations in the environment of pathogenic peptides modifies their self-propagating and neurotoxic properties.**
140. Tanzi, R. E., Moir, R. D. & Wagner, S. L. Clearance of Alzheimer's Aβ peptide: the many roads to perdition. *Neuron* **43**, 605–608 (2004).

141. Goedert, M. Tau gene mutations and their effects. *Mov. Disord.* **12**, S45–S52 (2005).
142. Stoothoff, W. H. & Johnson, G. V. Tau phosphorylation: physiological and pathological consequences. *Biochim. Biophys. Acta* **1739**, 280–297 (2005).
143. Montine, T. J., Amarnath, V., Martin, M. E., Strittmatter, W. J. & Graham, D. G. E-4-hydroxy-2-nonenal is cytotoxic and cross-links cytoskeletal proteins in P19 neuroglial cultures. *Am. J. Pathol.* **148**, 89–93 (1996).
144. Moore, D. J., West, A. B., Dawson, V. L. & Dawson, T. M. Molecular pathophysiology of Parkinson's disease. *Annu. Rev. Neurosci.* **28**, 57–87 (2005).
145. Singleton, A. B. *et al.* α-Synuclein locus triplication causes Parkinson's disease. *Science* **302**, 841 (2003). **The first evidence that a modest increase in the production of α-synuclein is sufficient to cause PD.**
146. Yavich, L., Tanila, H., Vepsalainen, S. & Jakala, P. Role of α-synuclein in presynaptic dopamine recruitment. *J. Neurosci.* **24**, 11165–11170 (2004).
147. Bates, G. Huntingtin aggregation and toxicity in Huntington's disease. *Lancet* **361**, 1642–1644 (2003).
148. Fox, J. H. *et al.* Cystamine increases L-cysteine levels in Huntington's disease transgenic mouse brain and in a PC12 model of polyglutamine aggregation. *J. Neurochem.* **91**, 413–422 (2004).
149. Wyttenbach, A. *et al.* Heat shock protein 27 prevents cellular polyglutamine toxicity and suppresses the increase of reactive oxygen species caused by huntingtin. *Hum. Mol. Genet.* **11**, 1137–1151 (2002).
150. Giffard, R. G. *et al.* Chaperones, protein aggregation, and brain protection from hypoxic/ischemic injury. *J. Exp. Biol.* **207**, 3213–3220 (2004).
151. Cohen, F. E. & Kelly, J. W. Therapeutic approaches to protein-misfolding diseases. *Nature* **426**, 905–909 (2003).
152. Zhao, L., Longo-Guess, C., Harris, B. S., Lee, J. W. & Ackerman, S. L. Protein accumulation and neurodegeneration in the woozy mutant mouse is caused by disruption of SIL1, a cochaperone of BiP. *Nature Genet.* **37**, 974–979 (2005).
153. Rousseau, E. *et al.* Targeting expression of expanded polyglutamine proteins to the endoplasmic reticulum or mitochondria prevents their aggregation. *Proc. Natl Acad. Sci. USA* **101**, 9648–9653 (2004).
154. Kieran, D. *et al.* Treatment with arimoclomol, a coinducer of heat shock proteins, delays disease progression in ALS mice. *Nature Med.* **10**, 402–405 (2004). **Pharmacological induction of protein chaperones results in therapeutic benefit in a mouse model of ALS.**
155. Siegel, G. J. & Chauhan, N. B. Neurotrophic factors in Alzheimer's and Parkinson's disease brain. *Brain Res. Rev.* **33**, 199–227 (2000).
156. Dore, S., Kar, S. & Quirion, R. Insulin-like growth factor I protects and rescues hippocampal neurons against β-amyloid- and human amylin-induced toxicity. *Proc. Natl Acad. Sci. USA* **94**, 4772–4777 (1997).
157. Counts, S. E. & Mufson, E. J. The role of nerve growth factor receptors in cholinergic basal forebrain degeneration in prodromal Alzheimer disease. *J. Neuropathol. Exp. Neurol.* **64**, 263–272 (2005).
158. Gash, D. M., Zhang, Z. & Gerhardt, G. Neuroprotective and neurorestorative properties of GDNF. *Ann. Neurol.* **44**, S121–S125 (1998).
159. Ross, C. A. Huntington's disease: new paths to pathogenesis. *Cell* **118**, 4–7 (2004).
160. Wilczak, N. & de Keyser, J. Insulin-like growth factor system in amyotrophic lateral sclerosis. *Endocr. Dev.* **9**, 160–169 (2005).
161. Hattiangady, B., Rao, M. S., Shetty, G. A. & Shetty, A. K. Brain-derived neurotrophic factor, phosphorylated cyclic AMP response element binding protein and neuropeptide Y decline as early as middle age in the dentate gyrus and CA1 and CA3 subfields of the hippocampus. *Exp. Neurol.* **195**, 353–371 (2005).
162. Gooney, M., Messaudi, E., Maher, F. O., Bramham, C. R. & Lynch, M. A. BDNF-induced LTP in dentate gyrus is impaired with age: analysis of changes in cell signaling events. *Neurobiol. Aging* **25**, 1323–1331 (2004).
163. Monti, B., Berteotti, C. & Contestabile, A. Dysregulation of memory-related proteins in the hippocampus of aged rats and their relation with cognitive impairment. *Hippocampus* **15**, 1041–1049 (2005).
164. Adlard, P. A., Perreau, V. M. & Cotman, C. W. The exercise-induced expression of BDNF within the hippocampus varies across life-span. *Neurobiol. Aging* **26**, 511–520 (2005).
165. Yurek, D. M. & Fletcher-Turner, A. Lesion-induced increase of BDNF is greater in the striatum of young versus old rat brain. *Exp. Neurol.* **161**, 392–396 (2000).
166. Dore, S., Kar, S., Rowe, W. & Quirion, R. Distribution and levels of [^{125}I]IGF-I, [^{125}I]IGF-II and [^{125}I]insulin receptor binding sites in the hippocampus of aged memory-unimpaired and -impaired rats. *Neuroscience* **80**, 1033–1040 (1997).
167. D'Costa, A. P., Xu, X., Ingram, R. L. & Sonntag, W. E. Insulin-like growth factor-1 stimulation of protein synthesis is attenuated in cerebral cortex of aging rats. *Neuroscience* **65**, 805–813 (1995).
168. Woods, A. G., Guthrie, K. M., Kurlawalla, M. A. & Gall, C. M. Deafferentation-induced increases in hippocampal insulin-like growth factor-1 messenger RNA expression are severely attenuated in middle aged and aged rats. *Neuroscience* **83**, 663–668 (1998). **Evidence that the capacity of brain cells to increase neurotrophic factor signalling is impaired during ageing.**
169. Sonntag, W. E., Ramsey, M. & Carter, C. S. Growth hormone and insulin-like growth factor-1 (IGF-1) and their influence on cognitive aging. *Ageing Res. Rev.* **4**, 195–212 (2005).
170. Grondin, R. *et al.* Glial cell line-derived neurotrophic factor increases stimulus-evoked dopamine release and motor speed in aged rhesus monkeys. *J. Neurosci.* **23**, 1974–1980 (2003).
171. Martinez-Serrano, A., Fischer, W. & Bjorklund, A. Reversal of age-dependent cognitive impairments and cholinergic neuron atrophy by NGF-secreting neural progenitors grafted to the basal forebrain. *Neuron* **15**, 473–484 (1995). **The authors show that it is possible to recover age-dependent cognitive deficits by transplantation of neurotrophic factor-producing cells into the basal forebrain.**
172. Lopez-Lopez, C., LeRoith, D. & Torres-Aleman, I. Insulin-like growth factor I is required for vessel remodeling in the adult brain. *Proc. Natl Acad. Sci. USA* **101**, 9833–9838 (2004).
173. Murer, M. G., Yan, Q. & Raisman-Vozari, R. Brain-derived neurotrophic factor in the control human brain, and in Alzheimer's disease and Parkinson's disease. *Prog. Neurobiol.* **63**, 71–124 (2001).
174. Scott, S. A. & Crutcher, K. A. Nerve growth factor and Alzheimer's disease. *Rev. Neurosci.* **5**, 179–211 (1994).
175. Zuccato, C. *et al.* Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. *Science* **293**, 493–498 (2001). **The first evidence that mutant huntingtin perturbs transcriptional regulation of neurotrophic factor production.**
176. Duan, W. *et al.* Paroxetine retards disease onset and progression in Huntingtin mutant mice. *Ann. Neurol.* **55**, 590–594 (2004).
177. Dehmelt, L. & Halpain, S. The MAP2/Tau family of microtubule-associated proteins. *Genome Biol.* **6**, 204 (2005).
178. Al-Chalabi, A. & Miller, C. C. Neurofilaments and neurological disease. *Bioessays* **25**, 346–355 (2003).
179. Trojanowski, J. Q. & Lee, V. M. The role of tau in Alzheimer's disease. *Med. Clin. North Am.* **86**, 615–627 (2002).
180. Norris, E. H. & Giasson, B. I. Role of oxidative damage in protein aggregation associated with Parkinson's disease and related disorders. *Antioxid. Redox Signal.* **7**, 672–684 (2005).
181. O'Neill, C. *et al.* Dysfunctional intracellular calcium homoeostasis: a central cause of neurodegeneration in Alzheimer's disease. *Biochem. Soc. Symp.* **67**, 177–194 (2001).
182. Oddo, S. *et al.* Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Aβ and synaptic dysfunction. *Neuron* **39**, 409–421 (2003).
183. Gauthier, L. R. *et al.* Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. *Cell* **118**, 127–138 (2004).
184. Zhang, B., Tu, P., Abtahian, F. & Trojanowski, J. Q. Neurofilaments and orthograde transport are reduced in ventral root axons of transgenic mice that express human SOD1 with a G93A mutation. *J. Cell Biol.* **139**, 1307–1315 (1997). **Reports direct evidence that a mutation that causes ALS impairs axonal transport in motor neurons.**
185. Hutton, M. Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* **393**, 702–705 (1998).
186. Ishihara, T. *et al.* Age-dependent emergence and progression of a tauopathy in transgenic mice overexpressing the shortest human tau isoform. *Neuron* **24**, 751–762 (1999).
187. Brandt, R., Hundelt, M. & Shahani, N. Tau alteration and neuronal degeneration in tauopathies: mechanisms and models. *Biochim. Biophys. Acta* **1739**, 331–354 (2005).
188. McGeer, P. L. & McGeer, E. G. Local neuroinflammation and the progression of Alzheimer's disease. *J. Neurovirol.* **8**, 529–538 (2002).
189. Dickson, D. W., Lee, S. C., Mattiace, L. A., Yen, S. H. & Brosnan, C. Microglia and cytokines in neurological disease, with special reference to AIDS and Alzheimer's disease. *Glia* **7**, 75–83 (1993).
190. Eikelenboom, P., Hack, C. E., Rozemuller, J. M. & Stam, F. C. Complement activation in amyloid plaques in Alzheimer's dementia. *Virchows Arch.* **56**, 259–262 (1989).
191. Itagaki, S., McGeer, P. L. & Akiyama, H. Presence of T-cytotoxic suppressor and leucocyte common antigen positive cells in Alzheimer's disease brain tissue. *Neurosci. Lett.* **91**, 259–264 (1988).
192. Eikelenboom, P. & Stam. F. C. Immunoglobulins and complement factors in senile plaques. An immunoperoxidase study. *Acta Neuropathol. (Berl.)* **57**, 239–242 (1982).
193. Nath, A. *et al.* Autoantibodies to amyloid β-peptide (Aβ) are increased in Alzheimer's disease patients and Aβ antibodies can enhance Aβ neurotoxicity: implications for disease pathogenesis and vaccine development. *Neuromolecular Med.* **3**, 29–39 (2003).
194. Schenk, D. *et al.* Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature* **400**, 173–177 (1999). **The first evidence that the immune system can be activated to specifically remove amyloid from the brain, suggesting a potential for immunization therapies in the treatment of AD.**
195. Teismann, P. & Schulz, J. B. Cellular pathology of Parkinson's disease: astrocytes, microglia and inflammation. *Cell Tissue Res.* **318**, 149–161 (2004).
196. Sargsyan, S. A., Monk, P. N. & Shaw, P. J. Microglia as potential contributors to motor neuron injury in amyotrophic lateral sclerosis. *Glia* **51**, 241–253 (2005).
197. Smith, R. G. *et al.* Cytotoxicity of immunoglobulins from amyotrophic lateral sclerosis patients on a hybrid motoneuron cell line. *Proc. Natl Acad. Sci. USA* **91**, 3393–3397 (1994).
198. Miller, R. G., Mitchell, J. D., Lyon, M. & Moore, D. H. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Amyotroph. Lateral Scler. Other Motor Neuron Disord.* **4**, 191–206 (2003).
199. Reisberg, B. *et al.* A 24-week open-label extension study of memantine in moderate to severe Alzheimer disease. *Arch. Neurol.* **63**, 49–54 (2006).
200. Wang, J. *et al.* Caloric restriction attenuates β-amyloid neuropathology in a mouse model of Alzheimer's disease. *FASEB J.* **19**, 659–661 (2005).
201. Lazarov, O. *et al.* Environmental enrichment reduces Aβ levels and amyloid deposition in transgenic mice. *Cell* **120**, 701–713 (2005). **Reports the first evidence that exercise/cognitive stimulation can enhance clearance of Aβ from the brain.**
202. Lim, G. P. *et al.* A diet enriched with the ω-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. *J. Neurosci.* **25**, 3032–3040 (2005).
203. DeKosky, S. T. Statin therapy in the treatment of Alzheimer disease: what is the rationale? *Am. J. Med.* **118**, S48–S53 (2005).
204. Lipton, S. A. Paradigm shift in NMDA receptor antagonist drug development: molecular mechanism of uncompetitive inhibition by memantine in the treatment of Alzheimer's disease and other neurologic disorders. *J. Alzheimers Dis.* **6**, S61–S74 (2004).
205. Duan, W. *et al.* p53 inhibitors preserve dopamine neurons and motor function in experimental parkinsonism. *Ann. Neurol.* **52**, 597–606 (2002).
206. Bae, B. I. *et al.* p53 mediates cellular dysfunction and behavioral abnormalities in Huntington's disease. *Neuron* **47**, 29–41 (2005).
207. Ellis, A. C. & Rosenfeld, J. The role of creatine in the management of amyotrophic lateral sclerosis and other neurodegenerative disorders. *CNS Drugs* **18**, 967–980 (2004).

208. Kordower, J. H. *et al.* Neurodegeneration prevented by lentiviral vector delivery of GDNF in primate models of Parkinson's disease. *Science* **290**, 767–773 (2000).
Reports the efficacy of gene therapy in a non-human primate model of PD.
209. Dobrowolny, G. et al. Muscle expression of a local IGF-1 isoform protects motor neurons in an ALS mouse model. J. Cell Biol. 168, 193–199 (2005).
210. Levy, Y. S., Gilgun-Sherki, Y., Melamed, E. & Offen, D. Therapeutic potential of neurotrophic factors in neurodegenerative diseases. *BioDrugs* **19**, 97–127 (2005).
211. Gelinas, D. S., DaSilva, K., Fenili, D., St Georger-Hyslop, P. & McLaurin, J. Immunotherapy for Alzheimer's disease. *Proc. Natl Acad. Sci. USA* **101**, S14657–S14662 (2004).
212. Harper, S. Q. *et al.* RNA interference improves motor and neuropathological abnormalities in a Huntington's disease mouse model. *Proc. Natl Acad. Sci. USA* **102**, 5820–5825 (2005).
213. Logroscino, G. *et al.* Dietary lipids and antioxidants in Parkinson's disease: a population-based, case-control study. *Ann. Neurol.* **39**, 89–94 (1996).
214. Luchsinger, J. A., Tang, M. X., Shea, S. & Mayeux, R. Caloric intake and the risk of Alzheimer disease. *Arch. Neurol.* **59**, 1258–1263 (2002).
215. Luchsinger, J. A. & Mayeux, R. Dietary factors and Alzheimer's disease. *Lancet Neurol.* **3**, 579–587 (2004).
216. Mattson, M. P. & Shea, T. B. Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. *Trends Neurosci.* **26**, 137–146 (2003).
217. Carro, E., Trejo, J. L., Busiguina, S. & Torres-Aleman, J. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. *J. Neurosci.* **21**, 5678–5684 (2001).
218. Laurin, D., Verrault, R., Lindsay, J., MacPherson, K. & Rockwood, K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch. Neurol.* **58**, 498–504 (2001).
219. Mattson, M. P. & Wan, R. Beneficial effects of intermittent fasting and caloric restriction on the cardiovascular and cerebrovascular systems. *J. Nutr. Biochem.* **16**, 129–137 (2005).
220. Jeffery, B., Barlow, T., Moizer, K., Paul, S. & Boyle, C. Amnestic shellfish poison. *Food Chem. Toxicol.* **42**, 545–557 (2004).
221. Lee, J., Bruce-Keller, A. J., Kruman, Y., Chan, S. L. & Mattson, M. P. 2-Deoxy-D-glucose protects hippocampal neurons against excitotoxic and oxidative injury: evidence for the involvement of stress proteins. *J. Neurosci. Res.* **57**, 48–61 (1999).
222. Di Monte, D. A. The environment and Parkinson's disease: is the nigrostriatal system preferentially targeted by neurotoxins? *Lancet Neurol.* **2**, 531–538 (2003).
223. Lee, J. M., Zipfel, G. J. & Choi, D. W. The changing landscape of ischaemic brain injury mechanisms. *Nature* **399** (Suppl. 6738), A7–A14 (1999).
224. Youdim, K. A. & Joseph, J. A. A possible emerging role of phytochemicals in improving age-related neurological dysfunctions: a multiplicity of effects. *Free Radic. Biol. Med.* **30**, 583–594 (2001).
225. Di Matteo, V. & Esposito, E. Biochemical and therapeutic effects of antioxidants in the treatment of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. *Curr. Drug Targets CNS Neurol. Disord.* **2**, 95–107 (2003).

Acknowledgement
This research was supported by the Intramural Research Program of the National Institute on Aging, National Institutes of Health, USA.

Competing interests statement
The authors declare no competing financial interests.

DATABASES

The following terms in this article are linked online to:
Entrez Gene:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
α-Synuclein | BAD | BAX | BCL-X_L | BDNF | calbindin | caspase 3 | Cu/Zn-SOD | DJ1 | GDNF | Huntingtin | IGF1 | IGF2 | Parkin | PARP | Parvalbumin | Tau | XIAP
OMIM:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
ALS | Alzheimer's disease | FTDP-17 | Huntington's disease | Parkinson's disease

FURTHER INFORMATION

Alzheimer's Association: http://www.alz.org
National Parkinson Foundation: http://www.parkinson.org
ALS Association: http://www.alsa.org
Hereditary Disease Foundation:
http://www.hdfoundation.org
Mattson's homepage:
http://www.grc.nia.nih.gov/branches/lns/index.html
Access to this links box is available online.